ORIGINAL ARTICLE

Bevacizumab Use for Recurrent High-Grade Glioma at McGill University Hospital

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ABSTRACT: ***Background:*** Bevacizumab, a humanized recombinant anti-vascular endothelial growth factor antibody, was approved in Canada in 2010 for the treatment of high-grade glioma. We report the effectiveness and safety of bevacizumab in the treatment of patients with recurrent high-grade gliomas at a single institution. ***Methods:*** Twenty-seven consecutive patients with high-grade glioma (anaplastic glioma and glioblastoma) at first or subsequent relapse were treated with bevacizumab alone or in combination with chemotherapy. The primary endpoint was progression-free survival (PFS) and secondary endpoints were objective response rate, six month PFS, overall survival (OS), and safety profile. ***Results:*** The clinical benefit rate (complete and partial responses plus stable disease) was 59%. Median PFS was 4.3 (95% CI, 3.0–10.9) months, with a six month PFS rate of 43%. Median OS after current relapse was 8.9 (95% CI, 5.8–not reached) months. Ten episodes of grade 3/4 adverse events were observed in nine patients, including fatigue (n = 3), thrombocytopenia (n = 4), and myelotoxicity, febrile neutropenia, and pulmonary embolism (each n = 1). ***Conclusions:*** We consider the efficacy and safety profile of bevacizumab is comparable to other cohorts of patients treated for recurrent high-grade glioma at other international institutions.

RÉSUMÉ: L'utilisation du Bevacizumab dans le traitement de la récidive d'un gliome de haut grade de malignité au Centre universitaire de santé McGill. ***Contexte :*** Le Bevacizumab, un anticorps recombinant humanisé dirigé contre le facteur de croissance endothélial vasculaire, a été approuvé au Canada en 2010 pour le traitement du gliome de haut grade de malignité. Nous rapportons l'efficacité et la sécurité du Bevacizumab dans le traitement de patients présentant une récidive de gliomes de haut grade de malignité dans notre institution. ***Méthode :*** Vingt-sept patients consécutifs atteints de gliomes de haut grade de malignité (gliomes anaplasiques et glioblastomes) ont été traités par le Bevacizumab seul ou en combinaison à la chimiothérapie à la première récidive ou au moment de récidives subséquentes. Le critère d'évaluation primaire était la survie sans progression (SSP) et les critères d'évaluation secondaires étaient le taux de réponse objective, une SSP de 6 mois, la survie globale (SG), et le profil de sécurité. ***Résultats :*** Le taux de bénéfice clinique (réponse complète et partielle avec maladie stable) était de 59%. La SSP médiane était de 4,3 mois (IC à 95% : 3,0 à 10,9) avec un taux de SSP de 6 mois de 43%. La SG médiane après la récidive en cours était de 8,9 mois (IC à 95% de 5,8 à non atteinte). Dix épisodes d'incidents thérapeutiques de grade ¾ ont été observés chez 9 patients, dont de la fatigue (n = 3), une thrombocytopénie (n = 4) et une myélotoxicité, une neutropénie fébrile et une embolie pulmonaire (n = 1 chacun). ***Conclusions :*** Nous considérons que le profil d'efficacité et de sécurité du Bevacizumab que nous avons observé est comparable à celui d'autres cohortes de patients traités pour une récidive d'un gliome de haut grade de malignité dans d'autres institutions internationales.

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High-grade gliomas are the most common and aggressive group of primary central nervous system (CNS) tumors in adults and are characterized by diffuse infiltration of brain parenchyma and prominent angiogenesis. Their treatment has always been problematic and, despite recent significant advances in brain imaging, neurosurgery, and medical therapy[1], prognosis remains dismal. Glioblastoma is currently associated with a median overall survival (OS) of approximately 14.5 months after diagnosis and six months after recurrence[2]; median progression-free survival is approximately 7.0 months after diagnosis. For anaplastic astrocytomas, median OS is two to three years after diagnosis and approximately 11 months after recurrence[3].

New therapeutic targets have recently emerged following advances elucidating the pathogenesis of gliomas. One target that has emerged is vascular endothelial growth factor (VEGF), a key protein regulator of new blood vessel formation and tumor angiogenesis. Vascular endothelial growth factor overexpression is related to the degree of tumor development and prognosis[4]. In particular, glioblastoma is characterized by sustained angiogenesis and frequently exhibits VEGF overexpression[5,6].

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Bevacizumab (Avastin®) is a therapeutic humanized recombinant monoclonal antibody that binds to and inhibits the activity of VEGF[7]. It has shown activity against various tumors such as colorectal, lung, renal, ovarian, and breast cancer[8-11]. Preclinical models show that bevacizumab has activity against glioblastoma both alone and in combination with radiotherapy and temozolomide[12,13]. Several clinical studies have demonstrated the activity of bevacizumab in the treatment of recurrent gliomas when used as monotherapy or in combination with chemotherapy[14-17]. The BRAIN phase II study in glioblastoma patients after first or second relapse following radiotherapy plus temozolomide revealed compelling results in patients treated with bevacizumab alone (n = 85) or bevacizumab plus irinotecan (n = 82), respectively: six month progression-free survival (PFS) rate (43% vs. 50%), objective response rate (ORR) (28% vs. 38%), and median OS (9.2 vs. 8.7 months)[18]. Notably, primary endpoints including ORR rate and six month PFS rate were significantly (P <0.0001) higher than the rates of 5% and 15%, respectively, expected with salvage chemotherapy according to external historical controls.[18] Because of these promising results in a disease with few treatment options, the US Food and Drug Administration approved the use of bevacizumab for the treatment of recurrent glioblastoma in May 2009 on the basis of phase II trial results[19]. Bevacizumab was subsequently approved in March 2010 by Health Canada as a single agent for the treatment of glioblastoma following relapse or progression.

In this report, we evaluate the effectiveness, feasibility, and safety of using bevacizumab in the treatment of patients with recurrent high-grade gliomas at a single Canadian cancer center.

Methods

All consecutive adult (≥18 years) patients who received bevacizumab alone or in combination with chemotherapy for recurrent high-grade glioma (anaplastic glioma and glioblastoma) at the Montreal Neurological Institute (McGill University, Canada) were retrospectively identified and their charts reviewed. Patients initiated treatment between July 2008 and December 2010. The choice of bevacizumab therapy as a single agent or combination with chemotherapy, as well as the choice of concomitant chemotherapeutic agent(s), was at the discretion of the attending physician who was directly responsible for the care of each patient and was also based on the patient's insurance status. Bevacizumab 5–10 mg/kg was administered intravenously every two weeks.

All patients underwent brain magnetic resonance imaging (MRI) at baseline (immediately prior to bevacizumab-based chemotherapy) and four to eight weeks later to assess response. Interpretable fluid-attenuated inversion recovery (FLAIR) and post-gadolinium T1-weighted sequences were required for each assessment. Response to therapy was evaluated using RANO criteria[20]: complete response (CR) was defined as complete disappearance of all measurable disease; partial response (PR) as a ≥50% decrease in the largest cross-sectional tumor area; and progressive disease (PD) as a ≥25% increase in largest cross-sectional tumor area or appearance of new lesion; all other conditions were considered stable disease (SD). Stability or improvement of FLAIR sequences was required to define CR, PR, or SD. Distant recurrence (new enhancing foci distant from the original area of the enhancing tumor) and diffuse recurrence (≥25% increase in area of abnormal FLAIR hyperintensity) were also identified.

The primary endpoint of the analysis was PFS. Secondary endpoints were ORR, OS, six month PFS, and safety profile. Time-to-event data (OS and PFS) were analyzed using the Kaplan-Meier method. Overall survival was defined as the time from bevacizumab treatment initiation to death resulting from any cause and PFS as the time from bevacizumab treatment initiation to progression or death. Adverse events were graded according to NCI-CTCAE (v3.0) criteria. Information on adjunctive corticosteroid use was noted.

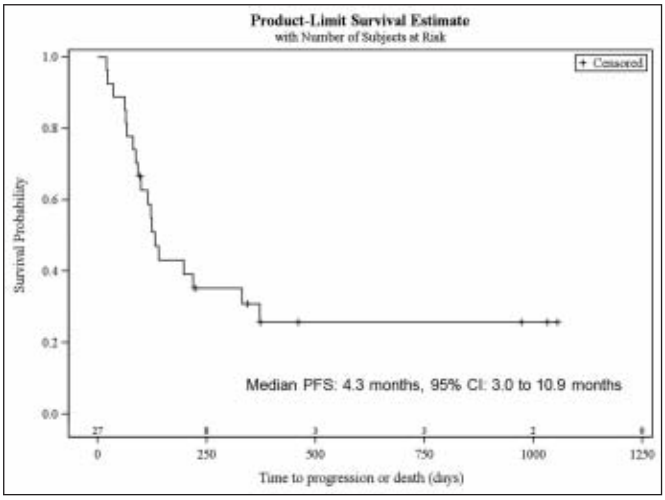

Figure 1: *Kaplan-Meier plot for progression-free survival.*

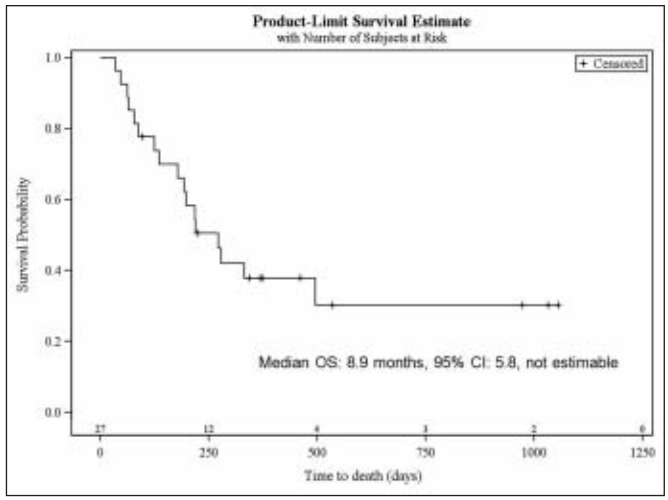

Figure 2: *Kaplan-Meier plot for overall survival after relapse.*

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Table 1: Characteristics of the research group

Patient characteristics	
Patients, *n*	27
Median age at diagnosis, years (range)	39 (23–62)
Gender, *n* (%)	
Male	15 (56)
Female	12 (44)
Histologic diagnosis, *n* (%)	
Glioblastoma	17 (63)
Anaplastic gliomas	10 (37)
Median previous regimens, *n* (range)	2 (0–4)
Prior therapy, *n* (%)	
Surgery	21 (78)
Gross total resection	10
Subtotal/partial resection	11
Radiotherapy	24 (89)
Chemotherapy	25 (93)
Prior chemotherapy, *n**	
Temozolomide monotherapy	24
Temozolomide + procarbazine	9
Temozolomide + everolimus	1
Cabozantinib monotherapy	1
Cediranib monotherapy	1
Lomustine monotherapy	1
Irinotecan monotherapy	1
No chemotherapy	2
Chemotherapy concurrent with bevacizumab, *n* (%)	
Temozolomide only	4 (15)
Temozolomide + procarbazine	11 (41)
Lomustine	5 (19)
Irinotecan + temozolomide + procarbazine	2 (7)
Monotherapy	5 (19)

*Indicates the number of patients who had received each specific chemotherapy at any time. Some of these patients may have received a specific chemotherapy on multiple occasions for different relapses.

Results

Patient Characteristics

Outcomes for a total of 27 consecutive patients treated with bevacizumab were reviewed. Baseline demographic and clinical characteristics of this study population are summarized in Table 1.

Histologic diagnosis was glioblastoma (n = 17), or anaplastic gliomas (n = 10). All patients had received prior surgery (n = 21) and/or radiotherapy (n = 24). Ten patients had received gross total resection and 11 subtotal/partial resection, while the remaining six patients had biopsy only. Twenty-five patients had received prior chemotherapy either first-line or following subsequent relapse/recurrence. Chemotherapy included temozolomide alone (n = 24) or in combination with either procarbazine (n = 9) or everolimus (n = 1) and, in isolated cases, single-agent cabozantinib, cediranib, lomustine, and irinotecan. Cabozantinib and cediranib were given as part of clinical trials. The bevacizumab dose used was 5 mg (n = 21), 7.5 mg (n = 1) or 10 mg (n = 5) every two weeks. Bevacizumab was most commonly used in combination or sequentially with chemotherapy (22 of 27 patients), including temozolomide with procarbazine (n = 11), lomustine (n = 5), temozolomide only (n = 4), and temozolomide with procarbazine and irinotecan (n = 2). The remaining five patients received bevacizumab monotherapy. In addition, six patients received bevacizumab across multiple lines of treatment post-progression.

Efficacy

Best response to bevacizumab was as follows: PR (n = 1), SD (n = 15), PD (n = 9), and unknown (n = 2). For the overall population, ORR (CR + PR) was 3.7% and the clinical benefit rate (CR + PR + SD) was 59%. Median PFS was 4.3 (95% CI, 3.0–10.9) months (Figure 1), with a six month PFS rate of 43%. Median OS after current relapse was 8.9 (95% CI, 5.8–not reached) months (Figure 2). There was no significant difference (P = 0.66) in OS comparing the subpopulation who were treated with bevacizumab after first relapse (n = 9) and those treated after second or later relapse (n = 18; some were treated up to sixth relapse) (Figure 3). There was a clinically significant reduction in cerebral edema in 12 patients (44%). Steroid dose was decreased in 17 patients (63%).

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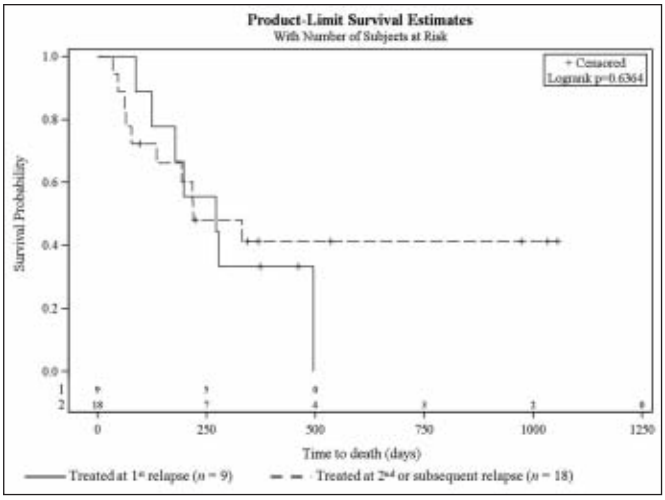

Figure 3: *Kaplan-Meier plot for overall survival after bevacizumab treatment at first vs. second or subsequent relapse.*

Safety

Ten episodes of grade 3/4 adverse events were observed in nine patients. These included grade 3 fatigue (n = 3); grade 3 thrombocytopenia (n = 2); grade 4 thrombocytopenia (n = 2); grade 4 myelotoxicity (n = 1); grade 4 pulmonary embolism (n =1); and grade 3 febrile neutropenia (n = 1).

Discussion

Standard treatment for newly diagnosed glioblastoma includes surgery, followed by radiotherapy administered concomitantly with temozolomide, and then followed by adjuvant temozolomide treatment for 6–12 months[21]. Unfortunately, virtually all patients with high-grade glioma develop recurrent or progressive disease, usually within months after initial diagnosis. This is a particular problem in patients with glioblastoma. Therefore, alternative treatment strategies for patients at the time of disease progression need to be developed. The use of bevacizumab as an antiangiogenic agent in the treatment of high-grade glioma constitutes an important advance in the management of patients. Phase II studies conducted in United States and European centers have demonstrated a significant improvement in ORR and PFS in glioblastoma patients treated with bevacizumab and irinotecan[14,16] when compared to conventional treatments[22].

In our study we determined the efficacy and safety of bevacizumab in the treatment of patients with high-grade glioma (anaplastic gliomas and glioblastoma) at a single Canadian institution immediately after its approval in Canada. We were able to retrospectively evaluate bevacizumab in a cohort of 27 patients. We consider the efficacy of bevacizumab was favorable compared to other cohorts of patients with high-grade glioma treated with bevacizumab-based therapy for recurrent disease at other international institutions (Table 2). The clinical benefit rate (CR + PR + SD) was 59%. Median OS and PFS were 8.9 and 4.3 months, respectively, with a six month PFS rate of 43%.

Table 2: Therapeutic outcome following treatment of recurrent high-grade glioma with bevacizumab plus chemotherapy or as monotherapy according to different studies

Reference	Chemotherapy	No. of patients	Outcome
Current report	Various[1]	27 (17 grade IV; 10 grade III)	PFS6: 43%, Median PFS: 4.3 mo Median OS: 8.9 mo ORR: 3.7%, CBR: 59%
Wong et al.[23]	Various (meta-analysis)	548 (all grade IV)	PFS6: 45%, OS6: 76% Median TTP: 6.1 months, ORR: 55%
Poulsen et al.[24]	Irinotecan	52 (27 grade IV; 25 grade III)	PFS6: 32%, ORR: 25%,
Soffietti et al.[25]	Fotemustine	31 (22 grade IV; 9 grade III)	Median TTP: 2.6 mo ORR: 35%
Reardon et al.[26]	Etoposide	59 (27 grade IV; 32 grade III)	PFS6: 44% in grade IV and 41% in grade III
Guiu et al.[27]	Irinotecan	77 (49 grade IV; 28 grade III)	ORR: 36%
Gilbert et al.[28]	Irinotecan	57 (grade III/IV[2])	PFS6: 37%
Sathornsumetee et al.[29]	Erlotinib	57 (25 grade IV; 32 grade III)	PFS6: 28% in grade IV and 44% in grade III Median OS: 10.5 mo in grade IV and 17.5 mo in grade III ORR: 48% in grade IV and 31% in grade III
Verhoeff et al.[30]	Dose-intense temozolomide	23 (15 grade IV; 8 grade III)	PFS6: 17.4%, Median PFS: 3.5 mo Median OS: 4.4 mo ORR: 22%
Elandt et al.[31]	Liposomal doxorubicin	21 (15 grade IV; 6 grade III)	PFS6: 19%, Median PFS: 3.0 mo ORR: 48%
Calabrich et al.[32]	Irinotecan or temozolomide	39 (27 grade IV; 10 grade III; 1 grade II)	Median PFS: 9.4 mo, Median OS: 18.7 mo PFS6: 61%
Gallardo Martin et al.[33]	Irinotecan	15 (10 grade IV; 5 grade III)	PFS6: 73%, Median PFS: 9.6 mo ORR: 53%

[1]Two patients received monotherapy. [2]Numbers for each grade not specified. Abbreviations: CBR, clinical benefit rate; mo, month; ORR, overall response rate; OS, overall survival; OS6, 6-month overall survival; PFS, progression-free survival; PFS6, 6-month progression-free survival; TTP, time to progression.

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However, ORR at 3.7% was low compared to other studies. One potential reason for the low ORR was the assessment of response by FLAIR MRI instead of post contrast-infused MRI. Almost all responses were stable disease, which appears to reflect response to bevacizumab in other clinical indications. Median OS was comparable for patients treated with bevacizumab after first relapse compared to those after second or subsequent relapse, whereas median PFS and ORR were lower in the latter subpopulation (data not shown). It could therefore be speculated that earlier introduction of bevacizumab might translate into improved survival.

Direct comparison of these retrospective findings with those from other prospective reports is problematic and complicated by the following: 1) treated target populations differ with respect to the proportions of patients with different histologic grade, i.e. grade III versus grade IV disease, which is known to have a significant impact on prognosis; 2) the variety of chemotherapies used, which may potentially exhibit differential efficacy when used in combination with bevacizumab; and 3) the number of prior relapses experienced, with increasing number of relapses diminishing the likely response to therapy. The majority of our patients were treated with different combinations of classic chemotherapies, i.e. temozolomide ± procarbazine (56%), lomustine (19%), and temozolomide + procarbazine + irinotecan (8%), while five patients (19%) received single-agent bevacizumab, and some had been treated intensively for up to six relapses. Despite evidence for bevacizumab + irinotecan being effective in the registration trial in glioblastoma, the majority of patients at our institution received a combination of bevacizumab with temozolomide and procarbazine; this decision was based on our previous experience with this regimen and because of concerns over toxicity related to irinotecan.

It is reasonable to expect that patients experiencing such a high number of prior relapses would be less likely to respond to further therapy. Nevertheless, median PFS, and the six month PFS rate in our cohort were generally at least or more favorable than those studies that included mixed populations with grade III and IV disease (Table 2). Table 2 does not include all studies of bevacizumab-based therapy in patients with a mixture of recurrent grade III/IV disease but does include most of the larger, recent studies in this setting. It does not include populations that were exclusively treated with bevacizumab-based therapy in the recurrent grade IV (glioblastoma) setting. Results in this exclusively grade IV situation are best summarized by the meta-analysis by Wong et al[23], which is included in Table 2 for comparison. This meta-analysis included a total of 15 studies from 2005 to 2009, in which 548 patients (median age 53 years) with recurrent glioblastoma were treated with bevacizumab-based therapy. Median OS and six month PFS rate were 9.3 months and 45%, respectively, which were comparable to our findings (8.9 months and 43%).

Other clinical benefits associated with bevacizumab therapy included a reduction in steroid dose in a meaningful proportion of patients. Other reports have suggested important steroid dose reduction[34,35]. The safety profile of bevacizumab has already been well-established, notably in the BRAIN study[18]. No unexpected toxicities were observed in our series.

In conclusion, our findings in this small retrospective series of patients further support previously reported data that bevacizumab-based regimens are active in the treatment of patients with relapsed high-grade gliomas.

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