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Clinical study

Impact of adverse events of bevacizumab on survival outcomes of patients with recurrent glioblastoma

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ABSTRACT

Background: Bevacizumab is widely used for treatment of recurrent glioblastoma (rGB). It is well known that adverse events (AEs) due to bevacizumab can cause early discontinuation of treatment. However, the association between AEs and survival outcomes is not well defined.
Methods: We retrospectively identified patients with rGB, who were treated with single-agent bevacizumab or bevacizumab-based combination regimens from 07/2005 through 07/2014, and who discontinued bevacizumab due to either AEs or physician's decision. Those who discontinued bevacizumab because of tumor progression were excluded. Demographic, treatment, and survival data were collected from the database.
Results: Of 298 adults with rGB treated with bevacizumab in our database, 65 patients discontinued bevacizumab due to AEs (n = 39, 60%) or physician's decision (n = 26, 40%). There were no statistically significant differences in regards to age, performance status, extent of resection, number of lesions, the time between diagnosis and first recurrence, time between diagnosis and initiation of bevacizumab, number of recurrences before bevacizumab initiation, and duration of bevacizumab treatment between the two groups. Interestingly, patients who discontinued bevacizumab because of AEs progressed earlier after bevacizumab discontinuation (3.9 months vs 5.7 months; p = 0.02), had significantly shorter progression-free survival (PFS) (10.4 months vs 14.2 months; p = 0.01) and shorter overall survival (OS) from bevacizumab initiation (13.9 months vs 32.5 months; p = 0.01) as well as shorter OS from tumor diagnosis (20 months vs 49.3 months; p = 0.007) when compared to patients who discontinued bevacizumab due to a physician's decision.
Conclusions: Our results indicate that the development of AEs to bevacizumab or bevacizumab-containing regimens is associated with unfavorable glioma-related survival outcomes in patients with rGB.

1. Introduction

Glioblastoma is the most common and aggressive primary brain cancer in adults despite advanced diagnostic modalities and optimal initial multidisciplinary treatment. Tumor progression or recurrence with nearly universal mortality is seen in almost all the patients. The median survival from the time of diagnosis for most patients is 14–15 months, with a 2-year survival rate of 26% [1,2].

Standard of care for recurrent glioblastoma (rGB) is variable and many patients elect to enroll onto clinical trials at the time of progression. Most studies report a limited response rate and when present, of short duration. As such, the median PFS and OS for rGB are 14 weeks and 30 weeks, respectively [3,4]. The survival after resection of rGB remains poor [5] and there is ongoing investigations to evaluate the efficacy of re-irradiation and salvage chemotherapy.

Bevacizumab (Avastin, Genetech/Roche), an antibody that sequesters VEGF from the circulation, was granted accelerated approval in 2009 from the US Food and Drug Administration for the treatment of rGB [6]. Several studies tested bevacizumab as single-agent reporting PFS (4–4.2 months), 6-month PFS (29–42%) and OS (7.8–9.2 months) [3,7]. In addition, other studies used bevacizumab in combination with lomustine showing a 9-month OS of 63% [8,9], or with irinotecan [10], carboplatin [11,12], and etoposide [13]. Despite this research effort there continues to be limited level 1 evidence to support the use of a bevacizumab or bevacizumab-based combination regimens with the recent results

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from the randomized phase II trial (BELOB) not being supported by the phase III confirmatory trial (EORTC 26101) [9]. These combinations do not prolong the OS and may increase toxicity.

Although the median number of cycles of bevacizumab monotherapy is approximately 4 months, the exact time to discontinue bevacizumab in practice is not known. Aside from tumor progression, adverse events (AEs) or physician's decision are alternate reasons that may prompt discontinuation of therapy; however, the effects of these AEs on survival outcomes are not well defined. This study investigates the impact of AEs of bevacizumab on glioma-related survival of patients with rGB and provides insights into the events that lead to an improved outcome for these patients.

2. Methods

2.1. Patients

We conducted a retrospective data analysis of The University of Texas MD Anderson Cancer Center institutional database of all adult glioblastoma and gliosarcoma (GS) patients treated with single-agent bevacizumab or bevacizumab-containing regimens, and who discontinued bevacizumab due to either AEs or physician's decision from July 2005 through July 2014. This study was approved by the MD Anderson Institutional Review Board. AEs were recorded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC Version 4.0) [http://ctep.info.nih.gov]. Those who discontinued bevacizumab because of tumor progression were excluded. Demographic, treatment, and survival data were collected from the database. All patients had pathologically-confirmed diagnosis of glioblastoma or GS at original diagnosis. To simplify the analysis, patients were included in this study when bevacizumab was initiated when there was radiologic evidence of first recurrence. Patients receiving bevacizumab at initial diagnosis (including those with suspicion of pseudoprogression) were excluded.

2.2. Survival

PFS was defined as the duration between the date of initiation of bevacizumab to the date of tumor progression (second recurrence), death or last follow-up. PFS from the date of bevacizumab discontinuation was defined as the duration from the date of bevacizumab discontinuation to the date of tumor progression (second recurrence), death or last follow-up. OS was defined as the duration between the date of initiation on bevacizumab to the date of death or last follow-up. Death was confirmed by review of medical records, death certificate, and/or the social security index database.

2.3. Statistical analysis

Survival analyses using Kaplan-Meier curves, the Cox proportional hazard method and log-rank test were performed to compare curves between patients who discontinued bevacizumab due to AEs and those who discontinued bevacizumab due to a physician's decision. When the date of death was not known, the record was censored (for OS) in the analysis as of the date of last follow-up. Statistical significance was considered at a p-value ≤ 0.05.

3. Results

We identified a total of 298 patients with rGB/GS treated with bevacizumab. 233 patients were excluded because they had disease progression, died or were lost to follow-up while receiving bevacizumab. A total of 65 patients discontinued bevacizumab due to AEs (n = 39, 60%) or physician's decision (n = 26, 40%) (Fig. 1). There were no statistically significant differences in regards to age, performance status, extent of resection, number of lesions, the time between diagnosis and first recurrence, time between diagnosis and initiation of bevacizumab, number of

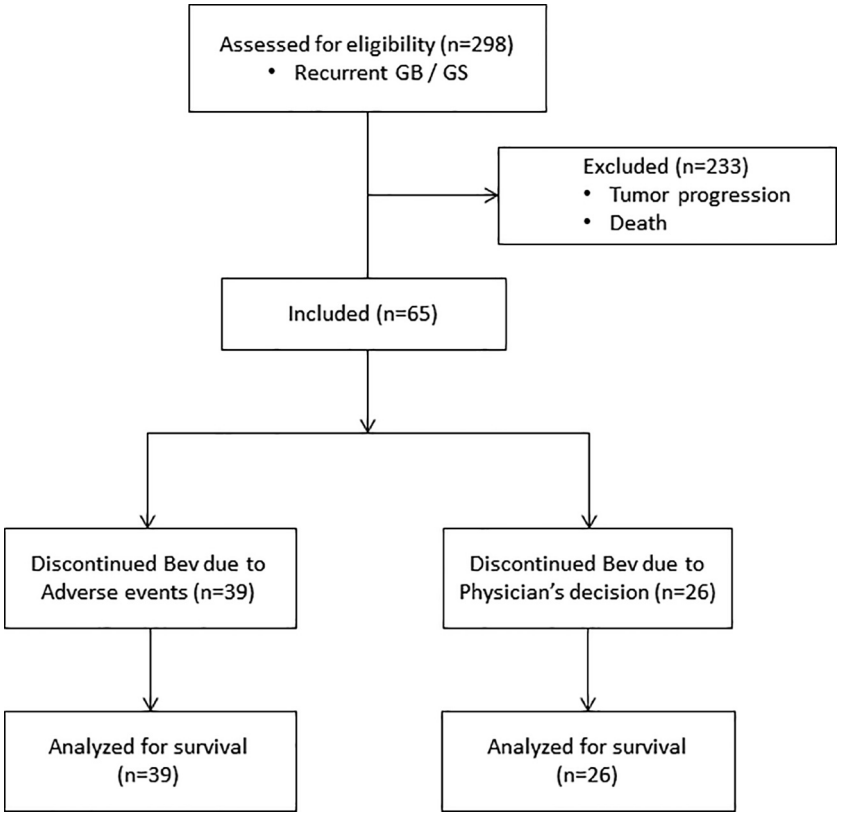

Fig. 1. Study flow diagram.

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recurrences before bevacizumab initiation, and duration of bevacizumab treatment between the two groups. The rates of single-agent bevacizumab (20.5% vs 19.2%) or bevacizumab-combination regimen (79.5% vs 80.7%) were similar in both groups. Bevacizumab and irinotecan was used in equal frequency (51.3% vs 50.0%). The demographics of both groups "Adverse events" and "Physician's decision" are detailed in Table 1. There was no significant difference between AE occurrences in the single-agent bevacizumab subgroup compared to that in the bevacizumab-containing regimen subgroup (61.5% vs 59.6%, respectively). Fatigue and bleeding were the most common AEs, respectively. However, higher AE grades were seen in the bevacizumab-combination regimen subgroup.

AEs included fatigue (n = 7) [Grade 3, n = 7], bleeding (n = 7) [Grade 2 rectal hemorrhage, n = 2; Grade 3 anal hemorrhage, n = 1; Grade 2 vitreous hemorrhage, n = 1; Grade 2 intracranial hemorrhage, n = 1; Grade 2 upper gastrointestinal hemorrhage, n = 1; Grade 2 hematuria, n = 1], thrombocytopenia (n = 6) [Grade 3, n = 4; Grade 4, n = 2], neutropenia (n = 5) [Grade 3, n = 5], ischemic stroke (n = 3) [Grade 1, n = 2; Grade 2, n = 1], abdominal pain (n = 3) [Grade 3, n = 3], wound healing-related complications (n = 2) [Grade 3, n = 2], deep venous thrombosis/pulmonary embolism (n = 2) [Grade 3, n = 2], hypertension (n = 2) [Grade 3, n = 1; Grade 4, n = 1] and proteinuria (n = 2) [Grade 2, n = 1; Grade 3, n = 1] (Table 2). Of note, all the patients with neutropenia and thrombocytopenia received bevacizumab plus chemotherapy. Weight change was also observed, almost half of the patients gained weight (mean increase of 9.9 lbs., range 2.2–20.3 lbs.), more frequently observed in those who discontinued bevacizumab due to an AE compared to patients who discontinued due to physician's decision (64% vs 49%, p = 0.28). Reasons to discontinue bevacizumab based on physician's decision consisted of radiologically and clinically stable disease (n = 24) and completion of a planned period of treatment (n = 2).

Table 1
Demographics by reason for discontinuing bevacizumab: "Adverse events" or "Physician's decision".

	Adverse effects	Physician's decision	*p-value*
Patients, n (%)	39 (60)	26 (40)	
Sex, n (%)			
• Male	25 (57.6)	15 (57.7)	*NS*
• Female	14 (42.4)	11 (42.3)	
Age (years)			
• Median	57.7	55.4	*NS*
• Range	24.4 – 72.3	26.6 – 76.5	
Median KPS %	80	80	*NS*
Extent of resection, n (%)			
• Gross total	22 (56.4)	19 (73.0)	*NS*
• Subtotal/biopsy	17 (43.6)	7 (27.0)	*NS*
Chemoradiation, n (%)			
• Yes	39 (1 0 0)	24 (92.3)	*NS*
• No	0	2 (7.7)	
Lesion pattern, n			
• Single	30	25	
• Multiple	9	1	*NS*
Median time to start bevacizumab (months)	5.7	9.2	*NS*
Recurrences prior to bevacizumab	1	1	*NS*
Duration of bevacizumab (months)	4.5	9.7	*NS*
Bevacizumab-based regimen, n (%)			
• Single-agent bevacizumab	8 (20.5)	5 (19.2)	
• bevacizumab and irinotecan	20 (51.3)	13 (50.0)	
• bevacizumab and temozolomide	3 (7.7)	6 (23.0)	
• bevacizumab and lomustine	2 (5.1)	0	
• bevacizumab and carboplatin	3 (7.7)	1 (3.9)	
• bevacizumab and other	3 (7.7)	1 (3.9)	

Abbreviations: F = female, KPS = Karnofsky performance status, M = male, n = number, *NS* = non-significant, p = probability, % = percentage.

Table 2
Adverse events that led to discontinue bevacizumab.

Adverse effects	Patients, n = 39 (100%)	*Grade
Fatigue/generalized weakness	7 (18.0)	3
Bleeding	7 (18.0)	
• Rectal hemorrhage	2	2
• Anal hemorrhage	1	3
• Vitreous hemorrhage	1	2
• Intracranial hemorrhage	1	2
• Upper gastrointestinal hemorrhage	1	2
• Hematuria	1	2
Thrombocytopenia (platelets/mm^3)	6 (15.4)	
• 25,000–50,000/mm^3	4	3
• Less than 25,000/mm^3	2	4
Neutropenia	5 (12.8)	3
Ischemic stroke	3 (7.7)	
• Asymptomatic	2	1
• Moderate symptoms	1	2
Abdominal pain	3 (7.7)	3
Wound healing-related complications	2 (5.1)	3
Deep venous thrombosis/Pulmonary embolism	2 (5.1)	3
Hypertension	2 (5.1)	
• Life threatening consequences	1	4
• SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg	1	3
Proteinuria	2 (5.1)	
• More than 3.5 g/24 h	1	3
• 1.0–3.4 g/ 24 h	1	2

Abbreviations: DBP = diastolic blood pressure, DVT = deep venous thrombosis, GI = gastrointestinal, n = number, URI = upper respiratory infection, PE = pulmonary embolism, SBP = systolic blood pressure, % = percentage.
* National Cancer Institute Common Toxicity Criteria (NCI CTC Version 4.0).

Patients who discontinued bevacizumab due to an AE progressed earlier after bevacizumab discontinuation (3.9 months vs 5.7 months, p = 0.02) (Fig. 2), had significantly shorter PFS (10.4 months vs 14.2 months, p = 0.01) (Fig. 3), had significantly shorter OS from bevacizumab initiation (13.9 months vs 32.5 months, p = 0.01) (Fig. 4) and shorter OS from the diagnosis of glioblastoma/GS (20 months vs 49.3 months, p = 0.007) when compared to patients who discontinued bevacizumab due to a physician's decision.

4. Discussion

The optimal duration of bevacizumab therapy for rGB is not yet established. Most patients are treated until progression, but in those without progression, it may be used for prolonged periods

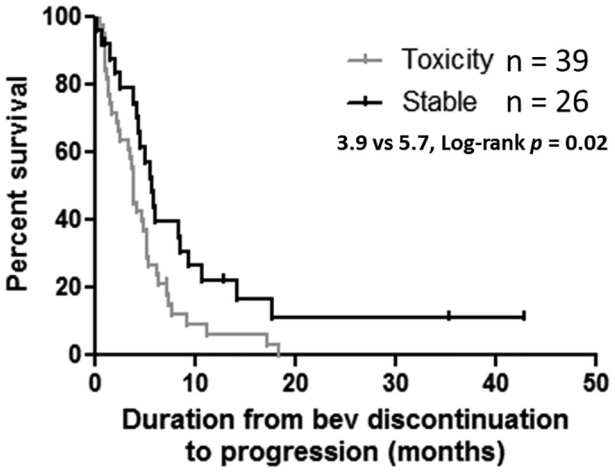

Fig. 2. Interval duration from bevacizumab discontinuation to progression in 2 groups: "Adverse events" vs "Physician's decision".

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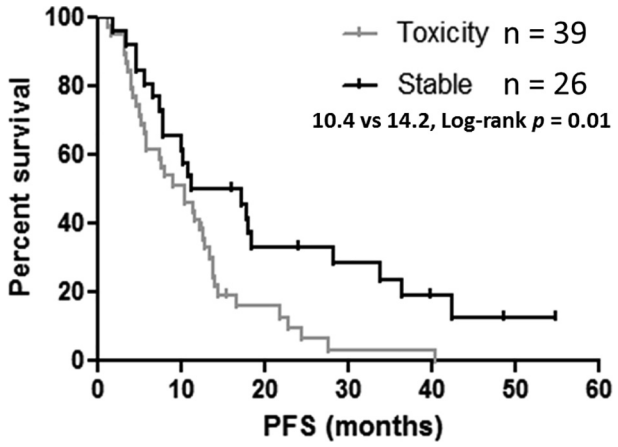

Fig. 3. PFS of patients who discontinued bevacizumab due to "Adverse events" or "Physician's decision".

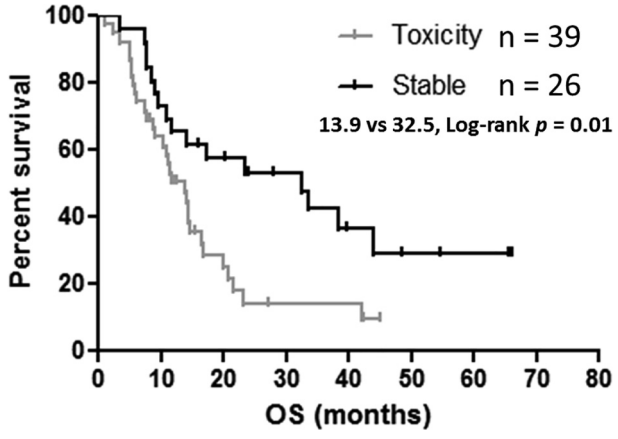

Fig. 4. OS of patients who discontinued bevacizumab due to "Adverse events" or "Physician's decision".

of time without clear stopping guidelines. However, continuation may lead to a higher incidence of AEs and may contribute to the development of a more aggressive phenotype [14–17]. Furthermore, discontinuation may result in a rebound effect due to loss of anti-edema properties [18]. The potential bevacizumab AEs include wound healing complications, bleeding, thromboembolic events, hypertension, proteinuria and infection. The incidence of thrombocytopenia and neutropenia are increased in patients receiving bevacizumab plus chemotherapy in comparison to those receiving chemotherapy only [19].

Some studies suggest that bevacizumab continuation beyond initial progression modestly improves survival in rGB patients [20]. Furthermore, those patients who progressed on a bevacizumab-containing regimen rarely responded to the second bevacizumab-containing chemotherapeutic regimen [21] demonstrating a median PFS of only 2 months, OS of 5.2 months and 6-month PFS of 0% [22]. These observations may influence the decision to either continue or discontinue bevacizumab in an individual patient.

In our study population, the discontinuation of bevacizumab therapy (as single-agent or as component of a multidrug regimen) due to AEs was associated with earlier tumor progression and shorter OS when compared to those patients who discontinued bevacizumab because of physician's decision. Clinical and radiological stable disease was the main reason to discontinue bevacizumab however it could have been an equally good justification to continue it. Non-medical reasons that may reinforce the decision to discontinue bevacizumab could include patient's request, cost, concern for treatment-related toxicity or physician's uncertainty about the optimal duration of bevacizumab treatment.

The development of systemic symptoms due to increased levels of pro-inflammatory cytokines is a well-known manifestation of active cancer [23]. Therefore, one may hypothesize that bevacizumab may further increase these cytokines in patients with glioblastoma expressing as AEs, for which meticulous evaluation of symptoms and rapid intervention would be required. However, it is difficult to predict the timing and severity of AEs to determine the appropriate time to discontinue bevacizumab. Switching to other chemotherapies or even holding therapy shortly after the patient's neurological condition improves and the tumor becomes radiologically stable seems to be an acceptable approach. Certainly, it may be difficult to distinguish between bevacizumab AEs from those caused by non-bevacizumab chemotherapies in a combination regimen. In this study, the data showed more AEs in the combination regimens (particularly bone marrow suppression which was not detected with single-agent bevacizumab) suggesting additional drug toxicity. In these cases, discontinuation of cytotoxic chemotherapy could be considered prior to holding bevacizumab.

Our study was limited by its retrospective design and completion in a tertiary institution. The retrospective nature of the review introduces inherent selection bias related to the patient population and outcome criteria. Although there was variability in the initial bevacizumab-containing regimens and in the therapies for subsequent disease progression chosen at the discretion of the treating physician, these factors were unlikely to influence outcome given that combination therapy with bevacizumab at initial treatment or after failure of single-agent bevacizumab has been reported to not significantly change outcome [7,10]. Despite these limitations, this study addresses important questions regarding the use of bevacizumab particularly when a decision to discontinue treatment has to be made in the setting of stable disease. These results warrant prospective studies to define the impact of AEs of bevacizumab on survival, as a prognostic factor and/or in drug discontinuation decision making.

5. Conclusion

The results of this study indicate that the development of AEs to bevacizumab or bevacizumab-containing regimens is associated with unfavorable glioma-related survival outcomes in patients with rGB. It may represent an early and pre-radiographic manifestation of tumor progression.

6. Disclosure

JF de Groot reports personal fees for activities with Celldex, Deciphera Pharmaceuticals, VBL Therapeutics and Novella, and research support from Sanofi-Aventis, AstraZeneca, EMD-Serono, Eli Lilly, Novartis and Deciphera Pharmaceuticals, outside the submitted work. JF de Groot is a member of the advisory boards of Genentech, Novartis, Celldex, Foundation Medicine, Inc., Novogen, Deciphera and AstraZeneca. This study did not involve use of any grant funds. 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.01.066.

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