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Safety and effectiveness of bevacizumab in the treatment of malignant gliomas

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Summary. *Aim:* The prognosis of malignant glioma is poor owing to the rapid and fatal progression of the disease. After surgery, few therapeutic options are available. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been proposed as an alternative treatment for recurrence. The aim of this study is to evaluate the safety profile of bevacizumab administered as part of the routine care of patients with malignant glioma at a tertiary level hospital. *Patients and methods:* Observational retrospective study. The study sample comprised patients who received at least one dose of bevacizumab for the treatment of malignant glioma from January 2009 to June 2012 at the Hospital Clinic, Barcelona, Spain. Medical records were reviewed, and the primary endpoint was the percentage of patients with adverse reactions. *Results:* The final sample comprised 27 patients, of whom 21 (78%) were diagnosed with glioblastoma. At least one adverse reaction was detected in 20 (74%) patients, and a severe adverse reaction was detected in 8 (30%). Adverse reactions led to hospitalization in 5 (18.5%) cases. Only 3 (11.1%) stopped treatment because of toxicity. Median time to progression was 2.8 months (interquartile range, 3.5; censored data, 14.8%). Median overall survival was 12.2 months (interquartile range, 12.8; censored data, 63.0%). *Conclusions:* The safety profile of bevacizumab in routine clinical practice is similar to that observed in clinical trials. The drug is well tolerated, although it can produce severe adverse reactions. In addition, bevacizumab seems to be less effective in patients with grade III glioma.

Key words: bevacizumab, malignant gliomas, glioblastoma, safety, adverse reactions

«La sicurezza e l'efficacia di bevacizumab nel trattamento dei gliomi maligni»

Riassunto. *Obiettivo:* La prognosi di glioma maligno è scarsa a causa della progressione rapida e fatale della malattia. Dopo l'intervento chirurgico, sono disponibili alcune opzioni terapeutiche. Bevacizumab, un anticorpo monoclonale contro il fattore di crescita endoteliale vascolare, è stato proposto come trattamento alternativo per la recidiva. Lo scopo di questo studio è quello di valutare il profilo di sicurezza di bevacizumab somministrato come parte del trattamento di routine dei pazienti con glioma maligno in un ospedale di terzo livello. *Pazienti e metodi:* studio retrospettivo osservazionale. Il campione di studio è costituito da pazienti che hanno ricevuto almeno una dose di bevacizumab per il trattamento del glioma maligno da gennaio 2009 a giugno 2012 al Hospital Clinic, Barcellona, Spagna. Le cartelle cliniche sono state riviste. L'endpoint primario è stato la percentuale di pazienti con reazioni avverse. *Risultati:* Il campione finale è stato di 27 pazienti, tra cui 21 (78%) sono stati diagnosticati con glioblastoma. Almeno una reazione avversa è stata rilevata in 20 pazienti (74%), mentre 8 (30%) hanno sviluppato una grave reazione avversa. Le reazioni avverse hanno portato al ricovero in 5 casi (18,5%). Solo 3 (11,1%) hanno interrotto il trattamento a causa di effetti tossici. Il tempo mediano di progressione è stato di 2,8 mesi (range interquartile, 3,5; dati censurati, 14,8%). La sopravvivenza

globale mediana è stata di 12,2 mesi (range interquartile, 12,8; dati censurati, 63,0%). *Conclusioni:* Il profilo di sicurezza di bevacizumab nella pratica clinica di routine è simile a quello osservato negli studi clinici. Il farmaco è ben tollerato, anche se può produrre gravi reazioni avverse. Inoltre, bevacizumab sembra essere meno efficace in pazienti con glioma di grado III.

Parole chiave: bevacizumab, gliomi maligni, glioblastoma, sicurezza, reazioni avverse

Introduction

Malignant glioma (high-grade glioma) is a tumour that is typically associated with a rapid and fatal outcome (1). The most common type of malignant glioma, glioblastoma (grade IV), has an overall survival of less than 15 months after diagnosis. Survival is better in patients with grade III glioma, such as anaplastic astrocytoma (about 3 years) and anaplastic oligodendroglioma (about 7 years). Moreover, the response of high-grade glioma to initial treatment tends to be unsatisfactory, and recurrences are common (2).

The current standard of care for malignant glioma is surgery followed by radiotherapy. In the treatment of glioblastoma, radiotherapy is accompanied by concomitant low-dose temozolomide and subsequent adjuvant treatment with the same drug at higher doses (1). In grade III glioma it is not clear whether the addition of concomitant or adjuvant temozolomide can improve prognosis. However, most patients who undergo first-line therapy experience recurrence. The best treatment for recurrent disease has not been established (1, 3).

Bevacizumab (Avastin®) is a humanized monoclonal antibody that binds to vascular endothelial growth factor (VEGF), an important mediator of angiogenesis, and blocks interaction with its receptor. Glioblastoma is associated with a high degree of microvascular proliferation, the extent of which correlates with an increased risk of recurrence. A direct correlation between overexpression of VEGF and poor prognosis has been reported (3).

Bevacizumab is authorized in Spain for the treatment of metastatic breast, colorectal, lung, renal, and gynaecological cancers. Gastrointestinal perforation, haemorrhage, and thromboembolism are the most severe adverse reactions. Fistulas, impaired wound healing, proteinuria, and cardiac congestive failure have also been observed in patients receiving bevacizumab. Other frequent adverse events (≥1/10) include hypertension, fatigue, and diarrhoea (4).

Several studies have been performed in patients with malignant glioma treated with bevacizumab in monotherapy or in combination with other drugs such as irinotecan. Most are phase II studies in the context of recurrence and show promising results. Based on two of these studies (5, 6), in May 2009 the United States Food and Drug Administration (FDA) approved the use of bevacizumab in patients with glioblastoma previously treated with other drugs. The European Medicines Agency has not yet authorized the drug for this indication; hence, in Europe, bevacizumab is restricted to off-label prescriptions.

The aim of this study was to evaluate the safety profile of bevacizumab in daily practice in patients diagnosed with malignant glioma at a tertiary level hospital. We compare our results to those of the two studies that led to FDA approval of bevacizumab for this indication. The secondary objectives were to measure effectiveness and response to treatment.

Material and methods

We performed a retrospective observational study at the Hospital Clinic, a tertiary level hospital in Barcelona, Spain. Patients were selected through the computerized chemotherapy prescription programme. The study sample comprised patients with a diagnosis of high-grade glioma (III or IV) who received at least one dose of bevacizumab between January 2009 and June 2012 (3.5 years). Medical records were consulted

to find information about adverse reactions and survival. Follow-up ended on December 31, 2012.

The primary endpoint was the percentage of patients with adverse reactions of any grade. The severity of adverse reactions was classified according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (CTCAE v.3.0). We only took into account those adverse reactions reported in the two studies (5, 6) that led to FDA approval and included in the European public assessment report (EPAR) product information for bevacizumab. Secondary endpoints were the percentage of patients with severe adverse reactions, delayed doses, visits to the emergency department or hospitalization due to adverse reactions, time to progression, and overall survival.

The statistical analysis was descriptive. Kaplan-Meier plots were constructed to analyse overall survival and time to progression (SPSS® v.11.0). Overall survival was defined as time from initiation of treatment with bevacizumab to the date of death or the last date of follow-up (censored data). Time to progression was calculated from the date of initiation of treatment to disease progression, according to the judgment of the attending clinician, radiologist, or both.

This study was approved by the Clinical Research Ethics Committee of the Hospital Clínic.

Results

Between January 2009 and June 2012, 27 patients received at least one dose of bevacizumab for the treatment of a malignant glioma. Table 1 shows patient demographic and clinical characteristics. Bevacizumab was not prescribed as first-line therapy after surgery in any case.

Adverse reactions (any grade) were recorded in 74.1% (20 patients). This percentage fell to 29.6% (8 patients) if only grade 3-4 adverse reactions were taken into account. A total of 64 adverse reactions (of any

Table 1. Patient demographic and clinical characteristics (n=27).

Patient characteristics	Value
Median age (years)	54 (IQR, 19.5)
Sex (M/F)	14 (51.9%)/13 (48.1%)
Histological type	
Glioblastoma multiforme	21 (77.8%)
Anaplastic astrocytoma	5 (18.5%)
Oligodendroglioma	1 (3.7%)
Previous treatment (prior to off-label bevacizumab)	
Surgery	26 (96.3%)
Complete resection	13 (48.1%)
Partial resection	9 (33.3%)
Not documented	4 (14.8%)
Radiotherapy	25 (92.6%)
First-line therapy with temozolomide	26 (96.3%)
Intravenous carmustine	2 (7.4%)
Clinical trial with bevacizumab/placebo	2 (7.4%)
Clinical trial with cilengitide/placebo	1 (3.7%)
Treatment with off-label bevacizumab	
Combination with irinotecan (100-250 mg/m^2)	6 (22.2%)[a]
Bevacizumab dose: 10 mg/kg every 2 wks	26 (96.3%)[b]
Median number of doses administered per patient	6 (IQR, 6)

IQR, interquartile range. M, male; F, female; wks, weeks

[a] Five patients received bevacizumab + irinotecan only in the first 3-6 doses, while one patient received all doses in combination therapy.

[b] Three patients received 8 mg/kg of bevacizumab in the first 3-5 doses (in combination with irinotecan), increasing to 10 mg/kg after stopping irinotecan, while one patient received all doses at 8 mg/kg (all in combination with irinotecan).

grade) were recorded, including alterations in analytic parameters (2.4 adverse reactions per patient). Table 2 presents detailed information about the type and severity of adverse reactions. The following dose had to be delayed in five cases (18.5%). Six patients (22.2%) visited the emergency department, and five patients (18.5 %) were hospitalized for adverse reactions. Treatment was stopped owing to toxicity only in 3 patients (11.1%): one with rectal bleeding, one with pulmonary embolism, and one with an inexplicable rise in hepatic transaminase levels (not included in table 2 because it was not clearly associated with bevacizumab).

Kaplan-Meier analysis showed that the median time to progression was 2.8 months (interquartile range, 3.5; censored data, 14.8%). Median overall survival was 12.2 months (interquartile range, 12.8; censored data, 63.0%). When grade IV tumours (21 patients) were analysed separately from grade III tumours (6 patients), median time to progression was 4.0 months (interquartile range, 5.1) and 2.5 months (interquartile range, 0.7), respectively (Figure 1 and 2). Median overall survival was 12.2 months (interquartile range not calculable because of the high percentage of censored data) for patients with grade IV tumours and 4.7 months (interquartile range, 3.7) for patients with grade III tumours (Figure 3 and 4).

Table 2. Number of patients with adverse reactions to bevacizumab, classified by grade of severity and type of reaction.

	Grade 1	Grade 2	Grade 3	Grade 4	Total (%[a])
Asthenia	1	1	1		**3 (11)**
Diarrhoea	1	1			**2 (7)**
Constipation			1		**1 (4)**
GI haemorrhage	1 (oral)		1 (rectum)		**2 (7)**
Airway haemorrhage	1 (nasal)				**1 (4)**
CNS haemorrhage				1	**1 (4)**
Hypertension	3		2		**5 (19)**
Infection with normal or grade 1-2 ANC		3 (upper respiratory infections/pneumonia)	(bladder/ 2 colostomy)		**5 (19)**
Infection with unknown ANC		2 (bladder/skin)			**2 (7)**
GI perforation			1 (colon)		**1 (4)**
Acneiform rash		1			**1 (4)**
Thrombosis – Pulmonary embolism				2	**2 (7)**
Thrombosis – DVT			2		**2 (7)**
Subtotal	**7**	**8**	**10**	**3**	**28**
Alterations in analytic parameters					
Hyperglycaemia		1		1	**2 (7)**
Anaemia	2		1		**3 (11)**
Hypokalaemia			1		**1 (4)**
Leucopenia	2				**2 (7)**
Lymphopenia	1	2			**3 (11)**
Neutropenia	4	2			**6 (22)**
Proteinuria	11	1			**12 (44)**
Thrombocytopenia	6		1		**7 (26)**
Subtotal	**26**	**6**	**3**	**1**	**36**
Total	**33**	**14**	**13**	**4**	**64**

ANC, absolute neutrophil count; GI, gastrointestinal; DVT, deep vein thrombosis; CNS, central nervous system.
[a]Percentage of total (n=27).

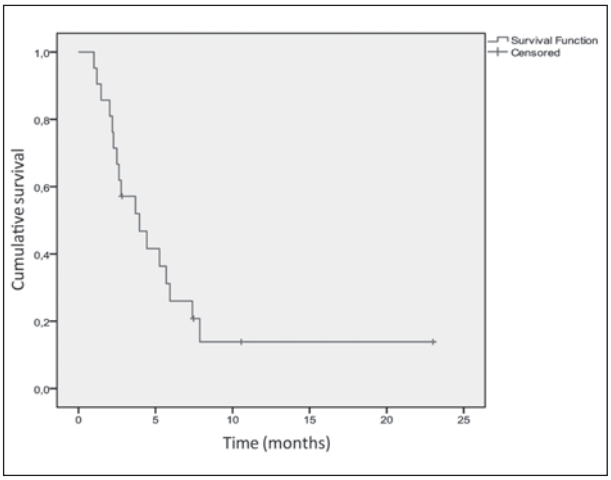

Figure 1. Time to progression of grade IV gliomas, by Kaplan-Meier analysis.

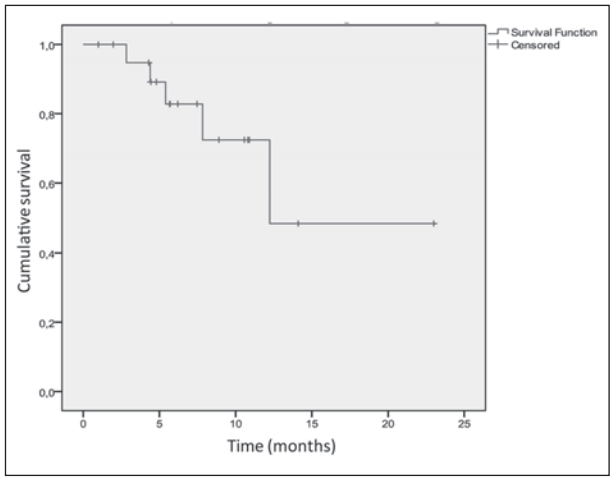

Figure 3. Overall survival of grade IV gliomas, by Kaplan-Meier analysis.

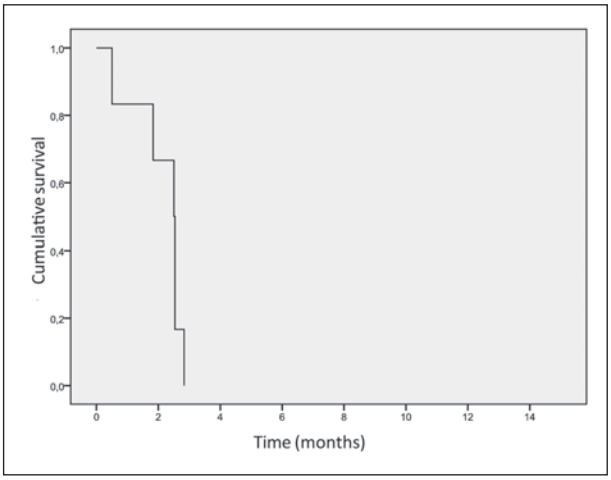

Figure 2. Time to progression of grade III gliomas, by Kaplan-Meier analysis (without censured data).

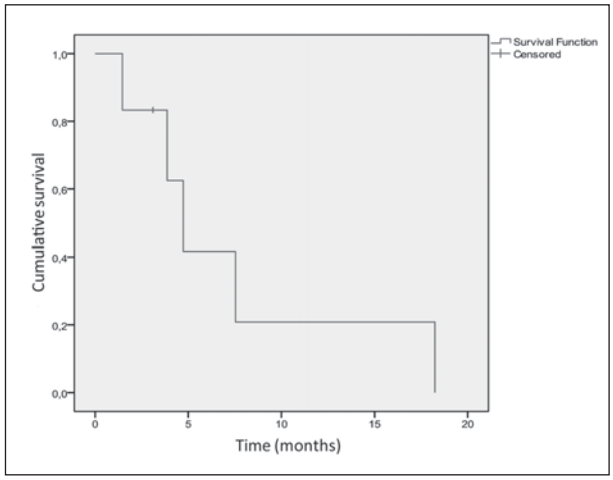

Figure 4. Overall survival of grade III gliomas, by Kaplan-Meier analysis.

Discussion

According to the results of this study, three out of four patients with high-grade glioma treated with bevacizumab have at least one adverse reaction. This proportion is high, even though it decreases if only severe adverse reactions are taken into account. The two studies that led to the FDA authorization of bevacizumab for glioblastoma multiforme reported similar results for toxicity (5-7). Friedman *et al.* reported a higher proportion of adverse reactions in the bevacizumab monotherapy treatment arm (98.8% of patients had adverse reactions [any grade]; 46.4% of patients had severe adverse reactions) and in the bevacizumab plus irinotecan arm (100% and 65.8%, respectively) (6). The increased percentage of adverse reactions is probably due to the prospective design of the study and the higher number of check-ups.

In our study, however, only 11.1% of patients needed to stop therapy owing to toxicity. This finding is similar to those of Kreisl *et al.*, who reported that 12.5% of patients were removed from the study

because of drug-associated toxicity (5). Overall, these studies conclude that bevacizumab is well tolerated in patients with recurrent glioma, particularly when compared with therapeutic alternatives, such as cytotoxic agents.

Regarding survival, Kreisl *et al.* found the median time to progression of grade III gliomas treated with bevacizumab to be 2.93 months and median overall survival 12 months (7). The first figure is similar to that obtained in our study (2.5 months), thus confirming that bevacizumab is less effective in this population. In our study, overall survival turned out to be much lower (4.7 months).

In the study by Kreisl *et al.*, the median time to progression of grade IV gliomas (glioblastoma) was 16 weeks, and median overall survival was 31 weeks; in the study by Friedman *et al.*, the equivalent times were 4.2 months and 9.2 months (5, 6). In our study, the median time to progression was very similar (4.0 months). Clearly, these patients obtained a benefit - albeit moderate - from bevacizumab. Median overall survival was higher in our study (12.2 months); however, these data must be interpreted with caution because of the large amount of censored data in the analysis.

Our study is subject to a series of limitations. First, as it is a retrospective study, the data collected depend on the quality of the data in the medical records. In addition, only already known adverse reactions were taken into account. Determination of the cause of new adverse reactions was not an objective, because it is complex and difficult to achieve with a retrospective design. Initially, the bevacizumab protocol for malignant glioma at our centre consisted of combination with irinotecan, although this regimen was subsequently switched to monotherapy. Thus, some patients received combination therapy during the first doses. A recent meta-analysis confirmed that the addition of irinotecan to bevacizumab provides no benefit in survival but can increase the rate of discontinuation (8).

In a recent retrospective study on bevacizumab in monotherapy or in combination with irinotecan (9), the median progression-free survival was 15.4 months in the combination arm and 5.1 months in the monotherapy arm. The difference between arms is extremely surprising, as it is considerably higher than the difference reported in the pivotal study by Friedman *et al.* and contradicts the results of the meta-analyses (6, 8). These results are also striking because overall survival (11.1 months) was lower than progression-free survival in the bevacizumab plus irinotecan group. Given that progression-free survival cannot be greater than overall survival, the results may be inaccurate, unless, of course, the results apply to two different patient samples.

Conclusions

The safety profile of bevacizumab in the routine treatment of malignant glioma is similar to that found in clinical trials. Bevacizumab can induce potentially life-threatening severe adverse reactions; however, it is generally better tolerated than other therapeutic options. In addition, bevacizumab seems to be less effective in patients with grade III glioma and is more beneficial in patients with grade IV glioma. Finally, the lack of robust scientific evidence highlights the need for randomized trials to elucidate the role of bevacizumab in the treatment of high-grade recurrent glioma.

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