Bevacizumab plus irinotecan in recurrent malignant glioma shows high overall survival in a multicenter retrospective pooled series of the Spanish Neuro-Oncology Research Group (GEINO)

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There is no 'standard of care' for recurrent malignant glioma (MG). Our aim is to confirm the efficacy and safety of bevacizumab 10 mg/kg plus irinotecan 125 mg/m^2 (or 340 mg/m^2 if enzyme-inducing antiepileptic drugs) every 2 weeks for a maximum of 1 year in a retrospective pooled series of patients with recurrent MG. The inclusion criteria were as follows: age 18 years and above, histology of MG, progression after radiation and temozolomide, Karnofsky performance status (KPS) of at least 60, and signed informed consent for bevacizumab compassionate use. Response was assessed by MRI using the Macdonald criteria and evaluation of the FLAIR sequence every 8 weeks. A total of 130 patients were enrolled; 72% had glioblastoma (GBM). The median age of the patients was 53 years (20–78); the median KPS was 80%; the median number of prior chemotherapy lines was 2 (1–5); the median interval between the diagnosis of MG and inclusion was 14.6 months (2–166); and the median number of bevacizumab infusions was 8 (1–39). The median follow-up duration was 7.2 months (1–47). The median overall survival (OS) was 8.8 months for GBM and 11.2 months for anaplastic glioma (AG). The median progression-free survival was 5.1 months for GBM and 4.6 months for AG. The response rate was 56% for GBM and 68% for AG. Neurological and KPS improvements were observed in 49 and 45% of patients. Only KPS less than 80% was associated with a worse significant response rate (odds ratio, 0.57; 95% confidence interval, 0.22–0.96). The most frequent grades 3–4 toxicities were asthenia (7%), diarrhea (6%), and thromboembolic events (5%). There were five toxic deaths (4%). Bevacizumab plus irinotecan in recurrent MG improves responses, progression-free survival, and OS compared with historical data. KPS of at least 80% was a predictive factor for response and OS. *Anti-Cancer Drugs* 23:659–665 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Malignant glioma (MG) is the most common primary brain tumor in adults. Standard treatment consists of maximal surgical resection, followed by radiotherapy plus concomitant and adjuvant temozolomide [1]. However, the median overall survival (OS) is only 12–15 months for patients with glioblastoma (GBM) and 2–5 years for patients with anaplastic glioma (AG) [2]. When relapse or progression occurs after radiotherapy and temozolomide, there is no standard treatment and OS ranges from 3 to 9 months [3–5]. OS is undoubtedly the best parameter to assess treatment efficacy, although in recent years, it was thought that the 6-month progression-free survival (PFS-6) was the best surrogate endpoint of OS for phase II trials. In patients with MG in the first relapse, the radiological response rate (RR) is usually less than 4–16% [3–6] and PFS-6 is usually less than 9–16%.

It is known that GBM is one of the most vascularized human tumors [7] and that GBM cells produce a wide

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variety of proangiogenic factors, including vascular endothelial growth factor (VEGF). Furthermore, VEGF increases vascular permeability and produces peritumoral edema, which is one of the causes of serious morbidity in these patients. Bevacizumab, a humanized monoclonal antibody against VEGF, was granted accelerated approval by the United States Food and Drug Administration (FDA) as a single agent for the treatment of progressive GBM following radiotherapy and temozolomide in May 2009 [8]. This decision was made on the basis of the results published on 215 patients enrolled in two phase II trials [9,10]. However, the European Medicines Agency (EMA), after analyzing the same trials, rejected this indication in November 2009 due to the lack of scientific evidence on the benefits of this treatment. This has given rise to a great debate [11,12] and to bevacizumab being used as a standard treatment for recurrent MG in the USA but not in Europe, where in some countries, it is not used in this indication and in others it is administered for compassionate use as a single agent or combined with irinotecan (CPT-11). Irinotecan is an inhibitor of topoisomerase I, a critical enzyme needed for DNA transcription. Irinotecan crosses the blood–brain barrier, and in monotherapy, has demonstrated efficacy (RR between 6 and 15%) and represents a treatment option in tumors resistant to temozolomide because their mechanisms of action and resistance do not overlap [13–15]. Various phase II studies with bevacizumab plus irinotecan have been published showing its efficacy in terms of RR and prolongation of PFS-6 and OS in comparison with historic controls [16].

On the basis of all these previous considerations and given that the efficacy of treatment with bevacizumab in combination with irinotecan is still not clearly established, we carried out a multicenter retrospective pooled analysis of two series of patients: after the first one (24 patients), eligibility criteria and protocol guidelines were implemented for the second one (106 patients). All patients had MG in progression after radiotherapy and temozolomide. All patients were treated with bevacizumab plus irinotecan as compassionate use in 13 hospitals belonging to the Spanish Neuro-Oncology Research Group (GEINO). In this article, we present the final data on the efficacy and safety of this series of 130 nonselected MG patients who were treated off study.

Materials and methods

This study was conducted in accordance with the Helsinki Declaration of the World Medical Association and all of its amendments, and IRBs of the participating institutions and Spanish regulations. All patients gave their written informed consent for bevacizumab compassionate use, a requirement necessary when a patient is treated with a drug that is still under investigation or with a marketed drug used in conditions other than those authorized. Physicians should request authorization for compassionate use treatment from the hospital pharmacy department and the hospital management, and after approval in the hospital, authorization for compassionate use treatment should be requested from the Spanish Agency for Medicines and Health Products [Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)].

Eligibility criteria

Data from 13 Spanish hospitals were collected. For entry into the study, all patients were required to fulfill the following eligibility criteria: age 18 years and above; histologically confirmed diagnosis of recurrent MG (including GBM, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma); have evidence of recurrent or progressive MG after radiotherapy and temozolomide on MRI obtained 4 weeks before study initiation; Karnofsky performance status (KPS) of at least 60; and life expectancy of more than 8 weeks. All patients were informed that bevacizumab had not been approved by EMA in this indication and that the study was investigational, and were required to provide a signed informed consent before starting treatment. Additional enrollment criteria were as follows: no evidence of intracranial, extracranial hemorrhage, or hemorrhagic diathesis; no evidence of uncontrolled hypertension; no evidence of clinically significant cardiovascular disease; leukocytes $\geq 3000/mm^3$; neutrophils $\geq 1500/mm^3$; platelets $\geq 100\,000/mm^3$; AST and bilirubin <2.5 times the upper limit of normal; creatinine <1.5 mg/dl; proteinuria $<1+$; PT/INR/PTT <1.2 times the upper limit of normal; and no prior bevacizumab treatment.

Treatment schedule

Bevacizumab (Avastin; F. Hoffman-La Roche Ltd, Basel, Switzerland) was administered at a dose of 10 mg/kg as an intravenous infusion for 30–90 min combined with irinotecan at a dose of 125 mg/m^2 intravenously every 2 weeks if the patient was not receiving enzyme-inducing antiepileptic drugs (EIAEDs) or irinotecan at a dose of 340 mg/m^2 intravenously if receiving EIAEDs. Bevacizumab and irinotecan were supplied by the Spanish public health program for compassionate use. Patients received treatment until evidence of progression, unacceptable toxicity, or a maximum of 1 year of treatment.

Evaluation of response

Response was determined by MRI after every 8-week treatment course (gadolinium-enhanced T1, T2, and FLAIR sequences) using the Macdonald criteria plus FLAIR imaging assessment. A complete response was defined as the disappearance of all enhancing tumors from baseline on two consecutive MRI scans, separated by at least 1 month, without corticosteroids and with an improvement or stabilization of neurological clinical

symptoms. A partial response was defined as a greater than 50% reduction in the product of the diameters of enhancing tumors from baseline with stable or improving T2 and FLAIR, separated by at least 1 month, without corticosteroids and with an improvement or stabilization in neurological clinical symptoms. Progressive disease was defined as more than a 25% increase in the sum of the products of enhancing tumors of all measurable lesions on MRI, clear worsening of any evaluable lesion, appearance of new lesions, clear worsening of clinical symptoms or tumor FLAIR imaging outside the field of radiotherapy, or increased corticosteroid use. Stable disease was applied to the rest of the situations. MRIs were evaluated by the local radiologist and investigators. No central review of MRI was performed.

Study objectives and statistical analysis

The primary objective of the study was to assess efficacy in terms of OS. The secondary objectives were RR, median PFS, PFS-6, percentage of patients with clinical and KPS improvement, toxicity profile, and predictive factors for response. OS was measured from the first day of treatment to the date of death from any cause or the date of the last follow-up. PFS was measured from the first day of treatment to the date of progression on MRI or death from any cause or the date of the last follow-up.

The Kaplan–Meier and Cox models were used for the calculation of PFS and OS, estimated with 95% confidence intervals (CI).

Results

Patient characteristics

Between July 2006 and November 2009, a total of 130 patients, median age 53 years (20–78), were enrolled in the study. The median KPS was 80%. At enrollment, 72.5% of the patients were taking dexamethasone, median 6 mg/day (1–18); 64% were taking any antiepileptic treatment; and 9% were receiving EIAEDs.

The initial histological diagnosis was GBM in the majority of patients. The median number of prior chemotherapy lines was 2 (1–5); 52.5% of patients had received two or more lines. All patients had received prior radiotherapy and temozolomide. The initial treatment was radiotherapy with concurrent temozolomide according to the Stupp regimen in 92 (71%) of patients; the others received temozolomide before radiotherapy [nine patients (7%)] or at relapse [29 patients (22%)]. Patients treated according to the Stupp regimen had received a median of five cycles (0–12) of adjuvant temozolomide, with three or more cycles in 75% of cases. Only 14 cases received two or less cycles of adjuvant temozolomide and the minimum time between the last day of radiation and inclusion was 8 weeks. The clinical characteristics, tumor type, and prior treatments are shown in more detail in Table 1.

Table 1 Baseline characteristics of the patients

Characteristics	Value
Age, median (range) (years)	53 (20–78)
KPS, *n* (%)	
60	27 (21)
70–80	69 (53)
90–100	34 (26)
Radicality of surgical resection, *n* (%)	
Complete	59 (45.4)
Partial	47 (36.1)
Biopsy	24 (18.5)
Histology, *n* (%)	
Glioblastoma	92 (72)
Grade 3 astrocytoma	27 (21)
Grade 3 oligoastrocytoma	9 (7)
Initial treatment, *n* (%)	
Stupp regimen	92 (71)
Radiotherapy	15 (11.5)
Radiotherapy + other chemotherapy	10 (7.5)
Neoadjuvant chemotherapy	9 (7)
Other	4 (3)
Number of cycles of adjuvant TMZ, median (range)	5 (0–12)
Prior chemotherapy lines, *n* (%)	
One line	62 (47.5)
Two lines	55 (42.5)
Three to five lines	13 (10)
Median interval from the first diagnosis to bevacizumab, months (range)	14.6 (2–166)
DXM at baseline	
No DXM treatment, *n* (%)	36 (27.5)
DXM treatment, *n* (%)	94 (72.5)
Median dose of DXM, mg (range)	6 (1–18)
Antiepileptic drugs, *n* (%)	
No	47 (36)
EIAEDs	12 (9)
Non-EIAEDs	71 (55)

DXM, dexamethasone; EIAEDs, enzyme-inducing antiepileptic drugs; KPS, Karnofsky performance status; TMZ, temozolomide.

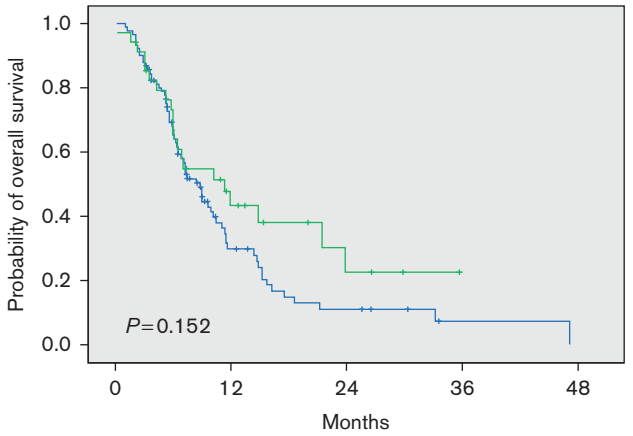
Efficacy

With a median follow-up of 7.2 months (1–47) at analysis, 74% of patients had progressed and 71% had died. The median OS was 9 months for all series (95% CI, 6.7–11.2), 8.8 months for GBM (95% CI, 6.9–10.6), and 11.2 months for AG (95% CI, 5.1–17.3) (Fig. 1). The 6-month OS was 67% for all patients (95% CI, 58.3–75), 66% for GBM (95% CI, 55.5–76), and 68% for AG (95% CI, 51.9–83). The median PFS was 5.1 months for all series (95% CI, 4.4–5.9), 5.1 months for GBM (95% CI, 4.4–5.8), and 4.6 for AG (95% CI, 3.1–6.1) (Fig. 2). PFS-6 was 42% for GBM (95% CI, 32–52) and 43% for AG (95% CI, 26.5–59). The median time to progression for all series was 5.3 months (95% CI, 4–6.6). An improvement in the neurological state and KPS was shown in 49 and 45% of symptomatic patients, respectively.

An overall response was observed in 70 patients (59%; 95% CI, 50.5–68.2), which was complete in nine (7.5%) (Table 2). By histology, the response was 56% (95% CI, 44.7–67) for GBM and 68% (95% CI, 49.5–82.6) for AG.

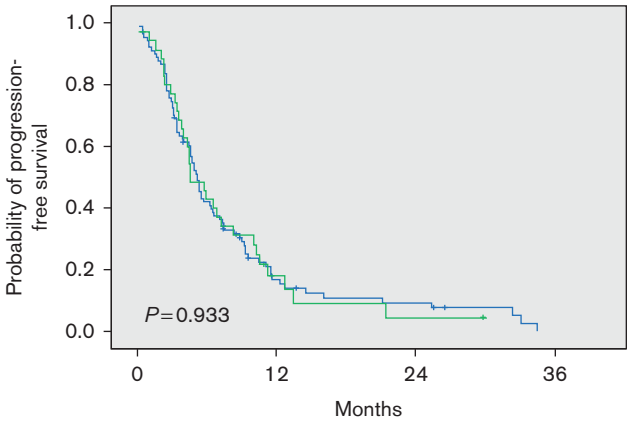
In the univariate analysis, only KPS less than 80% was a statistically significant predictive factor for worse response (odds ratio, 0.57; 95% CI, 0.22–0.96; $P = 0.038$) (Table 3). KPS of at least 80% (hazard ratio, 1.79; 95% CI,

Fig. 1



Overall survival by histology. GBM, blue line; no GBM, green line. Graphic by Kaplan–Meier. GBM, glioblastoma.

Fig. 2



Progression-free survival by histology. GBM, blue line; no GBM, green line. Graphic by Kaplan–Meier. GBM, glioblastoma.

Table 2 Clinical activity of the treatment schedule

	n (%)		
Response	All	GBM	AG
Complete	9 (7.5)	5 (6)	4 (12)
Partial	61 (52)	41 (50)	19 (56)
Stable disease	22 (18.5)	16 (20)	5 (15)
Progression	26 (22)	20 (24)	6 (18)
Not evaluated	12	10	2

AG, anaplastic glioma; GBM, glioblastoma.

1.17–2.75; $P = 0.008$) and not taking dexamethasone at inclusion were statistically significant predictive factors for better OS (hazard ratio, 1.94; 95% CI, 1.15–3.26; $P = 0.013$) (Table 4). No significant differences were found for age (> 50 years vs. ≤ 50 years), number of prior chemotherapy lines (1 or > 1), or histology (GBM vs. non-GBM) in RR, OS, or PFS.

Table 3 Univariate analysis of response factors

Variables	*n*	Response (%)	*P*-value	OR	95% CI
Diagnosis					
GBM	87	53	0.14	0.537	0.23–1.23
No GBM	34	68		1	
Age (years)					
≤ 50	54	52	0.229	0.635	0.3–1.33
>50	62	63		1	
Number of prior lines					
1	57	65	0.115	1.790	0.87–3.72
>1	65	51		1	
KPS (%)					
<80	53	47	0.038	0.57	0.22–0.96
≥ 80	65	66		1	
DXM					
Yes	87	54	0.315	0.664	0.3–1.48
No	36	64		1	

CI, confidence interval; DXM, dexamethasone; GBM, glioblastoma; KPS, Karnofsky performance status; OR, odds ratio.

Table 4 Univariate analysis of overall survival

Variables	*n*	*P*-value	HR	95% CI
Diagnosis				
GBM	90	0.155	1	
No GBM	36		1.43	0.87–2.34
Age(years)				
≤ 50	57	0.459	1	
>50	66		0.85	0.55–1.31
Number of prior lines				
1	60	0.705	1	
>1	68		0.92	0.61–1.40
KPS (%)				
<80	55	0.008	1	
≥ 80	69		1.79	1.17–2.75
DXM				
Yes	94	0.013	1	
No	34		1.94	1.15–3.26

CI, confidence interval; DXM, dexamethasone; GBM, glioblastoma; HR, hazard ratio; KPS, Karnofsky performance status.

Safety

A total of 1275 bevacizumab infusions were administered, with a median number of bevacizumab infusions per patient of 8 (1–39). There was a delay in treatment administration in 34% of patients, in most cases for nonhematologic toxicity (43.5%). Only 25% of patients required a dose reduction of bevacizumab, 73% for nonhematologic toxicity. Fifty-four percent of patients required dose reductions of irinotecan and 5.5% required withdrawal of irinotecan. The most common grades 3–4 toxicities were asthenia in nine patients (7%), followed by diarrhea in eight patients (6%), pulmonary thromboembolism in four patients (3%), deep vein thrombosis in three (2%) (all thromboembolic events were resolved with heparin and discontinuation of treatment), neutropenia in five patients (4%), cognitive deterioration in five patients (4%), mucositis in three patients (2%), thrombopenia in three patients (2%), hemorrhage out of the

central nervous system in three patients (2%), hypertension in two patients (1.5%), tumor hemorrhage in one patient (1%), and skin toxicity in one patient (1%). Five patients died as a result of possible toxicity (4%): two patients from leukoencephalomalacia without visible tumor, one from intestinal perforation, one from tumor hemorrhage, and one from pneumonia without neutropenia.

Discussion

The therapeutic options in progressive MG following treatment with radiotherapy and temozolomide are scarce. Surgical salvage is rarely possible because of the size and location of the relapse. Furthermore, no trial has so far shown that it had a significant impact on survival, except for the study of Brem *et al.* [17], in which 222 patients, following surgical salvage, were randomly assigned to receive a biodegradable polymer impregnated with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) at the tumor site versus control. The median OS of the patients who were implanted with the BCNU polymer was 7.4 months compared with 5.5 months for patients treated with surgery alone. The temozolomide treatment schedule of 150–200 mg/m^2/day for 5 days repeated every 28 days in recurrent MG showed a PFS-6 of 21% for GBM and 35% for AG in two pivotal phase II studies. These results were better compared with the historical controls, but for GBM, the RR was only 5% and the median OS was 2.9 months; for AG, the median OS was 5.4 months [5,18]. Temozolomide used in extended schedules of 100 mg/m^2/day for 7 days every 14 days [19] or 75–85 mg/m^2/day for 21 days every 28 days [20,21] or continuous 50 mg/m^2/day [22] yielded an RR ranging from 5 to 24%, a PFS-6 of 17–43% in patients, and a median OS between 5.9 and 6.1 months for GBM [20]. Nitrosoureas, carmustine (BCNU), and lomustine (CCNU) have shown an RR of only 4% in phase III trials [3].

Several phase II studies with bevacizumab have demonstrated its efficacy assessed in terms of RR, PFS, and OS. No trials have directly compared temozolomide or nitrosoureas treatment with bevacizumab in recurrent disease, but on the basis of historical controls, bevacizumab seems to be superior. The first phase II study, using bevacizumab and irinotecan in recurrent MG, showed an RR of 63% in 32 patients (61% for GBM and 66% for AG) [16]. Subsequent analysis reported an RR between 34 [23] and 57% [24], and PFS-6 of 38%, much higher than the 21% observed with temozolomide [5]. In a phase II randomized, noncomparative trial carried out in a series of 167 patients with a first or a second relapse of GBM who were assigned to receive 10 mg/kg of bevacizumab every 2 weeks alone or in combination with irinotecan [9], patients treated with bevacizumab monotherapy had an RR of 28% and PFS-6 of 43% in patients, whereas those treated with the combination therapy had an RR of 38% and PFS-6 of 50%. The median OS was 9.2 months in the group treated with bevacizumab alone and 8.7 months in the group treated with the combination. An update of this series has recently been reported with a median OS of 8.9 months (95% CI, 7.9–11.9) with the combination of bevacizumab plus irinotecan and 9.3 months (95% CI, 8.2–11.8) with bevacizumab alone, followed by the combination at progression [25]. Similar to our series, the corticosteroid dose could be reduced by at least 50% in most patients. Treatment was well tolerated, with three intracranial hemorrhages in both groups (5%). When the data were reviewed by two independent reviewers for the FDA analysis, they confirmed an RR of 26% in patients who received bevacizumab monotherapy, a median duration of response of 4.2 months, and PFS-6 of 36% [26]. The second trial reviewed by the FDA [10] assessed 56 patients treated with bevacizumab monotherapy and confirmed an RR of 20% with a median duration of response of 4 months. Xu *et al.* [27] have recently published a review of 282 patients with recurrent MG treated with bevacizumab plus irinotecan in eleven phase II trials. The mean reported median OS was 10.9 months and the authors claim that these results are statistically superior compared with other treatment protocols in this condition ($P = 0.024$).

The eligibility criteria of prospective trials usually select patients with the highest probability of survival and the least risk of toxicity. From this perspective, our study shows the results of a large cohort of consecutive patients selected only for having progression after radiotherapy and temozolomide treatment, and for having been treated with the combination of bevacizumab plus irinotecan. Our series includes some patients who would not have been able to enter in the previously mentioned prospective trials for failing to fulfill commonly used inclusion criteria such as KPS less than 70, age greater than 70 years, or multiple previous lines of chemotherapy. In fact, 79% of patients had received two or more previous chemotherapy lines, had associated diseases, etc. Despite this, we obtained a RR of 59% for the total population and a RR of 56%, a median PFS of 5.1 months, a PFS-6 of 42%, and, particularly, a median OS of 8.8 months for GBM. These results are similar to those obtained in patients selected for clinical trials (see Table 5). The retrospective series of Zuniga *et al.* [28] is the best OS reporting to date (11.5 months), with an RR of 71% and a median PFS of 7.6 months, but it should be taken into account that it is a small series of only 37 patients with GBM treated at a single institution.

It can be argued that the use of both the RR and the PFS as efficacy endpoints in MG treated with antiangiogenic drugs is currently being questioned because bevacizumab neutralizes VEGF and thus stabilizes the brain–blood barrier, causing a decrease in extravasation of fluid into brain parenchyma. This results in reduced brain edema and gadolinium enhancement on MRI. However, whether because of this antiedema effect or because it also has an

Table 5 Efficacy results of bevacizumab plus irinotecan in glioblastoma compared with other trials

Variables	Friedman *et al.* [9]	Vrendenburgh *et al.* [16]	Zuniga *et al.* [28]	Poulsen *et al.* [29]	Gil *et al.* (this study)
N	82	23	37	52	92
OS (95% CI) (months)	8.7 (7.8–10.9)	9.6 (8.1–13.9)	11.5 (8.3–15.6)	6.9 (3.9–9.1)	8.8 (7–10.6)
6-month OS (95% CI) (%)	NR	72 (58–89)	78 (60.8–88.4)	NR	66 (55.5–76)
PFS (95% CI) (months)	5.6 (4.4–6.2)	5.5 (4.1–8.3)	7.6 (4.8–10.5)	5 (4–7)	5.1 (4.4–5.9)
6-month PFS (95% CI) (%)	50 (36.8–63.9)	30 (16–57)	64 (45.7–77.1)	40 (16–67)	42 (32–52)
RR (95% CI) (%)	38 (26.5–50.8)	61 (39–74)	67.5 (NR)	30 (14–57)	56 (44.7–67)
CR (%)	2	3	5	15	6
PR (%)	35	59	62	15	50

CI, confidence interval; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.

antitumor effect, the OS rates are superior to those published before the advent of bevacizumab as a treatment for recurrent MG. Only the lack of data from a phase III trial of bevacizumab with an untreated control arm justifies that it has not been unanimously approved by the regulatory agencies. In our opinion, the OS of our large multicenter patient series confirms the improved results offered by the combination of bevacizumab plus irinotecan over the treatments used to date and currently approved by the EMA in recurrent MG after radiotherapy and temozolomide. In contrast is the phenomenon of pseudoprogression; however, the fact that 52.5% of our patients had received two or more previous lines of chemotherapy, that 75% of cases treated as Stupp regimen had received three or more cycles of adjuvant temozolomide and that only 14 cases received two or less cycles of adjuvant temozolomide minimizes the risk of having included patients with pseudoprogressive disease.

A caveat of this study is that it does not resolve the question about the value of irinotecan in this disease; thus, the BRAIN study showed an OS that was similar between bevacizumab monotherapy and in combination with irinotecan, despite a better RR and time to progression in favor of the combination [9,25].

When we analyzed the subgroup of patients who could benefit most from this treatment, effective but with a high economic cost, we found no statistical differences in age, number of previous chemotherapy lines, or histology (grades 3 vs. 4) in the univariate analysis. In our series, an initial histology of grade 3 did not seem to be predictive of statistically better survival than GBM once patients had progressed to radiotherapy and temozolomide. However, the fact that no differences in outcome were observed between these entities could simply be due to lack of power or because the mechanism of the agent (antiedema) is present irrespective of histology. In contrast, KPS of at least 80 and not taking dexamethasone at inclusion were statistically significant predictive factors of better OS (see Table 4). Only KPS of at least 80 was a statistically significant predictive factor for better response (see Table 3). In terms of this point, there are few data in previously published studies. In the FDA analysis of the study by Friedman *et al.* [9], it appeared that patients aged 65 years and above showed fewer responses than those less than 65 years, and those who were taking corticosteroids at inclusion had more responses than those who were not, whereas no difference was seen in KPS or sex. Although the sample is too small to allow any statistical analysis, the results of Friedman and colleagues on this point paradoxically differ from the results of our study, in which patients with good KPS and not taking corticosteroids obtained the maximum benefit in OS. It should be noted that 49% of our patients showed improvements in their neurological state and 45% of patients showed a better KPS.

In terms of the toxicity profile, the treatment is generally well tolerated if patients are adequately selected, but one must be alert to potentially serious complications such as thromboembolic events and hemorrhages. The study by Friedman *et al.* [9] reported a 26% rate of serious adverse events, of which the most common grades 3–4 toxicities were hemorrhage in eight patients (5%) and thromboembolic events (7%), and two deaths possibly related to the treatment were reported. In our series, we observed five deaths (4%) possibly related to toxicity: two because of neurological deterioration without radiological evidence of progression, one tumor hemorrhage, one intestinal perforation, and one pneumonia without neutropenia. It is possible that the two cases of neurological deterioration without clear radiological progression were the result of toxicity accumulated from the different treatments used over time (radiotherapy, various chemotherapy lines, and finally bevacizumab), but it is also possible that they were clinical progressions undetected on conventional MRI. We also observed a 5% rate of thromboembolic events, in the form of four cases of pulmonary thromboembolism and three cases of deep vein thrombosis. All cases were resolved with heparin treatment and discontinuation of treatment. In a series of Zuniga *et al.* [28], 12% of patients discontinued treatment due to a treatment-emergent adverse event; in our series, it was 11% of patients. Despite retrospective evaluations typically providing a lower estimate of associated mild toxicities, this did not occur with serious adverse events in our study because of a predefined data collection sheet.

In conclusion, although the true efficacy of the combination bevacizumab plus irinotecan will not be clearly established until a phase III trial is conducted, the data from our retrospective analysis of a large consecutive series of patients not selected by the restrictive criteria usually applied in prospective trials confirm the benefit in terms of OS and the clinical improvement of these patients compared with international historical series.

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Conflicts of interest

Consultant or advisory role: Miguel J. Gil, Carme Balañá, and Pedro Pérez-Segura (Roche S.A.).

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