Prelaj et al. Translational Medicine Communications (2018) 3:6
https://doi.org/10.1186/s41231-018-0023-2

Translational Medicine Communications

RESEARCH Open Access

Retrospective analysis to evaluate the efficacy and the safety of Bevacizumab in the treatment of recurrent malignant gliomas

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Abstract

Background: There is no consensus therapy recommended for recurrent malignant gliomas (MGs). In 2009, Bevacizumab (BEV) was approved by the FDA as single-agent for recurrent glioblastoma (GBM). The aim of this retrospective study was to evaluate the efficacy and the safety of BEV alone or in combination with Fotemustine (FTM) in recurrent MGs. This represents an interim analysis of a larger study on BEV in MGs patients.

Methods: We analyzed 17 recurrent MGs patients, 12 GBM (70.6%) and 5 anaplastic gliomas (29.4%), underwent first-line therapy with Stupp regimen. BEV was administered as off-label therapy, at a dose of 10 mg/kg every 14 days, in 13 patients as third-line therapy and in 4 patients as second-line therapy associated with FTM. The assessment of MGMT methylation and IDH1 mutation was conducted.

Results: One complete response (5.9%), 7 partial responses (41.2%), 3 stable diseases (17.6%) and 6 progression diseases (35.3%) were assessed using RANO criteria. Median PFS (mPFS) and OS (mOS) were 5 and 8.3 months respectively, with a 6 months-PFS of 41.2%. Methylated patients and wild-type IDH1 patients showed longer mPFS and mOS without statistical significance. Six patients (35.3%) experienced long response with high number of cycles (11-40), long PFS (11-40 months) and OS (12-42 months). BEV was well-tolerated with grade 1-2 proteinuria and hypertension in 53% and 47.1% of patients respectively. Only one patient developed grade 3 proteinuria after 30 cycles and another one developed pulmonary embolism. No other grade 3-4 toxicities were observed.

Conclusions: This retrospective study showed the efficacy and the safety of BEV alone or in association with FTM in the treatment of MGs.
The protocol (No: Beva-Glio/Sep 2016).

Keywords: Bevacizumab, Recurrent glioblastoma, Recurrent malignant glioma, Fotemustine, Retrospective study

Background

Malignant gliomas (MGs) are the most common primary malignant brain tumors in adults and include anaplastic gliomas (AG) and glioblastoma multiforme (GBM), which account for 6% and 54% of all gliomas respectively. GBM is the most common MG characterised by a high recurrence and mortality rate and low response rate to treatment [1]. The standard first-line treatment of GBM includes maximal safe surgical resection followed by radiotherapy plus concomitant and adjuvant temozolomide (TMZ), as defined in the EORTC phase III trial [2, 3]. However, despite the optimal standard therapy, recurrence rates remain high (~ 90%) with median survival ranges from 15 to 18 months for GBM [4] and from 2 to 5 years for AG [5]. Nowadays, there is no consensus therapy recommended for recurrent MGs and different treatment options are under investigation, such as second-line

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chemotherapy, immunotherapy, target therapy, radiotherapy and additional surgery. MGs are characterised by an intense vascular proliferation with an elevated expression of vascular endothelial growth factor (VEGF): for these biological characteristics MGs are, therefore, suitable targets of anti-angiogenic therapies [6]. Vessel density degree and VEGF level expression have been shown to directly correlate with the biologic aggressiveness of MGs and a worse prognosis [7–10].

It has been demonstrated that VEGF inhibition leads to a decreased growth of glioma cells and to reduce both peritumoral edema and, therefore, the need for corticosteroid therapy [9, 11]. This decrease of steroids use for prolonged periods reduce long-term adverse effects improving quality of life of patients.

In 2009, Bevacizumab (BEV), a humanized monoclonal antibody against VEGF-A, was approved by the United States Food and Drug Administration (FDA) [12] as a single-agent for the treatment of recurrent GBM. The approval was based on two phase 2 studies of BEV both alone and in combination with irinotecan (IRI) which demonstrated improvements in response rate (RR) and 6-month PFS (PFS-6) [8, 13]. In Europe, BEV was not approved by the European Medical Agency (EMA) due to the uncertain impact on overall survival (OS) and the lack of non-BEV control arm. Many other prospective or retrospective studies evaluated the efficacy of BEV as single-agent both in recurrent GBM and AG [13–17], or in combination with IRI [18], TMZ, carmustine, lomustine, carboplatin, etoposide and target therapies such as cetuximab, erlotinib, sorafenib [19]. In these clinical trials, single-agent BEV reached PFS-6 rates from 18 to 42. 6%, a median PFS from 2.8 to 4.2 months and a median OS from 6.5 to 10.5 months [19]. There is little data available on the combination of BEV with Fotemustine (FTM), the nitrosourea mostly used for recurrent MGs in Europe [20–23]. The combination of BEV plus FTM has been suggested as active and safe in untreated metastatic melanoma patients [24]. The aim of this retrospective study was to evaluate the efficacy and the safety of BEV alone or in combination with FTM in the treatment of recurrent MGs patients.

Methods

Study population

This retrospective study was approved by the ethics committee of S.M.Goretti Hospital of Latina, Sapienza University of Rome. From August 2011 through July 2016 we performed a retrospective analysis of recurrent MGs patients treated with BEV (off-label use) at Policlinico Umberto I of Rome and S.M.Goretti Hospital of Latina, both Sapienza University of Rome. This represents an interim analysis of a larger study on BEV in MGs patients.

BEV was administered as third-line therapy after second-line therapy with FTM or as second-line therapy in combination with FTM. All patients underwent first-line therapy with maximum safe resection and radiotherapy plus concomitant/adjuvant TMZ as Stupp schedule [3]. We excluded those patients treated with other adjuvant TMZ therapy, second and third-line therapies. Stupp schedule consists of radiotherapy (60 Gy/30 fractions) plus concomitant daily TMZ (75 mg/mq/die), followed by 6 cycles of adjuvant TMZ (50-200 mg/mq/die for 5 days every 28 days) for maintenance [2, 3]. FTM treatment, according to the Addeo schedule [25], consists of an induction phase dose of 80 mg/mq every 2 weeks for 5 consecutive weeks followed by a 4-week rest period and a maintenance phase dose of 80 mg/mq every 4 weeks. For all patients, the initial diagnosis was established by magnetic resonance imaging (MRI) and histologically using WHO criteria [26]. The progression after first-line and second-line therapy was assessed by MRI and histological examination when a surgery at recurrence was performed.

Clinical data included patients characteristics (gender, age and Karnofsky-Performance-Status (KPS) at recurrence pre-BEV), tumor characteristics (laterality and lobe, histotype, molecular markers at diagnosis) and treatment information (first-line and second-line therapy, surgery at recurrence, BEV as monotherapy or in combination, median cycles of BEV, corticosteroids use).

Treatment plan

All patients included in the analysis underwent treatment with BEV (off-label use) administered intravenously at a dose of 10 mg/kg every 14 days until disease progression or unacceptable toxicity. In patients having undergone re-resection, BEV was commenced 4-6 weeks after surgery and establishment of normal craniotomy wound healing. Blood pressure and proteinuria were monitored prior each administration of BEV.

Response and toxicity evaluation

All patients were followed clinically by a multidisciplinary team and radiologically by 3 Tesla MRI scans (contrast-enhanced T1-weighted, T2/FLAIR-weighted, perfusion-weighted and diffusion-weighted scans and MR spectroscopy). A baseline MRI scan, acquired prior to initiation of BEV treatment, was performed. The first MRI evaluation was made after 2 cycles of BEV or after the induction phase of FTM and then every two cycles of BEV or FTM in the maintenance phase, or whenever progression disease was clinically suspected.

Evaluation response was assessed according to RANO criteria [27] as complete (CR) and partial (PR) response, stable (SD) and progression (PD) disease. Overall

response rate (ORR) was defined as the sum of CR and PR and disease control (DC) was defined as the sum of CR, PR and SD. Diagnosis of recurrence was determined by MRI in all patients and by histological examination when a second surgical resection was made. Subgroup analysis according to the response to BEV in correlation to patients characteristics and biomarkers was performed using χ^2 test. Responder patients were defined as patients with SD, PR and CR.

We also evaluate the clinical benefit measuring change in corticosteroid use, functional status and neurologic symptoms. All adverse events, as worsening of previous symptoms or development of new symptoms during treatment, were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, version 4.03 [28]. Toxicity assessment was performed at each cycle or, if clinically indicated, at weekly intervals.

Statistical analysis

Survival analysis was conducted on the efficacy of BEV in recurrent MGs in terms of 6 months and 12 months PFS (PFS-6, PFS-1y) and OS (OS-6, OS-1y), median PFS (mPFS) and OS (mOS) from BEV treatment. Safety analysis evaluated the toxicity profile of BEV treatment. PFS was measured from the start of BEV therapy to diagnosis of PD evidenced by MRI or to death from any cause or to last follow-up assessment. OS was measured from the start of treatment with BEV to death from any cause or last follow-up. Median PFS and OS were estimated with their 95% confidence interval. Survival curves of PFS and OS were generated using the Kaplan–Meier method. Differences in PFS and OS were evaluated using the log-rank test (Mantel-Cox) for statistical significance, which was defined at the $p < 0.05$ level [29].

Results

Patients' characteristics

Between August 2011 and May 2016, 17 patients with recurrent MGs receiving BEV as second-line or third line treatment were included in the analysis. Of 17 patients, 15 patients were treated at Policlinico Umberto I of Rome and 2 patients at S.M.Goretti Hospital of Latina. Patient, tumor and treatment characteristics are summarized in Table 1.

Most patients were male (58.8%), the median age was 50 years (range 26-66 years) and median KPS was 80 (range 60-100). All patients had an histological diagnosis of MGs: GBM was the predominant histotype (70.6%), while grade III gliomas represented the 29.4% of the total. Fifteen patients (88.2%) presented a monolobar localization and 2 patients (11.8%) presented the involvement of two or more lobes.

Table 1 Patients' characteristics at recurrence

Patients $n = 17$	n (%)
Characteristics	
Gender	
Male	10 (59%)
Female	7 (41%)
Median age, years (range)	50 (26-66)
Karnofsky performance status	
Median (range)	80 (60-100)
90-100	4 (24)
70-80	12 (71)
60	1 (5)
Laterality	
Right	5 (29)
Left	12 (71)
Lobe	
Fronto-temporal	5 (29)
Parieto-temporal	3 (18)
Frontal	2 (12)
Temporal	4 (24)
Parietal	1 (5)
Multilobar	2 (12)
Histotype	
Glioblastoma multiforme	12 (71)
Grade III gliomas	5 (29)
MGMT promoter methylation status at diagnosis	
Methylated	9 (53)
Unmethylated	3 (18)
Unknown	5 (29)
IDH1 status at diagnosis:	
Mutated	5 (29)
Non mutated	3 (18)
Unknown	9 (53)
Surgery at recurrence	
Yes	15 (88)
No	2 (12)
Chemotherapy treatment	
First-line therapy	
STUPP (RT/TMZ-TMZ)	17 (100%)
Line of BEV treatment	
Second	4 (24)
Third	13 (76)
BEV treatment	
Monotherapy	13 (76)
Combined with FTM	4 (24)
Median cycles received, number (range)	8 (2-40)

The assessment of the O6-Methylguanine-DNA methyltransferase (MGMT) promoter methylation status was conducted in 12 patients (70.6%). MGMT promoter was methylated in 9 patients (52.9%) and unmethylated in 3 patients (17.5%). The assessment of the isocitrate dehydrogenase 1 (IDH1) mutation status was conducted in 8 patients (47%). IDH1 was mutated in 5 patients and wild-type in 3 patients.

All patients underwent surgery at diagnosis but only 2 patients underwent surgery at recurrence before BEV treatment. All patients underwent first-line therapy with maximum safe resection and Stupp treatment with a mPFS of 12.9 months (range 2-129.6). BEV was administered (off-label use) in 13 patients (76.5%) in third line therapy after a second-line therapy with FTM and in 4 patients (23.5%) as a second-line therapy in association with FTM. Patients treated with second-line FTM had a mPFS of 2.2 months (range 1.3-6.9).

All patients received at least two administrations of BEV and the median number of cycles administered was 8 (range 2-40). First response assessment using RANO criteria was performed after about 5 weeks after initiation of treatment (mean 35 ± 12 days). At the start of treatment 13 patients (76.5%) were on corticosteroid treatment.

Activity evaluation

All patients included in the study were assessable for response analysis. Among the 17 patients, one complete response (5.9%), 7 partial responses (41.2%), 3 stable diseases (17.6%) and 6 progression diseases (35.3%) were observed. ORR and DCR were of 47.1% and 64.7% respectively.

The mPFS was 5 months (95% CI 2-8 months) with a PFS-6 of 41.2% and a PFS-1y of 29.4%. The mOS was 8.3 months (95% CI 3.9-12.7 months) with an OS-6 of 58.8% and a OS-1y of 35.3%. In grade III gliomas patients, mPFS and mOS were higher than GBM patients without statistical significance (7 vs 5 months $p = 0.5$, and 8.3 vs 6 months, $p = 0.6$ respectively).

Six patients (35.3%) experienced a long response characterized by a high number of administered cycles (range 11-40), long PFS (range 11-40 months) and OS (range 12-45 months). Results are summarized in Table 2. Figure 1 shows the curves of PFS and OS from the start of BEV.

Activity according to MGMT methylation and IDH1 mutation

Methylated patients appeared to experience both longer mPFS (5 versus 2 months) and mOS (9.5 versus 2.5 months) than unmethylated patients, but this did not reach statistical significance ($p = 0.43$ and 0.24, respectively).

Table 2 Results obtained by using BEV in MGs

	n (%)
Objective responses	
Complete response (CR)	1 (5.9)
Partial response (PR)	7 (41.2)
Stable disease (SD)	3 (17.6)
Progressive disease (PD)	6 (35.3)
Overall response rate (ORR)	8 (47.1)
Disease control (DC)	11 (64.7)
Survival data	
6 months-PFS, %	41.2
12 months-PFS, %	29.4
Median PFS, months (range)	5 (1-40)
6 months-OS, %	58.8
12 months-OS, %	35.3
Median OS, months (range)	8.3 (1-45)

PFS progression free survival, *OS* overall survival

Wild-type IDH1 patients showed both longer mPFS (12 versus 2 months) and mOS (13 versus 9.5 months) than mutated IDH1 patients, but this did not reach statistical significance ($p = 0.82$ and 0.59 respectively).

Correlations between response and patient's characteristics/biomarkers

Subgroup analysis was performed to identify correlations between responder/non-responder patients and clinical characteristics or tumor biomarkers such as sex, histology, tumor side, MGMT methylation, IDH1 mutation and OS. The results showed a significant correlation between the response to BEV and OS ($p < 0.001$) and between the response to BEV and MGMT methylation ($p < 0.05$). We didn't find any other significant relationship among the other subgroup analysis.

Clinical benefit

Patients had an important clinical benefit from BEV treatment in terms of improvement of performance status, improvement of neurological symptoms and decrease of steroid use.

An improvement in neurological symptoms was observed in 8 patients (47.1%). Of them, 4 patients (50%) had a discontinuation of corticosteroid use and 1 patient had a reduction of corticosteroid dose (12.5%) at the time of response. KPS improved in 64.7% of patients.

In the 13 patients treated with corticosteroids, a discontinuation of dexamethasone was observed in 4 patients (30.8%) and a reduction of dexamethasone dosage was shown in 5 patients (38.5%). Of the 4 patients who were not receiving dexamethasone before BEV, all of them remained without corticosteroids.

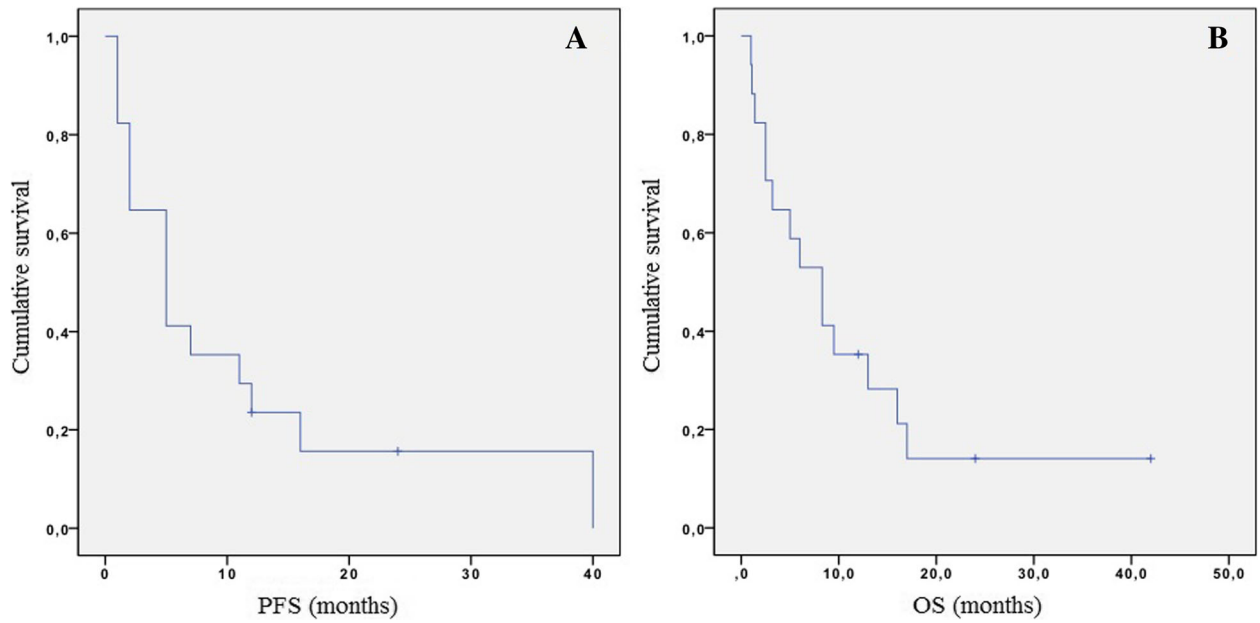

Fig. 1 Kaplan-Meier survival curves of PFS (**a**) and OS (**b**) from start of BEV treatment of the patients analysed in the study

Of the 11 responding patients, 4 patients discontinued steroids (36.4%), 3 patients reduced steroid dosage (27.3%) and 4 patients, who were not on corticosteroids, remained without steroid therapy (36.4%).

Toxicity evaluation

All 17 patients were evaluated for safety (Table 3). BEV was generally well-tolerated with grade 1-2 hypertension observed in 6 (35.3%) and 2 (11.8%) patients respectively. Grade 1-2 proteinuria was observed in 7 (41.2%) and 2 (11.8%) patients respectively. Only one patient developed grade 3 proteinuria after 30 cycles of treatment and another patient developed an uncomplicated pulmonary embolism (grade 3 thromboembolic event). We observed grade 1 skin toxicities in 17.6% of patients, as acneiform rash, eritema and skin ulcer. We observed grade 1 anemia in 17.6% of patients, grade 1 leucopenia in 11.8% of patients, grade 2 leucopenia in 23.5% of patients and grade 1-2 thrombocytopenia in 11.8% of patients. Grade 4 toxicities, hemorrhagic events, treatment interruption or death related to BEV were not documented.

Table 3 Toxicities by grade of severity, according to the CTCAE (version 4.03)

Chemotherapy-related toxicity	n (%)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	6 (35.3)	2 (11.8)	–	–
Proteinuria	7 (41.2)	2 (11.8)	1 (5.9)	–
Thromboembolic event	–	–	1 (5.9)	–
Headache	4 (23.5)	–	–	–
Skin alteration	3 (17.6)	–	–	–
Hypotension	2 (11.8)	–	–	–
Thrombocytopenia	1 (5.9)	1 (5.9)	–	–
Leukopenia	2 (11.8)	4 (23.5)	–	–
Anemia	3 (17.6)	–	–	–
Hypertransaminasemia	5 (29.4)	–	–	–
Astenia	1 (5.9)	3 (17.6)	–	–

Discussion

For newly diagnosed MGs, radiotherapy plus concomitant and adjuvant TMZ after maximal safe surgical resection has become the standard therapy [4, 30]. However, there is not yet consensus on the treatment of recurrent MGs and treatment recommendations are still based on non-controlled phase II trials. In the United States, BEV as a single-agent is a valuable and active treatment option for recurrent GBM and AG [30]. It was approved in 2009 for the treatment of recurrent GBM by the FDA [12] based on the results of two uncontrolled phase II trials [8, 13] which have shown improvements in RR and PFS both as single-agent and combination therapy. In Europe, BEV was not approved as a treatment option of GBM due to the lack of phase III studies and of an evident clinical benefit in terms of OS.

Several single-arm monotherapy trials, randomized trials and single-arm combination therapy studies containing BEV were developed [19]. Phase II clinical trials on BEV as monotherapy (Table 4) reported similar

Table 4 Survival results of the main clinical trials evaluating Bevacizumab as single-agent or in combination with FTM

Author (year)	Type clinical trial	Treatment	N pts	Histotype	Recurrence	mPFS (months)	PFS6 (%)	mOS (months)	DCR (%)	ORR (%)
Single-arm trials										
Kreisl (2009) [13]	Phase II	BEV	48	GBM	I/II/III...	3.7	29	7.1	NA	35
Chamberlain (2010) [14]	Retrospective	BEV	50	GBM	I/II	1	42	8.5	42	42
Raitzer (2010) [15]	Phase II	BEV	50	GBM	I/II/III...	2.7	25	6.4	NA	25%
Kreisl 2011 [16]	Phase II	BEV	31	AG	I	2.9	20.9	12	69	43
Nagane (2012) [17]	Phase II	BEV	29	GBM	I	3.3	33.9	10.5	79.3	27.6
Randomized trials (BEV arm)										
Friedman (2009) [8]	Phase II	BEV	85	GBM	I/II	4.2	42.6	9.2	NA	28.2
Taal (2014) [40]	Phase II	BEV	50	GBM	I	3	18	8	NA	38
Field (2015) [41]	Phase II	BEV	55	GBM	I	3.5	18	7.5	64	6
Puduvalli (2015) [42]	Phase II	BEV	41	GBM	I	3.6	NA	7	NA	NA
Hacibekiroglu (2015) [43]	Retrospective	BEV	24	MGs	I	4.1	37.5	6.4	58.3	20.8
Brandes (2016) [44]	Phase II	BEV	59	GBM	I	3.38	26.3	7.3	NA	29
BEV with FTM										
Vaccaro (2014) [20]	Observational prospective	BEV + FTM	26	MGs	I/II	4	23.1	6	92.5	31
Soffietti (2014) [21]	Phase II	BEV + FTM	54	GBM	I	5.2	42.6	9.1	89	52
Soffietti (2012) [23]	Phase II	BEV + FTM	32	AG	I	5	31	8.6	94	50
Liu (2015) [22]	Retrospective	BEV + FTM	176	GBM	I	5	33.3	8	90.9	46.5
Our study (2016)	Retrospective	BEV/BEV + FTM	17	MGs	I/II	5	41.2	8.3	64.7	47.1

N pts number of patients, *GBM* glioblastoma mutiforme, *MGs* malignant gliomas, *AG* anaplastic gliomas, *PFS* progression-free survival, *PFS6* PFS at 6 months, *OS* overall survival, *DCR* disease control rate, *NA* not available

results with mPFS of 1-4.2 months, PFS-6 of 18–42.6%, mOS of 6.4–12 months and RR of 28-43% [19, 31, 32]. Furthermore, a recent meta-analysis conducted by Wang et al. in 2014 [33] on the use of single angiogenesis inhibitors in the treatment of recurrent GBM, demonstrated a mPFS of 3 months and a mOS of 8.5 months in the group of clinical trials evaluating BEV. The combination therapy studies of BEV reported survival results and response rates similar to those reported by BEV monotherapy studies [19, 31, 34]. Some retrospective and prospective trials (Table 4) evaluated the efficacy of the combination of BEV with FTM [20–23]. The choice of this association was based on the rational that BEV could improve the activity of cytotoxic molecules without worsening primary toxicities of each agent [21, 22]. Soffietti et al. [21] showed that the association of BEV with FTM at first recurrence in GBM patients achieved RR of 52% and DCR of 89% and observed a mPFS of 5.2 months and a mOS of 9.1 months. Similar results were reported by a retrospective analysis conducted by Liu et al. [22] with RR of 46.5%, DCR of 90.9%, a mPFS of 5 months and a mOS of 8 months.

Soffietti et al. [23] in 2012, with the association of FTM and BEV in the treatment of first-relapsed grade III gliomas, reported response rates and survival results similar to those observed in the treatment of GBM.

BEV is a treatment generally well tolerated and the most common adverse events are hypertension, proteinuria, hemorrhage and thromboembolic complications, which are present in similar rates in the different clinical studies [32, 34, 35].

In our study, we observed a RR of 47.1%, mPSF of 5 months, PFS-6 of 41.2% and mOS of 8.3 months. These results were comparable with other retrospective and phase II trials on single-agent BEV or BEV associated with FTM reported in the literature (Table 4). Six patients experienced long response with a high number of administered cycles (range 11-40), long PFS ranged 11-40 months and OS ranged 12-45 months.

From our subgroup analysis, responder patients are statistically significantly correlated with a longer OS ($p < 0.001$) and the MGMT methylation ($p < 0.05$). Other clinical characteristics or tumor biomarkers seemed not to be correlated with the response to BEV.

In our retrospective analysis, methylated MGMT patients compared to unmethylated MGMT patients showed a longer mPFS (5 months vs 2 months, respectively) and a longer mOS (9.5 months vs 2.5 months,

respectively) but without statistical significance ($p = 0.44$ and $p = 0.24$, respectively). Moreover, wild-type IDH patients compared to mutated IDH1 patients experienced longer mPFS (12 months vs 5 months, respectively) and mOS (13 vs 9.5 months, respectively) but without statistical significance ($p = 0.82$ and $p = 0.59$, respectively).

The prognostic significance of MGMT promoter methylation in the treatment of MGs remains controversial.

A meta-analysis conducted by Zhang et al. [36] in 2013 showed that methylated MGMT status in GBM patients was associated with better PFS and OS regardless of therapeutic intervention and associated with longer OS with alkylating agents. However, in the setting of BEV treatment, MGMT and IDH seemed not to be good prognostic factors [37].

In our retrospective analysis, we observed that the clinical benefit with BEV was not defined only in terms of tumor response but also in terms of improvement of performance status, decreased dependency on corticosteroids and improvement in symptoms of disease.

In our study, BEV was generally well tolerated and the most common adverse events include hypertension and proteinuria of grade 1-2. No grade 3-4 were observed, except for only one patient who developed grade 3 proteinuria after 30 administrations of BEV and one grade 3 thromboembolic event (uncomplicated pulmonary embolism).

Moreover, the combination of BEV plus FTM was well tolerated. In the BEV + FTM group of patients, the rate of BEV related toxicities was consistent with those reported in other similar trials [20–23].

This study has limitations related to the retrospective design, the low sample size and the unselection of the population analysed. In addition, the population is heterogeneous for histology, time of recurrence and type of treatment (monotherapy or combination BEV). Despite these limitations, it's important to underline that survival results and response rate of BEV in previous prospective and retrospective studies are similar regardless of the specific histotype of MGs [16, 20], time of recurrence [8, 38, 39] and the use of BEV in monotherapy or in combination with other therapeutic agents [19, 31, 34]. Another limitation is that molecular markers, such as IDH1 mutation and MGMT status, were not available for all patients, even though their prognostic and/or predictive significance in the treatment with BEV are still not understood [37].

Future phase III studies are needed to establish if combination therapy with BEV is superior to single-agent therapy for recurrent MGs and the optimal therapeutic agent for the combination treatment with BEV. Further studies are needed also to investigate biomarkers and genetic patterns which may help to identify patients who may benefit from treatment with BEV reaching long-term responses.

Conclusions

In conclusion, our retrospective study showed that BEV as single-agent and in combination therapy, in off-label use, is a valid treatment option also in unselected recurrent MGs patients which provides significant survival benefits with acceptable toxicity profile. However, further phase III clinical trials are needed.

Abbreviations

AG: Anaplastic gliomas; BEV: Bevacizumab; CR: Complete response; CTCAE: Common Terminology Criteria for Adverse Events; DC: Disease control; EMA: European Medical Agency; FDA: Food and Drug Administration; FTM: Fotemustine; GBM: Glioblastoma; IDH1: Isocitrate dehydrogenase 1; IRB: Institutional Review Board; IRI: Irinotecan; KPS: Karnofsky-Performance-Status; MGMT: O6-Methylguanine-DNA methyltransferase; MGs: Malignant gliomas; mOS: Median overall survival; mPFS: Median progression free survival; MRI: Magnetic resonance imaging; ORR: Overall response rate; OS-1y: 12 months overall survival; PD: Progression disease; PFS-1y: 12 months progression free survival; PFS-6: 6 months progression free survival; PR: Partial response; RR: Response rate; SD: Stable disease; TMZ: Temozolomide; VEGF: Vascular endothelial growth factor

Acknowledgements

We thank the research nurses and the patients at Policlinico Umberto I of Rome and S.M.Goretti Hospital of Latina for taking patient samples and for participating in this study, respectively.

Availability of data and materials

The data and materials can be found from the first author and corresponding author.

Authors' contributions

AP and SER contributed equally to this work. AP, SER, VB ad ST, designed the study. AP, SP, CF1, CP selected patients, obtained informed consent and collected clinical data. AP, SER, and CF4 performed the experiments and performed statistical analyses. AP, SER and SM wrote the manuscript. All authors participated to interpret data as well as corrected and approved of the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol (No: Beva-Glio/Sep 2016) was retrospectively approved by the ethics committee of S.M.Goretti Hospital of Latina, Sapienza University of Rome. Consent for publication not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 13 February 2017 Accepted: 6 April 2018
Published online: 14 April 2018

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