Bevacizumab in glioblastomas: lights and shadows

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Summary

Glioblastomamultiforme (GBM) is the most vascularized of all solid tumors. Several molecules governangiogenetic processes in GBM, among these the vascular endothelial growth factor (VEGF) plays a predominant role. Increasing evidence has support the capability of bevacizumab, a humanized monoclonal antibody, to inhibit the VEGF. Several clinical trials have shown an improvement in quality of life and in progression free survival of GBM patients treated by bevacizumab. Many phase II and III studies have demonstrated the importance of this drug in terms of neurological symptoms relief and rapid radiological response. Thus, in 2009, Food and Drug Administration (FDA) approved the use of bevacizumab for the treatment of recurrent GBM. However, no increase in Overall Survival (OS) has been showed and several adverse events have been related to the treatment, such as intracranial hemorrhage and venous thromboembolism.The aim of this review is to critically evaluate the efficacy and the safety associated with bevacizumab and to identify the best strategy for its use in the management of GBM.

KEY WORDS: glioblastoma, angiogenesis, VEGF, bevacizumab.

Introduction

GBM is a grade IV brain tumor, according to the World Health Organization (WHO) classification. It is the most common malignant brain tumor, associated with a poor prognosis. In case of newly diagnosed GBM thestandard therapy is represented by maximal safe surgery and radiotherapy (RT) plus temozolomide (TMZ) followed by TMZ alone. TMZ is an alkylating agent and its mechanism of action is the methylation of guanine in O6 position. Despite this multimodal approach, the median OS is 14-15 months and less than 10% of patients survive 5 years after diagnosis (1, 2). Besides, after relapse or progression there is no standard treatment; OS is estimated from 3 to 9 months and the median progression free survival (PFS) is 10 weeks (3).Tumor progression is associated with alterations in multiple signaling transduction pathways. GBM are highly vascularized tumors and many angiogenetic factors are implicated in its growth. The most expressed is the VEGF, an endogenous cytokine that regulates angiogenesis and tumor blood vessel permeability (4). The angiogenesis inhibition could be an alternative therapeutic approach in GBM (5, 6). According to this hypothesis, some trials have investigated molecular target agents, such as anti-VEGF (7). Bevacizumabis is a humanized monoclonal antibody that neutralized VEGF's activity. It is currently approved for other metastatic cancers. In fact, the United States Food and Drug Administration (FDA) endorsed bevacizumab for the treatment of advanced colorectal cancer (8, 9), non-small cell lung cancer (10-12), metastatic renal cell carcinoma (13, 14), metastatic ovarian (15, 16) and breast cancer (17, 18). This article gives an overview of the current knowledge on bevacizumab in GBM, moving from the molecular rationale to the clinical efficacy data and current unsolved problems, describing mechanisms of resistance, adverse effects and potential areas for future research for anti-VEGF therapy in GBM.

Search methods

We have performed a systematic review of the current literature regarding the efficacy and the safety of the use of bevacizumab in recurrent gliomas. We searched digital databases including Pubmed, EMBASE and the Cochrane Library. The literature search was performed using different keywords such as "glioblastomamultiforme", "angiogenesis", "VEGF", "safety", "efficacy", "recurrent glioblastoma", "bevacizumab" variously associated together. We analyzed only the full versions of all relevant studies. The ab-

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stracted data included general information and patients' characteristics. Studies about GBM in pediatric patients were excluded because there are some differences in terms of glioma genesis between adult and pediatric GBM (19, 20).We evaluated all the selected information with a particular attention to the efficacy, the adverse events, the chemo-resistance and new strategies associated with the bevacizumab treatment in this tumor.

Antiangiogenetic factors

Angiogenesis plays an important role for growth and metastasis of solid tumors (21).This process allows the formation of new blood vessels. New vasculature is needed for tumor growth (22). Angiogenesis is mediated by different pro angiogenic factors, for example VEGF, and by endothelial, stromal, and tumor cells, which cause vessel growth and subsequent tumor expansion (23).VEGF consists of a family of glycoproteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D), and placenta growth factor. Their interaction with tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3), activates a downstream signal that causes angiogenesis. The most important role in angiogenesis is mainly played by VEGF-A (24).The expression of VEGF correlates with the grade of gliomas (4), and VEGF expression is also observed in meningioma and brain metastases.Furthermore VEGF is a vascular permeability factor, thus its overexpression causes massive vasogenic edema with worsening of the clinical conditions (25, 26). Recent studies indicate that antiangiogenetic therapies are potentially effective in GBM and can temporary normalize tumor vessels (6).

Bevacizumab in recurrent GBM

During the last years, anti angiogenic agents have been widely experimented in GBM treatment. Bevacizumab was approved by FDA on May 2009 for the treatment of recurrent GBM, on the basis of randomized phase II trials data (27). To date no relevant phase III studies have been performed to test bevacizumab alone or in association with chemotherapeutic agents for GBM in second line treatment or further. Trials on recurrent GBM have shown that bevacizumab alone is able to increase response rate on MRI, median and 6-month progression-free survival (PFS), and modestly overall survival, allowing an improvement of neurological function and a reduction of steroids (28).
Several schedules have been studied, but the association of bevacizumab with irinotecan is the most frequently tested. In a phase II trial published on October 2007, Vredenburgh et al. tested bevacizumab together with irinotecan in two cohorts of patients with diagnosis of first GBM relapse. The first cohort received bevacizumab 10 mg/kg and irinotecan every 14 days. The dose of irinotecan was 340 mg/mq for patients who were concomitantly treated with enzyme-inducing antiepilectic drugs (EIAEDs) and 125 mg/mq for patients not in treatment with EIAEDs. The second cohort received bevacizumab 15 mg/kg every 21 days and irinotecan 350 mg/mq (for patients in treatment with EIAEDs) or 125 mg/mq (for patients not in treatment with EIAEDs) on days 1, 8, 22, 29 of a 42-days cycle. Primary endpoint was 6 months PFS and it was reached, suggesting that this regimen did improve PFS in patients at the second line of treatment for GBM (11). The median OS was 42 weeks, with a 95% CI from 35 to 60 weeks. Data about toxicity showed a high risk of thromboembolic events (29). Another phase II trial conducted by Friedman et al. compared bevacizumab 10 mg/kg every 14 days with bevacizumab at the same doses together with irinotecan every 14 days in patients affected by GBM at the first or second relapse after treatment with TMZ and RT. Also in this study the primary endpoint was 6 months PFS. It was 42.6% in the bevacizumab group, and 50.3% in the bevacizumab plus irinotecan group; the median PFS time was 4.2 months and 5.6 months respectively; the median OS time was 9.2 months and 8.7 months respectively. So this study demonstrates that bevacizumab, alone or in combination with irinotecan, is active in treatment of GBM relapses (30). Encouraging results about bevacizumab alone for relapsing GBM was also shown in a phase II trial conducted by Kreisl et al. They enrolled 48 patients with recurrence of GBM pretreated with TMZ and RT, and treated them with bevacizumab at the doses of 10 mg/kg every 14 days. At the progression of disease they were treated with bevacizumab at the same doses plus irinotecan 340 mg/mq or 125 mg/mq (if they respectively assumed or not EIAEDs). Taking into account patients treated with bevacizumab alone, the 6-month PFS was 29% (95% CI, 18% to 48%); the median PFS time was 16 weeks (95% CI, 12 to 26 weeks) and the median overall survival was 31 weeks (95% CI, 21 to 54 weeks). For this group of patients the overall radiographic response rate evaluated with Levin criteria was 71%, while if evaluated with Macdonald criteria the response rate was 35%. Unfortunately, in the group treated with bevacizumab and irinotecan at the progression of disease (19 patients), no radiographic response was found using Macdonald criteria, and only one using Levine criteria. This caused an anticipated closure of patients' accrual for this phase of the study (31). A meta analysis conducted in 2012 by Zhang et al. confirmed that combination between bevacizumab and irinotecan in patients with recurrent GBM had a favorable impact on 6 months PFS and on objective response rate if compared with bevacizumab as single agent therapy; instead, in terms of overall survival the advantage was marginal. Patients treated with bevacizumab and irinotecan showed a higher rate of discontinuation. Fatigue, headache, nausea, diarrhea and hypertension were the most common adverse events reported by patients. The authors concluded that the choice between a single agent therapy based on bevacizumab, or the association regimen with irinotecan, needs to be individualized (32). Cecchi et al. on March 2013 published a retrospective observational analysis in which the use of bevacizumab alone was compared

to its association with irinotecan in recurrent GBM patients. In this study they enrolled patients treated with bevacizumab 10 mg/kg alone or in combination with irinotecan 340 mg/m^2 every two weeks. Primary endpoints were median PFS and OS and 6-month PFS and OS. Median PFS resulted 5.1 month in the bevacizumab group and 15.4 months in the group treated with bevacizumab plus irinotecan (p value = 0.20); 6-months PFS was 45% for bevacizumab group and 69% for bevacizumab plus irinotecan group. Median OS was 6.8 months for bevacizumab alone group and 11.1 months for bevacizumab plus irinotecan group (p value = 0.62). 6-months OS was 100% for bevacizumab alone group and 90% for bevacizumab plus irinotecan group. This study was designed to compare the results in PFS and OS of bevacizumab (alone or with irinotecan) used in everyday practice to data existing in literature. Though a small sample size (19 patients), results are comparable with data existing in literature (33). Also Hasselbach et al. tested the association of bevacizumab and irinotecan with a supplement of cetuximab. They conducted a phase II trial using bevacizumab (10 mg/kg) plus irinotecan (340 mg/m^2 for patients in therapy with EIAEDs or 125 mg/m^2 for patients not in therapy with EIAEDs) and cetuximab (400 mg/m2 as loading dose followed by 250 mg/m^2 every week). Median PFS and 6-month PFS were the primary endpoints. The median PFS was 16 weeks (95% CI: 13-20 weeks), while the 6-month PFS was 33% (95% CI: 19%-48%). Median OS was 30 weeks (95% CI: 23-37 weeks). The response rate measured in intention-to-treat (ITT) population was 26% (95% CI: 14%-41%). These results were encouraging, but data about safety showed a limited tolerability of this regimen. In fact 29 patients (67%) had skin toxicity, 15 patients (35%) had infections, of which 6 (14%) had grade 3-4 infections (34). Soffietti et al. performed a phase II trial in which the association between bevacizumab and fotemustine was tested in patients affected by recurrent GBM. The schedule consisted of a phase of induction with bevacizumab (10 mg/kg on day 1 and 15) and fotemustine (75 mg/m^2 on day 1 and day 8) followed by a maintenance phase with bevacizumab (10 mg/kg) and fotemustine (75 mg/m^2 every 3 weeks). The 6-month PFS was 42.6 % (95% CI 29.3-55.2) and the median PFS 5.2 months (95% CI 3.8-6.6). The 6-month OS resulted 75.9 % (95% CI 62.2-85.2) and the median OS 9.1 months (95% CI 7.3-10.3). These results were satisfying, but not sufficient to demonstrate an effective superiority of the association between bevacizumab and fotemustine over the single agent therapy with bevacizumab alone or fotemustine alone (35). Reardon et al. in 2012 tested a combination of bevacizumab, irinotecan and carboplatin in 40 patients with recurrence of GBM in a phase II, single arm trial. All patients received bevacizumab 10 mg/kg and irinotecan 340 mg/mq or 125 mg/mq (in case of concomitant therapy with EIAEDs or not respectively) every 14 days, while carboplatin was administered at an AUC 4 at the day 1 of a 28 days cycle. This trial showed a significant toxicity increase due to the combination of these three drugs. The percentage of patients who required a therapy discontinuation caused by side effects was high (28%, 11 patients); one patient died for treatment-related intestinal perforation. On the other hand, results in terms of survival were disappointing: the PFS at six months was only 46.5% (95% CI: 30.4-61.0%); the median OS was 8.3 months (95% CI: 5.9-10.7 months). The best radiographic response was not complete response but partial response, in 13 patients (33%). The authors concluded that this schedule does not improve progression free survival and overall survival if compared with bevacizumab alone (36). So the most common schedule of bevacizumab is 10 mg/kg every 2 weeks, but in a small study, including only fourteen patients (median age, 46 years) Kaloshi et al. retrospectively investigated the efficacy of bevacizumab 5 mg/kg every 3 weeks. Five patients (36%) had a partial response, 7 (50%) had stable disease, and 2 (14%) underwent to progression. This dosage was well tolerated by the patients in fact were not described grade III-IV toxicities. OS was 6.4 months so the authors concluded that 3-week schedule of 5 mg/kgbevacizumabwas substantial efficacy and safety in patients with recurrent GBM (37). Another schedule used in GBM recurrence was ICE (Ifosfamide, Carboplatin and Etoposide) together with bevacizumab. In 2013 Arakawa et al. published a retrospective analysis of 8 cases of patients affected by GBM treated with this schedule at the second recurrence. ICE regimen consisted of ifosfamide 750 mg/m^2/day, carboplatin 75 mg/m^2/day, and etoposide 75 mg/m^2/day on day 1, 2, and 3 in every 4-6 weeks; bevacizumab was administered at the doses of 10 mg/kg for 3 cycles, every two weeks. These patients already received ICE regimen as second line therapy after the first line therapy with TMZ. The six months PFS was 25% (95% CI, 0-55.0%). The median OS after onset was 23.3 months (95% CI, 16.2-55.8 months). Data about safety showed no grade 4 toxicity, and only one death, not treatment related. 60% of the grade 2 and 3 adverse events were hematological. Thus, this association can be considered safe and may improve clinical conditions in these patients (38). In a retrospective analysis Nghiempu et al. tried to compare the single agent therapy based on the association of bevacizumab and other antineoplastic agents to other regimens not comprising bevacizumab in their schedule. The most frequent drugs associated with bevacizumab in the treated group were irinotecan (31 of 44 patients), carboplatin (8 patients), lomustine (3 patients), etoposide (2 patients). In the control group, patients were treated with several regimens (25 of 79 patients treated with lomustine, 8 patients with carboplatin, 2 patients with irinotecan and 1 patient with carmustine). Other patients were enrolled in trials. Results showed a significant improvement in median PFS for the treated group (median PFS in the treated group was 4.25 months while in the control group was 1.82 months); even the median OS was better in the treated group (9.01 months) than that obtained in the control group (6.11 months) (39) (Tab. 1). In conclusion, it seems that bevacizumab is effective, safe and well tolerated in second line treatment of GBM. Among the various combination regimens tested, bevacizumab

Table 1 - Studies in which bevacizumab has been tested for the treatment of recurrent glioblastoma.

AUTHOR	TYPE OF STUDY	PATIENT SELECTION	TREATMENT	ENDPOINTS
Vredenburgh et al., 2007 (1)	Phase II trial	Patients with histologically proven GBM in progression after treatment with radiotherapy and TMZ	Two cohorts of patients: - bevacizumab 10 mg/kg and CPT-11 340 mg/mq (for patients in treatment with EIAEDs) or 125 mg/mq (for patients not in treatment with EIAEDs) every 14 days - bevacizumab 15 mg/kg every 21 days and CPT-11 350 mg/mq (for patients in treatment with EIAEDs) or 125 mg/mq (for patients not in treatment with EIAEDs) on days 1, 8, 22, 29 of a 42-days cycle	- Primary endpoint: six months PFS; - Secondary endpoints: OS, toxicity
Friedman et al., 2009 (2)	Phase II trial	Patients with histologically proven GBM in first or second relapse after treatment with radiotherapy and TMZ. KPS ≥ 70%; life expectancy greater than 12 weeks	Patients randomly assigned to receive: - bevacizumab 10 mg/kg every 14 days - bevacizumab 10 mg/kg and CPT-11 340 mg/mq (for patients in treatment with EIAEDs) or 125 mg/mq (for patients not in treatment with EIAEDs) every 14 days For a 6-weeks cycle	- Primary endpoint: six months PFS, objective response rate - Secondary endpoints: OS, safety
Kreisl et al., 2009 (3)	Phase II trial	Patients with histologically proven recurrence of GBM after treatment with standard external beam fractionated radiotherapy and TMZ. KPS ≥ 60%; life expectancy greater than 2 months	All patients were treated with bevacizumab 10 mg/kg every 14 days on a 28-days cycle. Patients with progressive disease on bevacizumab were treated with bevacizumab 10 mg/kg and CPT-11 340 mg/mq (for patients in treatment with EIAEDs) or 125 mg/mq (for patients not in treatment with EIAEDs) every 14 days for a 4-weeks cycle	- Primary endpoint: six months PFS - Secondary endpoints: objective response rate; exploratory analyses of correlation between response and PFS
Reardon et al., 2013 (7)	Phase II trial	Patients with histologically proven recurrence of GBM after treatment with radiotherapy and TMZ. KPS ≥ 70%	All patients received bevacizumab 10 mg/kg every 14 days; carboplatin was administered at an AUC of 4 on day 1 of a 28-days cycle; CPT-11 dose was 340 mg/mq for patients in treatment with EIAEDs and 125 mg/mq for patients not in treatment with EIAEDs on days 1 and 14.	- Primary endpoint: six months PFS - Secondary endpoint: safety
Arakawa et al., 2013 (8)	Retrospective analysis	Patients with histologically proven GBM at second relapse, previously treated with ICE (Ifosfamide-Carboplatin-Etoposide) regimen	All patients received ICE regimen (consisting of ifosfamide 750 mg/m^2/day on day 1, 2, and 3, carboplatin 75 mg/m2/day on day 1, 2, and 3, and etoposide 75 mg/m^2/day on day 1, 2, and 3 in every 4-6 weeks) in combination with 3 cycles of 10 mg/kg bevacizumab, every two weeks.	Six months PFS, median OS

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continued from Table 1 - Studies in which bevacizumab has been tested for the treatment of recurrent glioblastoma.

AUTHOR	TYPE OF STUDY	PATIENT SELECTION	TREATMENT	ENDPOINTS
Hasselbalch et al., 2010 (5)	Phase II trial	Patients with histologically proven primary GBM and MRI-verified recurrent or progressive disease (PD), previously treated with radiotherapy and TMZ	Bevacizumab and irinotecan administered every 2 weeks. Irinotecan dose was 340 mg/mq for patients in treatment with EIAEDs and 125 mg/mq for patients not in treatment with EIAEDs. Cetuximab was administered at the dose of 400 mg/m^2 as loading dose followed by 250 mg/m^2	- Primary endpoint: 6-month PFS - Secondary endpoints: TTP, OS
Nghiemphu et al., 2009 (9)	Retrospective analysis	Patients with tissue diagnosis of GBM and treated with radiation therapy and concurrent temozolomide chemotherapy at the time of diagnosis.	- treated cohort: patients who received treatment with off-label bevacizumab for recurrent GBM at 5 mg/kg every 2 weeks (most of them received concurrent irinotecan. Other patients received carboplatin or lomustine or etoposide) - control cohort: patients who had never received bevacizumab. Other treatments were admitted (mainly lomustine or carboplatin or carmustine or irinotecan)	PFS, OS
Soffietti et al., 2013 (6)	Phase II trial	Patients with histological diagnosis of glioblastoma at original surgery or at reoperation; first progression after radiotherapy and concomitant/adjuvant temozolomide; KPS ≥ 70%	Induction phase with bevacizumab at 10 mg/kg intravenously on day 1 and 15 and fotemustine at 75 mg/m^2 intravenously on day 1 and day 8, followed after an interval of 3 weeks by a maintenance phase with bevacizumab at 10 mg/kg and fotemustine at 75 mg/m^2 every 3 weeks	- Primary endpoint: 6-month PFS - Secondary endpoints: OS, RR and toxicity
Cecchi et al., 2013 (4)	Retrospective analysis	patients with histologically proven glioblastoma in first or second relapse, previously treated with standard radiotherapy and temozolomide	All patients received bevacizumab 10 mg/kg alone or associated with irinotecan 340 mg/m^2 intravenously every two weeks	6-month PFS, 6-month OS, median PFS, median OS

Caption
PFS: progression free survival
OS: overall survival
TTP: time to progression
RR: response rate
GBM: glioblastoma multiforme
TMZ: temozolomide
EIAEDs: enzyme inducing antiepileptic drugs
KPS: Karnofsky performance score

plus irinotecan turned out to be the best association in terms of efficacy and safety. The addition of carboplatin seems to have a very limited impact on survival endpoints. On the other hand, many open questions remain about the use of bevacizumab in this kind of patients. For example, it is still unclear if the association between bevacizumab and other drugs should be considered recommended, or not. The mechanism of action of bevacizumab in GBM is still controversial. In fact Prestegarden et al. described an independent angiogenesis from GBM cells proliferation. They demonstrated that this tumor growth originates from some stem like tumor cells, which exhibit a strong proliferative activity. So the authors argued that blocking the angiogenesis in GBM could be not sufficient to stop tumor growth (40). However, bevacizumab improves intratumoral blood circulation. The rationale of an association therapy of bevacizumab plus a cytotoxic or a

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cytostatic agent origins from the hypothesis that the normalization of tumor blood vessels induced by bevacizumab leads to an increased drug delivery into the tumor bed (27). In the end, no relevant phase III studies are available about the use of bevacizumab in recurrent GBM. This data would be important to assess even the correct dosage of bevacizumab and the right duration of the treatment.

Bevacizumab in newly diagnosed GBM

Despite treatments, patients with newly diagnosed GBM have poor prognosis. Given the results with bevacizumab in the treatment of recurrent GBM, some investigators evaluated the possible association of bevacizumab with standard therapy (RT with concomitant TMZ followed by TMZ) for patients with newly diagnosed GBM (2). Some pilot studies with a small number of patients, evaluated the safety of adding bevacizumab to standard protocol, anticipating larger phase II trials (41, 42).An example is represented by a phase II trial of Lai et al. In this study seventy patients with newly diagnosed GBM were treated withbevacizumab (10 mg/kg every 2 weeks) in association with RT (30 × 200 Gy), plus TMZ (75 mg/m^2 daily).The results showed a median OS of 19.6 and PFS of 13.6 months (43). From 2006 through 2010, Narayan et al. enrolled 51 patients with newly diagnosed GBM. Twenty- nine days after surgery, patients were treated with RT and concomitant TMZ (75 mg/m^2 daily for 42 days) in association with bevacizumab (10 mg/kg every 2 weeks), followed by 6 cycles of adjuvant therapy consisting of TMZ (150 mg/m^2 on Days 1-7 every 28 days) with bevacizumab (10 mg/kg on Days 8 and 22 every 28 days). PFS and OS at 12 months were 51% and 85.1% respectively. The treatment was well tolerated and Grade III/IV toxicities were observed in only 10 patients (19.6%). The conclusions were that the addition of bevacizumab to the standard therapy improved both PFS and OS in patients with newly diagnosed GBM, with an acceptable safety (44).
In another trial, Vrendenburgh et al evaluated 125 patients treated with standard RT plus concurrent TMZ (75 mg/m^2 for 42 days) and bevacizumab(10 mg/kg every 2 weeks). After RT, adjuvant therapy with TMZ (150-200 mg/m^2, on days 1 and 5 every 28 days) and bevacizumab (10 mg/Kg every 2 weeks) was carried on. Their results were very similar to the Narayan's study, in fact PFS at 6 months, 12 months and 24 months was 88%, 64% and 16%, respectively, while OS was 94%, 82% and 44%, respectively (45).
In patients with newly diagnosed GBM the efficacy and safety of combination of bevacizumab with standard therapy were finally evaluatedin phase III trials. The AVAglio study demonstrated an improvement in quality of life, conversely, the RTOG 0825 (46) trial showed a negative impact on neurocognitive functions. AVAglio is a phase III double-blind randomized trial 921 patients after surgery to bevacizumab or placebo plus standard therapy (RT and TMZ) followed by TMZ and then maintenance bevacizumab or placebo until progression.Primary outcomes were PFS and OS.The authors showed a median PFS of 6.2 months in the placebo arm and 10.6 months in the bevacizumab arm (47) (Tab. 2).
Furthermore other studies evaluated additional antiangiogenicagents, such as vatalanib, vandetanib, and ABT-510, in combination with TMZ and RT for the treatment of patients with newly diagnosed glioblastoma (48-50).

Radiological response

Bevacizumab produces a rapid decrease in contrast enhancement on computed tomography (CT) (CT)/ MRI. It is not associated to its antitumor effect but to reduction of vascular permeability to contrast agents caused by bevacizumab (51). This radiological response is yet evident 6 weeks after the beginning of Bevacizumab treatment (52). In brain tumors the Macdonald criteria have been used to evaluate response after treatment (53). These criteria have significant limitations. They mainly considered the enhancing tumor area on CT or MRI, but they did not evaluate the pseudo-response or expansion of the non-enhancing areas or clinical features after antiangiogenic treatment. Iwamoto et al. also confirmed that contrast enhanced MRI did not adequately evaluate disease status during bevacizumab treatment for recurrent GBM. In fact the authors reported different results such as that 46% of patients had larger enhancing lesions, 16% had a new enhancing lesion and 35% had progression of predominantly non enhancing tumors at the time of bevacizumab discontinuation (54). Because contrast enhancement is nonspecific, new criteria were developed to permit a better evaluation of the efficacy of new drugs. Thus, the Response Assessment in Neuro-Oncology Working Group (RANO) created new criteria to evaluate the response to treatment including antiangiogenic therapy (55). Unlike Macdonald criteria, the RANO criteria also considered clinical parameters, such as steroid treatment and neurological symptoms. Despite this further research is needed to study new imaging techniques, for example perfusion and diffusion-weighted-imaging (56, 57).

Conclusion

Bevacizumab is effective in patients with recurrent GBM, with tolerable toxicity. We have reported here some papers showing an improvement of PFS and OS in recurrent GBM patients treated with bevacizumab. However, the optimal bevacizumab dose and schedule is still debated. In general the most common schedule of bevacizumabis 10 mg/kg every 2 weeks, but a single center experience recently published by Kaloshi Get al., also demonstrated the efficacy and safety of a 3-week schedule of 5 mg/kg bevacizumab in patients with recurrent GBM (37).
However the optimal bevacizumab dose and schedule is still debated as well as the duration of the treat-

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Table 2 - Efficacy and safety of bevacizumab in patients with newly diagnosed GBM.

AUTHOR	TYPE OF STUDY	PATIENT SELECTION	TREATMENT	ENDPOINTS
Lai et al., 2011 [43]	Phase II study	70 Patients with newly diagnosed GBMenrolled between August 2006 and November 2008.	All patients received standard RT associated with daily 75 mg/m(2) TMZ, and Bevacizumab at 10 mg/kg every 2 weeks followed, after a 2-week interval, by TMZ at 150 to 200 mg/m(2) for 5 days every 4 weeks and continuation of Bevacizumab every 2 weeks.	- OS 19.6 months - PFS 13.6 months
Narayana et al., 2012 [44]	Clinical trial	51 patients with newly diagnosed GBM	All patient was treated with RT with bevacizumab 10 mg/kg on Days 14 and 28 and TMZ 75 mg/m(2) followed by 6 cycles of bevacizumab 10 mg/kg every 2 weeks with TMZ 150 mg/m(2)	- 6 month PFS rates 85.1% -12 month PFS rates 51%, - 12 month OS rates 85.1% - 24 month OS rates 42.5%
Chinot et al., 2011 [41]	Phase III trial double-blind randomized trial	921 patients with newly diagnosed GBM after surgery	Patients double-bind randomized in bevacizumab or placebo group associated with RT and TMZ followed by TMZ and maintenance bevacizumab or placebo until progression	- median PFS 6.2 months in placebo group - medan PFS 10.6 months in the bevacizumab group
Vrendenburgh et al., 2012 [45]	Clinical trial	-125 patients with newly diagnosed GBM - 5 patients stopped the protocol therapy	All patients received standard RT and concomitant 75 mg/m(2) daily TMZ.Bevacizumab was given at 10 mg/kg every 14 days after 4 weeks of surgery.	- 6-months PFS 88% -12-months PFS 64% - 24-months PFS 16% - 6-months OS 94% - 12-months OS 82% - 24-months OS 44%

ment.To date, there is not effective therapy following bevacizumab progression in treatment of recurrent GBM but the data supporting bevacizumab continuation among other solid tumors such as colorectal cancer cancers (58), led some authors to examine bevacizumab continuation recurrent GBM too (59, 60) (54). In fact Reardon et al. in a meta-analysis of 5 phase II trials suggested the prolongation of treatment after bevacizumab failure in recurrent GBM. Median OS and OS at 6 months for patients who continued bevacizumab therapy after progression were 5.9 months and 49.2%, compared with 4.0 months and 29.5% for those treated with a non-bevacizumab regimen. OS for patients who did not receive further therapy after initial PD was only 1.5 months. To confirm these findings are needed furthermore studies (61). Instead for newly diagnosed GBM, the phase III AVAGLIO study have shown better PFS when bevacizumab is associated with standard therapy.

Mechanisms of resistance to antiangiogenic treatment increase tumor invasion and progression (62). Mechanisms of resistance can be caused by mutation of the oncogenes (63), or by alterations in drug uptake and efflux (64). Furthermore GBM could adapt to the presence of VEGF inhibitors preserving tumor growth by alternative pathways. So new strategies to identify these escape mechanisms and appropriate salvage therapies arestill to be identified. For example clinical trials that evaluate the association between angiogenesis inhibitors and drugs such as c-Met are needed (65).It is also important to evaluate the safety. Bevacizumab is generally well tolerated. BRAIN study reported the most common adverse events (AEs) associated with the use of bevacizumab alone at the dose of 10 mg/kg every 2. The most frequent AEs were Fatigue (45.2% of patients), headache (36.9% of patients), hypertension (29.8% of patients) and thromboembolism (12.5% of patients). Only 4.8% of patients discontinued the treatment due to adverse events. Instead the death was observed in 2.4% of patients (66).However, in the Kreisl et al. study were not described discontinuations or deaths related to bevacizumab (67). The serious AEs, such as severe intracranial hemorrhage, gastrointestinal perforation, cardiac failure, were low.

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In an other work, Boksteinet al., evaluated the AEs at a different dosage. They evaluated 20 patients with recurrent GBM treated with a dose of 5 mg/kg of Bevacizumab associated with 125 mg/m^2 irinotecan every 2 weeks. The AEs were mild and andpercentageses of vascular complication were low (68). Despite the limitations of anti-angiogenesis drugs in GBM, bevacizumab still represent an important therapeutic strategy to treat this cancer. Despite the aggressive management in the treatment of GBM (neurosurgical resection, radiation, and systemic therapy) its prognosis remains poor. Probably it is associated to a complex genomic heterogeneity of GBM. In particular in this review we considered some studies that showed a progress in the treatment of recurrent GMB. Despite this, there are important issues to be solve, for example the dose and the timing of bevacizumabtreatment. In addition, more studies are needed to better understand the biology of GMB and to identify the mechanisms of tumor resistance. Further studiesand more research are required to address the problem of the poor prognosis of GBM.

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