Efficacy and safety of bevacizumab for the treatment of glioblastoma (Review)

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Abstract. Glioblastoma (GBM) is the most common and devastating primary malignant intracranial tumor in adults. The current first-line treatment for patients with newly diagnosed GBM is surgical resection followed by radiotherapy plus concomitant and adjuvant temozolomide. This treatment protocol may prolong the survival period of the patient, however it is not curative and more effective therapeutic strategies are required. GBM is a type of highly vascularized tumor with increased expression levels of vascular endothelial growth factor (VEGF), which is a significant mediator of angiogenesis. Since angiogenesis is essential for tumor growth, anti-angiogenic therapies hold potential for the treatment of GBM, and targeting VEGF has demonstrated promising results in previous studies. Bevacizumab (BEV) is a recombinant humanized monoclonal antibody that inhibits VEGF and is approved by the US Food and Drug Administration as a monotherapy treatment for patients with recurrent GBM and is associated with manageable toxicity. Previous studies have demonstrated that BEV may be an effective treatment for recurrent GBM, with prolonged progression-free survival and overall survival, and maintained patient quality of life and functional status. The present review article briefly outlines the mechanism of action of BEV and summarizes the current literature and clinical trial research on the role of BEV for the treatment of patients with recurrent and newly diagnosed GBM.

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Contents

1. Introduction
2. Mechanism of action and pharmacokinetics
3. Efficacy of bevacizumab treatment for patients with recurrent glioblastoma
4. Efficacy of bevacizumab treatment for patients with newly diagnosed glioblastoma
5. Safety of bevacizumab treatment in patients with glioblastoma
6. Discussion

1. Introduction

Glioblastoma (GBM) is the most common type of primary intracranial tumors, with an annual incidence of 5/100,000 individuals (1,2). The current standard treatment for patients with newly diagnosed GBM is surgery followed by external beam radiation and concomitant temozolomide (TMZ) chemotherapy and an additional 6 cycles of TMZ administration (3). In spite of advances in diagnosis and therapy, the prognosis is still relatively poor with a median overall survival (OS) of 14.6 months and a 5-year survival rate of 9.8% following diagnosis (4). The majority of patients with GBM experience recurrent disease, with a median time to recurrence of 7 months (5). The prognosis of recurrent GBM is severe with a median progression-free survival (PFS) and OS of 2.5 and 7.5 months (6), respectively. Therefore, there is an urgent need for more effective therapeutic strategies for the treatment of patients with GBM.

Angiogenesis is the formation of new blood vessels from existing vasculature, characterized by endothelial cell migration and proliferation. This normal physiological response occurs in wound healing and following hypoxic exposure; however, for tumor cells in an increased proliferative state, new vasculature is also required to access oxygen and facilitate metastasis (7,8). The angiogenic switch is mediated by various pro-angiogenic factors, predominantly vascular endothelial growth factor (VEGF), which are released by tumor, stromal and endothelial cells, resulting in vessel growth and tumor expansion (9,10). Previous preclinical studies investigating the use of bevacizumab (BEV) in GBM models have detected normalization of mature blood vessels, microvascular regression, and the inhibition of new blood vessels being formed in tumors (11). A previous study demonstrated that BEV is capable of inhibiting the action of VEGF on its receptor, preventing the proliferation and migration of endothelial cells, which in turn downregulates tumor vascularization and results in tumor cell hypoxia and death (12).

GBM is one of the most vascularized human tumors (1), which highly expresses VEGF, a significant mediator of angiogenesis (13). BEV is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets VEGF, which was approved by the US Food and Drug Administration (FDA) as a single agent for the treatment of recurrent GBM (14). However the European Medicines Agency (EMA) rejected this instruction due to a lack of evidence. Largely for this reason, BEV is currently used as the standard treatment for recurrent GBM in the United States, but not in Europe; although, in many countries BEV is administered for off-label use as a monotherapy or in combination with irinotecan (CPT-11), which is a topoisomerase I inhibitor. Previous studies, including the AVAglio (15) and Radiation Therapy Oncology Group (RTOG) 0825 (16) double-blinded, placebo-controlled phase III studies investigated BEV as an addition to the standard treatment of radiotherapy (RT) plus concomitant and adjuvant TMZ in patients with newly diagnosed GBM. OS did not reach significance in both trials; however PFS favored BEV administration in both.

In the present review, the mechanism of action of BEV is briefly introduced, with the focus on providing an overview and evaluation of the efficacy and safety of BEV as a monotherapy or in combination with cytotoxic chemotherapy and/or RT for the treatment of patients with recurrent and newly diagnosed GBM.

2. Mechanism of action and pharmacokinetics

BEV is a recombinant humanized monoclonal IgG1 antibody with a molecular weight of 149 kDa. BEV is capable of binding to and neutralizing the biological effects of VEGF, which is an important regulator of pathologic and physiologic angiogenesis (13). VEGF binds to and activates its target receptors, VEGF receptor (R)-1 and VEFGR-2, leading to their tyrosine phosphorylation and a subsequent signal transduction cascade, which activates vascular endothelial cells, pro-survival activity and elicits mitogenic signals to promote angiogenesis (17). BEV reduces tumor angiogenesis by blocking the biological activity of VEGF, thereby preventing vasogenic brain edema and tumor growth.

In the majority of previous clinical trials, BEV administration was characterized by a limited central compartment volume (Vc), low clearance (CL), and a long elimination half-life. The Vc and CL correspond to an initial half-life of 1.4 days and a terminal half-life of ~20 days (18). In another previous study, the mean steady-state volume of distribution for BEV ranged from 50-60 ml/kg (dose range, 0.1-10 mg/kg), whereas the steady-state volume did not alter with increasing dosages of BEV (19). The majority of previous clinical trials administered 5-15 mg/kg BEV every 2-4 weeks; therefore, whether higher doses of BEV produce faster clinical efficacy than low doses remains unknown. Wong *et al* (20) performed a meta-analysis regarding the treatment of recurrent GBM with BEV, concluding that there was no dose-response effect.

3. Efficacy of bevacizumab treatment for patients with recurrent glioblastoma

BEV was initially assessed in recurrent and previously treated GBM in combination with CPT-11, which is a topoisomerase I inhibitor; the response rate (RR) for the patients with GBM in an initial retrospective study was 43% (21), promoting the investigation of BEV with CPT-11 in subsequent clinical trials. The first completed, prospectively designed, single agent, phase II trial of BEV and CPT-11 for recurrent GBM was conducted by Vredenburgh *et al* (22,23). The patients were divided into two groups, an initial group 23) which were treated with 10 mg/kg BEV plus CPT-11 every 2 weeks, and a second group of patients 12) which were administered 15 mg/kg BEV every 21 days and CPT-11 on days 1, 8, 22 and 29. In both groups, 340-350 mg/m^2 CPT-11 was administered to patients receiving enzyme-inducing anti-epileptic drug (EIAED) and 125 mg/m^2 was administered to patients who were not receiving EIAEDs. The initial cohort demonstrated a RR of 63% in 23 patients with a median OS and median PFS of 9.2 and 5.3 months, respectively (22). Among all 35 patients included in the study, the PFS rate at 6 months (PFS-6) was 46% (95% CI, 32-66%), the 6-month OS rate (OS-6) was 77% (95% CI, 64-92%); whereas the median PFS and median OS were 24 weeks (95% CI, 18-36 weeks) and 42 weeks (95% CI, 35-60 weeks), respectively (23). In addition, 57% of the patients (95% CI, 39-74%) demonstrated at least a partial response (PR), and the 4-year survival rate was demonstrated to be 11% in this trial (24).

Friedman *et al* (25) conducted a randomized noncomparative phase II clinical trial of BEV with and without CPT-11 in 167 patients with recurrent GBM. Patients were randomized into groups of either 10 mg/kg BEV monotherapy every 2 weeks 85) or BEV in combination with CPT-11 82). The CPT-11 dose was based on the patient's anticonvulsant intake; patients taking EIAED received 340 mg/m^2 and patients not taking EIAED received 125 mg/m^2. Patients treated with BEV monotherapy demonstrated a RR of 28.2% (31/82 patients; 97.5% CI, 18.5-40.3%), whereas the PFS-6 was 42.6% (97.5% CI, 29.6-55.5%), and the median PFS and median OS were 4.2 months (95% CI, 2.9-5.8 months) and 9.2 months (95% CI, 8.2-10.7 months), respectively. Combination therapy of BEV and CPT-11 (25,26) demonstrated a RR of 37.8% (31/85 patients; 97.5% CI, 26.5-50.8%), whereas the PFS-6 was 50.3% (97.5% CI, 36.8-63.9%) and the median PFS and median OS were 5.6 months (95% CI, 4.4-6.2 months) and 8.7 months (95% CI, 7.8-10.9 months), respectively.

Kreisl *et al* (27) conducted another single-institution prospective study of BEV involving 48 patients with recurrent GBM. All patients were administered 10 mg/kg BEV monotherapy every 2 weeks until disease progression was detected. Following disease recurrence, patients were treated with BEV in combination with 340 or 125 mg/m^2 CPT-11 every 2 weeks, depending on EIAED use. The RR for BEV monotherapy was 35% [1 complete response (CR); 16 PRs], whereas the PFS-6 was 29% (95% CI, 18-48%) and the OS-6 was 57%. The median

PFS and median OS were 16 weeks (95% CI, 12-26 weeks) and 31 weeks (95% CI, 21-54 weeks), respectively (27).

Based on the findings of these two clinical studies (25,27), in May 2009 the FDA granted accelerated approval of single agent BEV for the treatment of patients with GBM (28).

Retrospective analyses of data from additional studies supplied more evidence for the efficacy of BEV monotherapy or combination therapy with cytotoxic or targeted agents in patients with recurrent GBM. Previous studies evaluating the efficacy of BEV monotherapy for patients with recurrent GBM have demonstrated objective RR (PR plus CR), overall survival, PFS and PFS-6 rates of 28.2-43%, 7.2-12 months, 1.0-4.2 months and 20.9-42.6%, respectively, as calculated from statistical treatment of the data (25-27,29-33). Furthermore, BEV plus chemotherapy combination therapy increased RR and PFS (25,27), and additional studies of BEV in combination with cytotoxic agents including carboplatin, erlotinib, etoposide, fotemustine, CPT-11 and dose-intense daily TMZ for patients with recurrent GBM also demonstrated RR, OS, PFS and PFS-6 rates of 20-67.6%, 4.3-11.5 months, 2.5-7.6 months and 25-63.7%, respectively (Table I) (17).

Zhang *et al* (34) performed a meta-analysis to evaluate the efficacy and safety of BEV monotherapy 183) compared with BEV plus CPT-11 297) for the treatment of recurrent GBM. In the BEV group, the mean objective RR was 33.9% (95% CI, 18.1-52.1%), the PFS-6 was 38.8% (95% CI, 18.8-57.0%) and the median OS was 8.63 months (95% CI, 8.54-8.72 months). In the combined group, the mean objective RR was 45.8% (95% CI, 28.2-66.7%), the PFS-6 was 48.3% (95% CI, 25.4-54.3%) and the median OS was 8.91 months (95% CI, 8.69-9.13 months). The rates of discontinuation of treatment were 5.5 and 20.0%, respectively. Zhang *et al* concluded that patients in the BEV plus CPT-11 group demonstrated increased PFS-6 (P=0.046), objective RR (P=0.013) and discontinuation rates (P<0.001), as compared with the BEV monotherapy group. No significant difference in OS was detected between the groups (P=0.487) (34).

However, the EMA rejected the use of BEV for the treatment of patients with recurrent GBM, with one of the reasons being a lack of positive benefit-risk for BEV. Furthermore, the EMA did not consider the differences in objective RR to be noteworthy and concluded that the validity of this parameter as a surrogate endpoint for clinical benefit had not been established. In addition, the results were presented in terms of OS and PFS, which were difficult to interpret due to the lack of a randomized concurrent control (35). Furthermore, the use of contrast-enhanced magnetic resonance imaging may overestimate the RR (17); therefore, RR and PFS may not be optimal surrogate endpoints for anti-angiogenic treatment. Anti-VEGF treatment can reduce vascular permeability (17), which may also account for the radiographic improvement; however, this may not necessarily reflect tumor cell death. Therefore, the clinical relevance of these findings in predicting OS in patients with GBM following BEV monotherapy remains uncertain.

4. Efficacy of bevacizumab treatment for patients with newly diagnosed glioblastoma

With potential synergistic activity demonstrated by BEV in the treatment of recurrent GBM, BEV administration may also benefit patients with newly diagnosed GBM. The first phase II study investigating this was performed by Lai *et al* (36), who conducted an open-label, prospective, multicenter single-arm phase II study of BEV in combination with the standard treatment of RT plus concomitant and adjuvant TMZ in 70 patients with newly diagnosed GBM. All patients were treated with intravenous 10 mg/kg BEV every 2 weeks and 75 mg/m^2 TMZ was administered orally daily during standard RT (2.0 Gy fractions totaling 60.0 Gy). Following completion of RT, patients were placed on a maintenance phase of TMZ (150-200 mg/m^2 on days 1-5 starting every 28 days) plus 10 mg/kg BEV every 14 days until disease progression was evident or for a maximum of 24 months. The median OS was 19.6 months (95% CI, 6.1-23.3 months) and the median PFS was 13.6 months (95% CI, 11.1-16.5 months). Lai *et al* compared these findings with the results of the trial conducted by Stupp *et al* (3) (OS, 14.6 months; median PFS, 6.9 months) and by the University of California, Los Angeles (OS, 21.1 months; median PFS, 7.6 months). Lai *et al* concluded that patients treated with BEV and TMZ during and after RT demonstrated improved PFS without improved OS, as compared with the findings presented by Stupp *et al* and the findings of the University of California, Los Angeles trial (19). Additional studies are required in order to determine whether first-line administration of BEV improves survival, as compared with the use of BEV at recurrence.

Various other phase II studies have evaluated the efficacy of the addition of BEV for the treatment of patients with newly diagnosed GBM (Table II). Narayana *et al* (37) investigated 51 patients with newly diagnosed GBM treated with RT and concomitant TMZ alongside 10 mg/kg BEV every 2 weeks, initiated 4 weeks post-surgery. This regimen was followed by 6 cycles of adjuvant standard-dose TMZ therapy with 10 mg/kg BEV administered on days 8 and 22 of each 28-day cycle. PFS-6 and 12-month PFS (PFS-12) rates were 85.1 and 51%, respectively, whereas the OS rates at 12 months (OS-12) and 24 months (OS-24) were 85.1 and 42.5%, respectively. Furthermore, 19.6% of the patients (10/51 patients) experienced grade III/IV toxicity, and asymptomatic intracranial bleeding was observed in 5 patients; however, no treatment-related mortality was observed. Narayana *et al* concluded that the addition of BEV to conventional therapy in patients with newly diagnosed GBM appears to improve both PFS and OS in patients with newly diagnosed GBM, with tolerable toxicity (37).

Vredenburgh *et al* (38) conducted an upfront, phase II trial in patients with newly diagnosed GBM 75), which evaluated the addition of BEV to standard RT and daily TMZ administration followed by the addition of BEV and CPT-11 to adjuvant TMZ. BEV was administered at 10 mg/kg every 2 weeks and was initiated a minimum of 4 weeks post-craniotomy. Following 2 weeks of RT, the patients began 6 to 12 cycles of 5-day TMZ with BEV and CPT-11 administration every 2 weeks. The median OS was 21.2 months (95% CI, 17.2-25.4 months), and 65% of the patients survived to 16 months (95% CI, 53.4-74.9%). The median PFS was 14.2 months (95% CI, 12-16 months). Vredenburgh *et al* concluded that this therapeutic regimen may improve the efficacy of treatment for patients with newly diagnosed GBM, as compared with historical controls (39). After 1 year Vredenburg *et al* reported on 125 patients with

Table I. Efficacy of bevacizumab alone or in combination with cytotoxic agents in recurrent glioblastoma.

			Response rate (%)		PFS		OS		
Author, year	Treatment regimen	Patients (n)	CR	PR	Median (months)	PFS-6 (%)	Median (months)	OS-6 (%)	(Ref.)
Stark-Vance *et al*, 2005	BEV + CPT-11	11	5	38	N/A	30	9	N/A	(21)
Vredenburgh *et al*, 2007	BEV + CPT-11	23	4.3	56.5	5.3	38	9.23	72	(22)
Vredenburgh *et al*, 2007	BEV + CPT-11	35	57	N/A	5.5	46	9.7	77	(23)
Friedman *et al*, 2009	BEV	85	28.2	N/A	4.2	42.6	9.2	N/A	(25)
Cloughesy *et al*, 2010	BEV + CPT-11	82	37.8	N/A	5.6	50.3	8.7	N/A	(26)
Kreisl *et al*, 2009	BEV and BEV + CPT-11	48	35*	N/A	3.7	29	7.2	57	(27)
Chamberlain *et al*, 2010	BEV	50	42	N/A	1	42	8.5	N/A	(29)
Raizer *et al*, 2010	BEV	50	N/A	N/A	2.7	25	6.5	54	(30)
Kreisl *et al*, 2011	BEV	30	N/A	43	2.93	20.9	12	N/A	(31)
Nagane *et al*, 2012	BEV	29	27.6	N/A	3.3	33.9	10.5	N/A	(32)
Hofer *et al*, 2011	BEV	176	N/A	N/A	N/A	N/A	8.3	N/A	(33)
Norden *et al*, 2008	BEV + CT	33	34	N/A	4	42	8.2	65	(41)
Gilbert *et al*, 2011	BEV + CPT-11	57	26.3	N/A	N/A	37	N/A	N/A	(42)
Gil *et al*, 2012	BEV + CPT-11	92	56	N/A	5.1	42	8.8	66	(43)
Zuniga *et al*, 2009	BEV + CPT-11	37	5.4	62.2	7.6	63.7	11.5	78	(44)
Quant *et al*, 2009	BEV + CT	35	0	23	N/A	N/A	N/A	N/A	(45)
Poulsen *et al*, 2009	BEV + CPT-11	52	30	N/A	5	40	6.9	N/A	(50)
Raval *et al*, 2007	BEV + CPT-11	20	47.3	N/A	4.2	25	7	55	(51)
Bokstein *et al*, 2008	BEV + CPT-11	19	10.5	36.8	4.2	25	7.0	55	(52)
Taillibert *et al*, 2010	BEV + CPT-11	224	N/A	N/A	4.8	39.4	8.3	N/A	(53)
Keyrouz *et al*, 2010	BEV + CPT-11	30	63	N/A	5	33.4	8.7	N/A	(54)
Pope *et al*, 2006	BEV + CPT-11 or etoposide	14	0	50	N/A	N/A	N/A	N/A	(55)
Nghiemphu *et al*, 2009	BEV + CT	44	N/A	N/A	4.25	41	9	N/A	(56)
Desjardins *et al*, 2012	BEV + TMZ	32	28	N/A	3.7	19	8.5	N/A	(57)
Verhoeff *et al*, 2010	BEV + TMZ	15	20	N/A	2.5	17	4.3	N/A	(58)
Soffietti *et al*, 2011	BEV + Fotemustine	54	48.1	N/A	5.2	44	9.1	N/A	(59)
Trevisan *et al*, 2010	BEV + Fotemustine	59	43.4	N/A	N/A	32	6.7	N/A	(60)
Hasselbach *et al*, 2010	BEV + Cetuximab	32	34	N/A	3.8	30	7.2	N/A	(61)
Shapiro *et al*, 2013	BEV + HFSRT	24	N/A	N/A	7.5	N/A	12.2	N/A	(62)
Sathornsumetee *et al*, 2010	BEV + Erlotinib	24	48	N/A	4.2	28	10	N/A	(63)
Niyazi *et al*, 2012	BEV + RT	20	N/A	N/A	8	N/A	12.1	N/A	(64)
Hundsberger *et al*, 2013	BEV + RT	10	N/A	N/A	5.7	N/A	8.4	N/A	(65)
Gutin *et al*, 2009	BEV + RT	20	50	N/A	7.3	60	12.5	N/A	(66)

*Macdonald criteria. PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; PFS-6, 6-month PFS rate; OS-6, 6-month OS rate; BEV, bevacizumab; CPT-11, irinotecan; N/A, not available; CT, chemotherapy; HFSRT, hypofractionated stereotactic radiotherapy; RT, radiotherapy.

Table II. Efficacy of bevacizumab alone or in combination with cytotoxic agents in newly diagnosed glioblastoma.

			PFS			OS			
Author, year	Treatment regimen	Patients (n)	Median (months)	PFS-6 (%)	PFS-12 (%)	Median (months)	OS-6 (%)	OS-12 (%)	(Ref.)
Gilbert *et al*, 2014	RT + TMZ + BEV	320	10.7	80	44	15.7	87	67	(15)
	RT + TMZ	317	7.3	54	31	16.1	86	65	
Chinot *et al*, 2014	RT + TMZ + BEV	458	10.6	79	40	16.8	93	72.4	(16)
	RT + TMZ	463	6.2	50	27	16.7	90	66.3	
Lai *et al*, 2011	RT + TMZ + BEV	70	13.6	88	N/A	19.6	N/A	N/A	(36)
Narayana *et al*, 2012	RT + TMZ + BEV	51	13	85.1	51	23	N/A	85.1	(37)
Vredenburgh *et al*, 2011	RT + TMZ + BEV + CPT-11	75	14.2	N/A	62.7	21.2	N/A	78.7	(38)
Vredenburgh *et al*, 2012	RT + TMZ + BEV + CPT-11	125	13.8	87.2	64	N/A	94	82	(39)
Hainsworth *et al*, 2012	RT + TMZ + BEV + everolimus	68	11.3	N/A	N/A	13.9	N/A	N/A	(67)
Herrlinger *et al*, 2013	RT + BEV + CPT-11	N/A	N/A	N/A	N/A	16.6	N/A	N/A	(68)
	RT + TMZ	N/A	N/A	N/A	N/A	14.8	N/A	N/A	

PFS, progression-free survival; OS, overall survival; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; OS-6, 6-month OS rate; OS-12, 12-month OS rate; RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab; N/A, not available; CPT-11, irinotecan.

newly diagnosed GBM that were treated with standard external beam irradiation plus concurrent TMZ followed by adjuvant BEV, TMZ, and CPT-11 (39); the PFS at 6 months, 1 year and 2 years was 88, 64 and 16%, respectively; whereas OS was 94, 82 and 44%, respectively.

Previously, two large randomized phase III trials evaluated the role of BEV in combination with TMZ and RT in patients newly diagnosed with GBM. The first, entitled RTOG 0825 (15), was a randomized phase III double-blind, placebo-controlled trial sponsored by RTOG, including 637 patients enrolled into BEV or placebo plus standard RT and TMZ groups following surgery for GBM. During maintenance therapy, patients were treated with BEV or placebo plus TMZ until disease progression was evident or the toxicity became intolerable (Fig. 1A). In the patients who received BEV, the median OS was demonstrated to be 15.7 months, as compared with 16.1 months in the patients who received placebo. The hazard ratio for mortality in the BEV group was 1.13. The median PFS in the BEV and placebo groups was 10.7 months and 7.3 months, respectively; and the hazard ratio for progression or mortality was 0.79 (15). Another randomized phase III double-blind, placebo-controlled trial, was sponsored by Hoffman-La Roche, entitled the AVAglio (16) trial (Fig. 1B). A total of 921 patients were enrolled following surgery for GBM and were subsequently randomized into BEV or placebo groups plus standard RT and TMZ followed by TMZ and treatment maintenance with BEV or placebo until disease progression was demonstrated (Fig. 1B). OS rates at 1 year following treatment with BEV or placebo were 72.4 and 6.3% (P=0.049); whereas the 2-year follow-up OS rates were 33.9 and 30.1% (P=0.24), respectively. The median PFS rates in the BEV and placebo groups were 10.6 and 6.2 months, respectively, with a hazard ratio for progression or mortality of 0.64 (95% CI, 0.55-0.74; P<0.001) (16). Notably, both trials concluded that the addition of BEV standard treatment did not improve OS in patients with newly diagnosed GBM; however, the median PFS was increased in the BEV group, as compared with the placebo group in both trials.

5. Safety of bevacizumab treatment in patients with glioblastoma

Although BEV is an enticing agent for the treatment of GBM, it has well-recognized complications (40). Common and significant adverse events of all grades that have been associated with BEV monotherapy for patients with recurrent GBM include fatigue (32-63%), headache (20-36.9%), hypertension (12.5-29.8%), hemorrhage (overall, 27.4%), thromboembolic event (8-12.5%), and proteinuria (2.1-10%) (25,27,29,30). In previous studies, the most common adverse events detected following treatment with a combination of BEV and cytotoxic agents were hemorrhage (overall, 17.6-40.5%), fatigue (11.4-75.9%), hypertension (3.5-26.6%), and diarrhea (74.7%) (23,25,41-45).

The safety of BEV when combined with TMZ and RT in the standard chemoradiotherapy schedule for patients with newly diagnosed GBM was evaluated in the RTOG 0825 and AVAglio studies. In the AVAglio study, adverse events of all grades were demonstrated in 98.5% of the patients who received BEV treatment, as compared with 96.0% in the

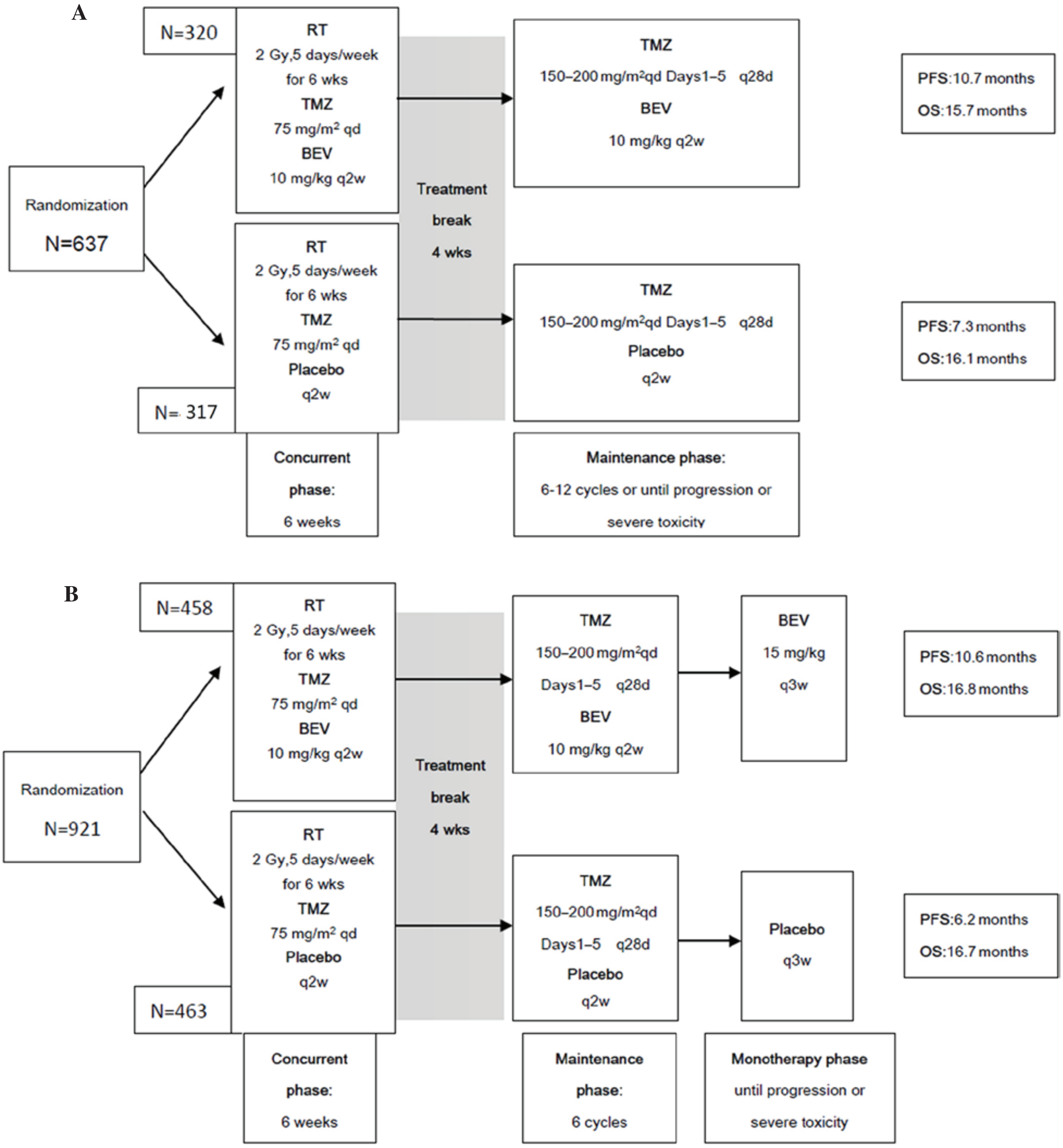

Figure 1. (A) RTOG 0825 study design. (B) AVAglio study design. RTOG, Radiation Therapy Oncology Group; RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab; PFS, progression-free survival; OS, overall survival; qd, once daily; q2w, every 2 weeks; q28d, every 28 days; q3w, every 3 weeks.

placebo group. Adverse events of ≥grade 3 were demonstrated in 66.8 and 51.3% of patients, respectively. The rate of serious adverse events was 38.8% in the BEV group, as compared with 25.6% in the placebo group, and adverse events ≥grade 3 that are often associated with BEV were 32.5 vs. 15.8% (16). Similarly, the RTOG 0825 study (15) concluded that the incidence of adverse events was increased in the BEV group, as compared with the placebo group; and the most common adverse events detected were hypertension, hemorrhage, proteinuria, and thromboembolic events (Table III).

Hypertension, which was demonstrated to be the most common adverse event in patients treated with BEV, may lead to hemorrhage, thromboembolic event, cerebral ischemia and proteinuria. VEGF normally increases endothelial transcription of nitric oxide (NO) synthase, leading to the increased production of NO, which is a potent vasodilator. Anti-VEGF agents, including BEV, are capable of decreasing NO production, which may induce vasoconstriction and result in hypertension. At the renal level, this vasoconstriction induces sodium retention which may contribute to hypertension (46). Furthermore, anti-VEGF agents may reduce the concentration of microvascular beds, a phenomenon known as 'rarefaction', thus increasing systemic vascular resistance and blood pressure (46). A previous meta-analysis of clinical trials that randomized patients with numerous tumor types concluded that there was a significant dose-dependent increase in the risk of hypertension in patients

Table III. Major adverse events following bevacizumab treatment with and without chemotherapeutics in patients with glioblastoma.

	Bevacizumab alone		Bevacizumab with chemotherapeutics		Bevacizumab with temozolomide and RT	
Toxicities	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue	32-63	3.6-55	11.4-75.9	4-8.9	20	7.4
Headache	20-36.9	18	32.9	0	N/A	N/A
Hypertension	12.5-29.8	8.3	3.5-26.6	1.3-2	39.3	11.3
Thromboembolic event	8-12.5	6-9	5-11.4	4	14.1	12.6
Proteinuria	2.1-10	N/A	2.5-5.7	1.3	15.6	5.4
Wound dehiscence	4-6	2.4	3.6-5.5	1.3-5.5	6.9	3.3
Hemorrhage						
Overall	27.4	0	17.6-40.5	2.5	37.1	1.3
Intracranial	2.4	0-4	2.9-3.8	1.3	3.3	2.0
Bowel perforation	2.1-9	2.1	2.5	2.5	1.7	1.1
Anemia	10	N/A	N/A	N/A	N/A	N/A
Neutropenia	2.4	1.2	7	4-15	N/A	N/A
Diarrhea	21.4	1.2	74.7	5.1-6	N/A	N/A

Selected adverse events reported in large (≥35 patients) phase II or III studies and retrospective analyses. Bevacizumab alone (25,27,29,30). Bevacizumab with chemotherapeutics (23,25,41-45) for recurrent glioblastoma. Bevacizumab plus temozolomide and RT (16) for newly diagnosed glioblastoma. RT, radiotherapy.

with tumors following treatment with BEV (47). Standard schedules for the treatment of BEV-associated hypertension are yet to be elucidated. Some scholars have suggested that the general principles of hypertension management should be followed (40); however, this theory lacks sufficient evidence.

Proteinuria is a characteristic adverse event often exhibited in patients following treatment with anti-VEGF agents. A previous meta-analysis demonstrated that the incidence of grade III/IV proteinuria in patients treated with BEV was 2.2% (RR, 4.8) (48), and a significant dose-dependent increase in the risk of proteinuria was detected in patients with tumors who received BEV (47). The incidence of BEV-related proteinuria appears to be lower in patients with GBM, as compared with other cancers. A previous randomized noncomparative phase II trial demonstrated grade 1 proteinuria in only 4% of patients, and grade 3 proteinuria in just 1 of the 167 patients (25). Why proteinuria is less common in patients with brain tumors has yet to be examined, however it may be associated with a shorter median duration of therapy.

For patients with malignant brain tumors, intracranial hemorrhage may be a life-threatening event. Anti-VEGF agents inhibit the proliferation and survival of vascular endothelial cells, particularly in tissues with a high dependence on VEGF, leading to dysregulation of the coagulation cascade, injury to the mucosal membrane of the airway, damage to the tumor-infiltrated vascular wall as a consequence of an antitumor effect, decreased matrix deposition in the supporting layers of the vessels, and occasionally, treatment-induced thrombocytopenia. All of these events may be associated with the mechanisms of hemorrhage (15). Although the rate of hemorrhage has previously been demonstrated to be as high as 40% (25), the majority are low-grade systemic hemorrhages, including epistaxis; and life-threatening intracranial hemorrhages have been demonstrated in <3.8% of patients treated with BEV (Table III).

Thromboembolic events, including venous thromboembolism and arterial thromboembolism, are also common in GBM treated with anti-VEGF agents. However, due to the variable and often high rates of venous thromboembolic events demonstrated in patients with GBM (41,49), it is often difficult to determine whether the reported incidence of venous thromboembolic events exceeds the anticipated rate normally associated with the disease. Conversely, as arterial thromboses are uncommon in patients with GBM, arterial thromboembolism is considered to be directly associated with anti-angiogenic therapy, and patients who develop arterial thrombosis should cease anti-angiogenic treatment. Treatment of arterial thrombosis should be guided by the disease process, recognizing that the optimal management of stroke, myocardial infarction and peripheral vascular occlusion may be distinct (41).

In addition to common toxicity, other common adverse events detected following BEV treatment in patients with recurrent or newly diagnosed GBM include fatigue, diarrhea, headache and impaired wound healing. The majority of these adverse events appear to reflect the destruction of VEGF in normal organs and tissues induced by the on-target, class-specific actions of anti-VEGF agents. These adverse events must be monitored in order to guarantee the basic quality of life of patients treated with BEV.

6. Discussion

Whether it is used as a single-agent or in combination with other cytotoxic agents, BEV has been demonstrated to be an effective therapy with tolerable toxicity for the treatment of patients with GBM. As compared with historical controls of patients with recurrent GBM, BEV-related treatment prolonged PFS and OS (25,27). Double-blinded, placebo-controlled phase III studies concluded that the addition of BEV to the first-line treatment improved PFS in patients with newly diagnosed GBM (15,16). Hypertension and proteinuria were characteristic adverse events in the course of treatment. Various life-threatening adverse events, including intracranial hemorrhage and thromboembolic events were demonstrated in patients with GBM; however, the fatal event rate was low and these events have also been associated with GBM itself. However, problems remain regarding the role of BEV in the treatment of GBM.

Firstly, BEV may be used as monotherapy or in combination with chemotherapy and/or RT in the treatment of patients with recurrent GBM. Whether combination therapy with BEV is superior to BEV as a single agent in the treatment of patients with recurrent GBM remains uncertain. If combination therapy with BEV proved superior to BEV monotherapy, the optimal therapeutic partner has yet to be identified.

Secondly, there are no clear standards for the optimal dose and duration of BEV treatment for patients with recurrent GBM. The majority of clinical trials have used 5-15 mg/kg BEV every 2-4 weeks; however it is yet to be elucidated whether higher doses of BEV improve clinical efficacy. Furthermore, it remains unclear whether BEV dosage should be adjusted according to the patient's age, the degree of glioma malignancy, the progress of the disease throughout the process of treatment, or whether the original treatment should be changed or terminated according to the patient's toxicity tolerance.

Thirdly, further research is required into how to manage the adverse events associated with BEV treatment. Toxicity is inevi›, however reducing toxicity may improve the quality of life of the patients. Whether the management of adverse events associated with BEV should or should not follow the general principles is still uncertain, and further studies are required.

In conclusion, the main issue with BEV therapy is the lack of biomarkers and genetic models to identify patients who may benefit from BEV treatment (17). It is hoped that further studies investigating biomarkers and genetic patterns will identify patients who may benefit from treatment with BEV or other anti-angiogenic agents, and these studies may also suggest other treatable cellular targets that may be critical to the advancement of treatment for patients with GBM (17). Therefore, more randomized controlled trials are required for patients with GBM in order to provide definitive answers on the optimal therapeutic partner, dose and length of treatment.

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