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REVIEW

Bevacizumab for the Treatment of Glioblastoma

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Abstract: Glioblastoma (GBM) or grade IV glioma is the most common primary brain tumor in adults. Standard treatment median overall survival (OS) is only 14–15 months and less than 10% of patients will survive 5 years after diagnosis. There is no standard treatment in recurrent GBM and OS ranges from 3 to 9 months. GBM is 1 of the most vascularized human tumors and GBM cells produce vascular endothelial growth factor (VEGF). Bevacizumab, a humanized monoclonal antibody against VEGF, has demonstrated activity in vitro and in phase II trials in relapse, as well as in 1 phase III trial as first line therapy. Bevacizumab also improves quality of life for patients suffering GBM. This paper reviews the mechanism of action of bevacizumab, its metabolism and pharmacokinetic profile. It summarizes the clinical studies in recurrent and newly diagnosed GBM, its potential side effects and complications and its place in therapy.

Keywords: glioblastoma, bevacizumab, VGEF, chemotherapy, antiangiogenesis

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Introduction

Glioblastoma (GBM), or grade IV glioma according to the World Health Organization classification, is the most common primary brain tumor in adults. Standard treatment consists of maximal surgical resection followed by radiotherapy (RT) plus concomitant and adjuvant temozolomide.[1] However, median overall survival (OS) is only 14–15 months and less than 10% of patients will survive 5 years after diagnosis.[2] When relapse or progression occurs after RT and temozolomide, there is no standard treatment and OS ranges from 3 to 9 months. The median progression free survival (PFS) is estimated at 10 weeks, and the radiological response rate (RR) is usually less than 4%–16%.[3–5]

Angiogenesis is the normal process by which new vessels are formed from pre-existing vasculature. It is a physiological development that occurs in wound healing and when cells are exposed to hypoxia. However, tumor cells in an increased proliferative state also need new vasculature, as a greater supply of oxygen is needed in order to grow.[6,7] The angiogenic switch is mediated by the release of a wide variety of proangiogenic factors, mainly vascular endothelial growth factor (VEGF), and by endothelial, stromal, and tumor cells, which cause vessel growth and tumor expansion.[8,9]

It is known that GBM is one of the most vascularized human tumors[10] and that GBM cells produce proangiogenic factors, including VEGF. VEGF consists of a family of 5 glycoproteins named VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor. They bind with their corresponding tyrosine kinase receptors (VEGFR-1, VEGFR-2, and VEGFR-3), activating a downstream signal that results in the development of angiogenesis, increased vascular permeability, and lymphangiogenesis. Of the 5 glycoproteins, VEGF-A (or simply VEGF) plays the most important role in tumor angiogenesis, as elevated levels in patients with cancer, specifically breast, lung, colon, uterus, and ovary cancers, confer a worse prognosis.[11,12]

Bevacizumab, a humanized monoclonal antibody against VEGF, was granted accelerated approval by the United States Food and Drug Administration (FDA) as a single agent for the treatment of recurrent GBM. However, the European Medicines Agency (EMA) rejected this indication due to a lack of evidence. For this reason, bevacizumab is being used as the standard treatment for recurrent GBM in the United States but not in Europe, although in many countries bevacizumab is administered for off-label use, as a single agent or combined with irinotecan. Very recently, results of a phase III study of bevacizumab added to standard treatment of RT plus concomitant and adjuvant temozolomide in newly diagnosed GBM showed a significantly increased in PFS.

The purposes of this review are first to analyze the biological basis for the use of bevacizumab and its metabolism and pharmacokinetic profile, second to review efficacy and safety data in reported phase II–III clinical trials, and finally to discuss its current place in therapy.

Mechanism of Action

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody (93% human and 7% murine sequences) with a molecular weight of 149 kDa. Bevacizumb selectively binds, with high affinity, to all isoforms of human VEGF, and it neutralizes VEGF's biologic activity through steric blocking of the binding of VEGF to its receptors VEGFR-1 and VEGFR-2, on the surface of endothelial cells. Receptor activation normally induces their tyrosine phosphorylation and the subsequent series of signal transduction events elicit mitogenic and pro-survival activity signals for the vascular endothelial cells. Bevacizumab is composed of a human immunoglobulin G1 and 6 framework regions of a murine monoclonal antibody that binds to VEGF.[13]

Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. This is located in a nutrient medium containing the antibiotic gentamicin. Bevacizumab is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at $\leq$0.35 ppm.[14] Bevacizumab was the first anti-VEGF therapy to be approved by the FDA, in 2004, and by the EMA, in 2005, for the treatment of metastatic colorectal cancer in combination with cytotoxic chemotherapy.[15] Since then, it has been approved by the FDA for the treatment of advanced non-small cell lung cancer,[16] metastatic renal cell carcinoma,[17] metastatic breast cancer[18] and advanced ovarian carcinoma.[19]

It is known that GBM is one of the most vascularized human tumors[10] and that GBM cells

produce a wide variety of proangiogenic factors, including VEGF. VEGF serves a particularly critical role for both angiogenesis and regulation of vascular permeability of the blood-brain barrier. It increases vascular permeability and produces peritumoral edema, which is one of the causes of serious morbidity suffered by these patients. Bevacizumab binds VEGF and prevents the interaction of VEGF with target receptors VEGFR-1 and VEFGR-2 on the surface of endothelial cells. Neutralizing the biological activity of VEGF reduces tumor angiogenesis, thereby inhibiting tumor growth and vasogenic brain edema. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumor activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.[20]

Pharmacokinetics

The pharmacokinetic (PK) data for bevacizumab are available from several clinical trials in patients with solid tumors. In all clinical trials, bevacizumab was administered as an intravenous (IV) infusion. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes,[13] which, in case of good tolerance, can be reduced to 60 minutes in second infusions and 30 minutes in third and later infusions.

Published kinetic data are mainly derived from 2 phase I studies.[21,22] In the first study, the antibody was administered alone as a weight-based dose ranging from 0.1 mg/kg to 10 mg/kg in groups of 4–5 patients.[21] The clearance (CL) was low (around 0.16 mL/min) and stable at the therapeutic range of 1–10 mg/kg. In the second study, bevacizumab was combined with various anticancer drugs (doxorubicin, carboplatin plus paclitaxel, 5-fluorouracil plus folinic acid) and was administered at the dose of 3 mg/kg weekly, in 12 patients.[22] The terminal half-life was estimated to be 13 days.

In a meta-analysis of 8 clinical trials, including 4,629 bevacizumab infusions from 491 patients with solid tumors who received 1–20 mg/kg at a dosing frequency ranging from weekly to every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (half-life range was 11 to 50 days) for both men and women.[23] The analysis also reported a central compartment volume of distribution (V_c) of 2.39 L for a typical female and 3.29 L for a typical male, which is the range that has been described for IgGs and other monoclonal antibodies. Body weight and gender were the most significant covariates to explain interpatient variability for CL and V_c. After correcting for body weight, men have a 26% faster CL than women[23] and male patients had a larger V_c (>20%) than female patients.[13] Nevertheless, this result has no impact on the current dosage (5–10 mg/kg man or woman) according to the official labeling. In this meta-analysis there was no significant difference in the PK of bevacizumab in relation to age (the median age was 59 years with 5th and 95th percentiles of 37 and 76 years, respectively).[23] Bevacizumab CL was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumor burden when compared with the typical patient with median values of albumin and tumor burden.

The bevacizumab distribution pattern was consistent, with the tissue distribution of a humanized IgG1 monoclonal antibody.[24] The distribution of bevacizumab was limited to the tumor vasculature, with minimal extravascular distribution.[25] The typical value for peripheral volume (V_p) was 1.69 L and 2.35 L for female and male patients, respectively, when bevacizumab was co-administered with anti-neoplastic agents.

Results obtained from 2 phase II studies including 69 patients suggest that minimum steady state concentrations (determined at 3 months) are similar when bevacizumab is given at 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks.[26]

Assessment of bevacizumab metabolism and elimination in rabbits following a single IV dose of ^{125}I-bevacizumab suggested that its metabolic profile was similar to that expected for an endogenous IgG1 molecule; elimination is primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely on elimination through the kidneys or liver. Binding of the IgG1 to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.[14,21]

Overall, in all clinical trials, bevacizumab behavior was characterized by a low CL, a limited V_c, and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be

maintained with a range of administration schedules (such as 5–10 mg/kg once every 2 or 3 weeks).

Efficacy at Tumor Recurrence

The first documented use of bevacizumab in patients with GBM was a small series of patients with recurrent GBM treated by Stark-Vance.[27] She used bevacizumab 5 mg/kg plus irinotecan 125 mg/m^2 every 2 weeks and showed activity in recurrent GBM (see Table 1). These data were presented in an abstract at the 2005 meeting of the European Association of Neuro-Oncology (EANO) and they opened the door to clinical trials of bevacizumab for the treatment of recurrent GBM. Another short retrospective study using bevacizumab 10 mg/kg plus irinotecan 125 mg/m^2 every 2 weeks confirmed this activity in RR, defined as decreased contrast enhancement on the Magnetic Resonance Image (MRI).[28]

The first phase II study with the use of bevacizumab at 10 mg/kg plus irinotecan 125 mg/m^2 or 340 mg/m^2 for patients on enzyme-inducing antiepileptic drugs (EIAEDs) in recurrent malignant glioma showed an RR of 61% in 23 patients.[29] The same authors published a subsequent second cohort of patients using bevacizumab 15 mg/kg and irinotecan 125 mg/m^2 or 340 mg/m^2 for patients on EIAEDs at days 1, 8, 22 and 29.[30] They reported an RR of 57% and a PFS at 6 months of 38%. However PFS and RR might not be optimal endpoints for anti-angiogenic treatment because the use of contrast-enhancement MRI may overestimate the RR. Anti-VEGF treatment can reduce vascular permeability, which can also account for the radiographic improvement, but this may not necessarily reflect tumor cell death. Decreased enhancement could be because of both tumor cell death and reduction in vascular permeability. Thus, a more precise radiological measurement of treatment response is needed; for this reason, it is essential to include the entire FLAIR signal abnormality in T2 weighted MRI evaluation for measuring response. The recently published radiology assessment in neurooncology (RANO) criteria attempted to improve upon the MacDonald response criteria and to recognize post-bevacizumab radiologic changes that confound interpretation.[31] Other methods like PET scanning with different radioisotopes such as ^{18}F-fluorothymidine, metionine, thallium, amino acids, and glucose could be used as an imaging biomarker. However, this technique measures the activity of a tumor mass, reducing PET signature but not

Table 1. Efficacy results from studies of bevacizumab alone or plus irinotecan in recurrent GBM.

Author	n	Study	Treatment	OS, months (95% CI)	6 m-OS, % (95% CI)	PFS, months (95% CI)	6 m-PFS, % (95% CI)	RR, % (95% CI)
Stark-Vance[27]	11	Retrospective	Bev 5 + CPT	9	NR	NR	30	42
Norden[28]	33	Retrospective	Bev 10 + CT	NR	65	4	42	34
Vrendenburgh[29]	23	Phase II	Bev10 + CPT	9.6 (8.1–13.9)	72 (58–89)	5.5 (4.1–8.3)	30 (16–57)	61 (39–74)
Friedman[32]	82	Phase II	Bev10 + CPT	8.7 (7.8–10.9)	NR	5.6 (4.4–6.2)	30 (16–57)	37.8 (26.5–50.8)
	82	Phase II	Beva 10	9.2 (8.2–11.8)	NR	4.2 (2.9–5.8)	50.3 (36.8–63.9)	28.2 (18.5–40.3)
Kreisl[34]	48	Phase II	Beva 10	7.2 (5.2–13.5)	57 (44–75)	4 (3–6.5)	29 (18–48)	35 (10.9–31–3)
Gil[36]	92	Retrospective	Bev10 + CPT	8.8 (7–10.6)	66 (55.5–76)	5.1 (4.4–5.9)	42 (32–52	56 (44.7–67)
Zuniga[37]	37	Retrospective	Bev10 + CPT	11.5 (8.3–15.6)	78 (60.8–88.4)	7.6 (4.8–10.5)	64 (45.7–77.1)	67.5 NR
Poulsen[38]	52	Retrospective	Bev10 + CPT	6.9 (3.9–9.1)	NR	5 (4–7)	40 (16–67)	30 (14–57)
Nghiemphu[39]	44	Retrospective	Bev10 + CPT	9	NR	4.2	41	NR
Bokstein[56]	20	Retrospective	Bev 5 + CPT	7 (1.7–16)	55	4.2 (0.7–10.5)	25	47.3

Abbreviations: Bev, bevacizumab; CR, complete response; CT, chemotherapy; CPT, irinotecan; GBM, glioblastoma; NR, not reported; OS, overall survival; PR, partial response; PFS, progression free survival; RR, response rate.

necessarily eliminating tumor cells. Therefore, the clinical relevance of these findings to predict OS in patients with GBM who are treated with bevacizumab still remains in doubt.

OS is considered the most important parameter in assessing the efficacy of any treatment protocol. There are no results of trials that directly compare temozolomide or nitrosourea treatment with bevacizumab in recurrent disease, but based on historical controls, bevacizumab seems to be superior. A phase II randomized non-comparative trial, carried out in a series of 167 patients with first or second relapse of GBM, assigned these patients to receive 10 mg/kg of bevacizumab every 2 weeks. Alone or in combination with irinotecan 125 mg/m^2 or 340 mg/m^2 if EIAEDs were used.[32] Patients treated with bevacizumab monotherapy had an RR of 28% and PFS-6 of 43%, whereas those treated with the combination therapy had an RR of 38% and PFS-6 of 50%. The median OS was 9.2 months in the group treated with bevacizumab alone and 8.7 months in the group treated with the combination. An update of this series was reported with a median OS of 8.9 months (95% CI, 7.9–11.9) with the combination of bevacizumab plus irinotecan and 9.3 months (95% CI, 8.2–11.8) with bevacizumab alone followed by the combination at progression.[33]

Another single arm, single-institution study included 56 patients with recurrent GBM. All patients were treated with bevacizumab 10 mg/kg every 14 days alone until progression. Irinotecan was added after progression. For bevacizumab alone, the RR was 35% and the 6-month OS was 57%.[34] On the basis of the results of these 2 clinical trials, the FDA approved bevacizumab, along with temozolomide, in May 2009 for the treatment of GBM that progresses to RT.[35] In contrast, the EMA did not approve bevacizumab as second-line treatment because of a lack of scientific evidence. Currently, bevacizumab is administered in Europe in some centers for off-label use.

Results of the Grupo Español de Neurooncología (GEINO) protocol were recently published. 13 Spanish hospitals participated in that protocol and 130 patients with recurrent malignant glioma were included, 91 with GBM. Treatment consisted of bevacizumab 10 mg/kg plus irinotecan 125 mg/m^2 (or 340 mg/m^2 if EIADs) every 2 weeks for a maximum of 1 year. The primary endpoint of the study was OS. The median OS for GBM was 8.8 months (95% CI: 5.1–17.3). The 6-month OS was 66 (95% CI: 55.5–76), the median PFS was 5.1 months (95% CI: 4.4–5.8), the 6-month PFS was 42% (95% CI: 32–52), and RR was 56% (95% CI: 44.7–67).[36] Other retrospective studies using the same schedule have shown similar results (see Table 1).[37,38]

Another retrospective review compared a series of 44 patients treated with bevacizumab 10 mg/kg plus irinotecan 125 mg/m^2 (or 340 mg/m^2 if EIADs) every 2 weeks for recurrent GBM with a series of 79 patients who were not treated with bevacizumab at the same institution. Authors compared PFS and OS between the 2 groups, and performed a subgroup analysis based on age and performance status. They found a significant improvement in PFS (P = 0.01) and OS (P = 0.04) in favor of the group treated with bevacizumab.[39]

Moreover, bevacizumab has been shown to decrease both tumoral and peritumoral edema in patients with GBM, thereby reducing the requirement for chronic corticosteroid use. Several studies have reported that corticosteroid dose reductions were feasible in a range of 33% to 72% of patients with recurrent GBM who were taking dexamethasone when bevacizumab treatment started.[27,28,32,34,36,40] Patients who did not receive corticosteroids at the baseline of the BRAIN study continued without receiving corticosteroids in more than 75% of cases in the bevacizumab-alone arm and more than 65% of cases in the bevacizumab plus irinotecan combination arm. In patients on steroids at baseline, 54% were able to reduce their dexamethasone doses during the course of treatment.[40] The ability of bevacizumab-based therapy to reduce corticosteroid usage is an important benefit, as chronic corticosteroid use in patients with GBM is associated with significant morbidity and numerous side effects, including a cushingoid pattern of weight gain, hyperglycemia, skin fragility and bleeding, myopathy, lymphopenia, infection, and thromboembolism.

In contrast with adult patients, no sustained responses were observed in a small phase II study with eight pediatric patients diagnosed with recurrent GBM.[41]

As a result of the debate about the value of adding irinotecan to bevacizumab therapy, the identification of an alternative partner for bevacizumab has been an active area of research in recent years. Bevacizumab in

combination with other cytotoxic drugs or targeted agents both in newly diagnosed and recurrent GBM has been tested in phase II trials. Trials with bevacizumab plus erlotinib,[42] etoposide,[43] temozolomide,[44] fotemustine,[45] cetuximab,[46] or carboplatin (AUC 4–6 mg/mL/min) every 28 days have been reported.[47] All these regimens were associated with a similar PFS benefit and a similar radiographic RR when compared with historical bevacizumab alone or bevacizumab plus irinotecan regimens (see Table 2).

Bevacizumab has been demonstrated to have a role as therapy against radiation necrosis of the central nervous system (CNS). The mechanisms of radiation-induced injury are not completely understood. Current opinion is that radiation necrosis is a continuous process from endothelial cell dysfunction to tissue hypoxia and necrosis, with concomitant liberation of vasoactive compounds such as VEGF that can lead to progressive blood–brain barrier dysfunction and edema. In a randomized, double-blind, placebo-controlled study, a total of 14 patients diagnosed by radiography or biopsy with CNS radiation necrosis and progressive neurologic symptoms or signs were randomized to either Group A to receive i.v. bevacizumab at a dose of 7.5 mg/kg at 3-week intervals for 2 treatments, or to Group B to receive intravenous placebo at 3-week intervals for 2 treatments.[48] None of them were GBM. Patients underwent MRI scans before beginning treatment and 3 weeks after the second dose of bevacizumab/placebo. At that point, patients responding to the treatment or placebo and showing no adverse effects that would require discontinuation received 2 more cycles of the same treatment and were evaluated by MRI at 3 weeks after the fourth treatment. The initial study goal was to define the response to treatment as a reduction in bi-directional measurements on T_2-weighted FLAIR images by ≥25% in the product of the 2 measures. Most patients did not have primary CNS tumors. Of the 7 patients randomized to placebo, 5 had worsening neurological signs or symptoms from 3.1 to 8.8 weeks after receiving first dose and 2 showed MRI progression of radiation necrosis on MRI. All patients receiving bevacizumab showed improvements in neurologic signs and symptoms by the 6th-week clinic visit, and MRI responses were confirmed in all bevacizumab patients by the same time point. However, all patients receiving placebo showed progressive disease, as confirmed by MRI. The 7 patients in the placebo arm showed an increase in volume of T_2-weighted FLAIR edema by 6 weeks, whilst patients receiving bevacizumab showed a median percentage change decrease in T_2-weighted FLAIR edema of −59%. 6 patients who were initially randomized to placebo who then crossed over to receive bevacizumab after progression showed statistically significant decreases in volume, as measured by 2 volume endpoints.

Moreover there is emerging evidence that bevacizumab may work synergistically with RT. The potential for such synergistic benefits has been supported by the ability of antiangiogenic agents to normalize blood vessels, thereby reducing hypoxia via enhanced oxygenation and counteracting the effects of radiation-induced VGEF secretion from tumor cells.[49] Bevacizumab has been evaluated with fractionated stereotactic radiotherapy (SRS), 30 Gy in 5 fractions, in a series of 25 patients with recurrent GBM or anaplastic glioma. This treatment was deemed feasible with an RR of 50%, 6 month PFS of 65% and median OS of 12.5 months.[50] This compares favorably with the median OS of 8–10 months for a series of patients treated with SRS alone.

Efficacy in Newly Diagnosed GBM

2 phase II studies have demonstrated that the combination of bevacizumab and concurrent RT and

Table 2. Efficacy results of bevacizumab plus other cytotoxic drugs than irinotecan in recurrent GBM.

Autor	Partner	N	OS, months	PFS, months	6-month PFS, %	RR, %
Sathornsumetee[42]	Erlotinib	24	10	NR	28	48
Reardon[43]	Etoposido	13	4.8	2	7.7	0
Verhoeff[44]	Temozolomide	15	4	2.5	17	20
Soffietti[45]	Fotemustina	54	9.1	5.2	44	48
Hasselbach[46]	Cetuximab	32	7.2	3.8	30	34
Reardon[47]	Carboplatin	25	5.8	2.3	16	0

Abbreviation: NR, not reported.

temozolomide for patients with newly diagnosed GBM was active and well tolerated. Seventy patients were included in the trial of Lai et al.[51] Therapy with bevacizumab (10 mg/kg every 2 weeks) plus temozolomide (75 mg/m^2 daily), and external beam RT (30 × 200 Gy), began between 3–5 weeks after surgery on the same day. After completion of RT, patients were placed on a maintenance phase of bevacizumab (10 mg/kg every 2 weeks) plus temozolomide (150–200 mg/m^2 on days 1 through 5 starting every 28 days) until progression or a maximum of 24 months of treatment. At this point, patients were then maintained on bevacizumab only. The OS was 19.6 and the median PFS was 13.6 months. The authors compared these results with those reported in a previous cohort at the University of California Los Angeles (21.1 months of OS and 7.6 months of median PFS) and with the results of Stupp's trial (14.6 months of OS and 6.9 months of median PFS).[1,2] In the second trial, Vrendenburgh et al reported a total of 125 patients treated with standard external beam irradiation plus concurrent temozolomide (75 mg/m^2 for 42 days) and bevacizumab 10 mg/kg every 2 weeks, starting on day 1 of radiation therapy.[52] After RT was completed, adjuvant temozolomide chemotherapy was continued at 150 to 200 mg/m^2, on days 1 through 5 beginning every 28 days, and bevacizumab was continued at 10 mg/Kg every 2 weeks. 120 patients (96%) completed the protocol-specified radiation therapy. PFS at 6 months, 1 year and 2 years was 88%, 64% and 16%, respectively, while OS was 94%, 82% and 44%, respectively.

Two other randomized phase III trials have investigated the efficacy of upfront bevacizumab for newly-diagnosed GBM: one was sponsored by the Radiation Therapy Oncology Group (RTOG) and there are no results at the moment. The other, named the AVAGLIO study, is sponsored by Hoffman-La Roche. Results were recently presented at the 17th Annual Meeting of the Society for Neuro-Oncology (SNO). This phase III double-blind trial randomized 921 patients after surgery for GBM to bevacizumab or placebo plus standard RT and temozolomide followed by temozolomide and then treatment maintenance with bevacizumab or placebo until progression (see Fig. 1). Co-primary objec-

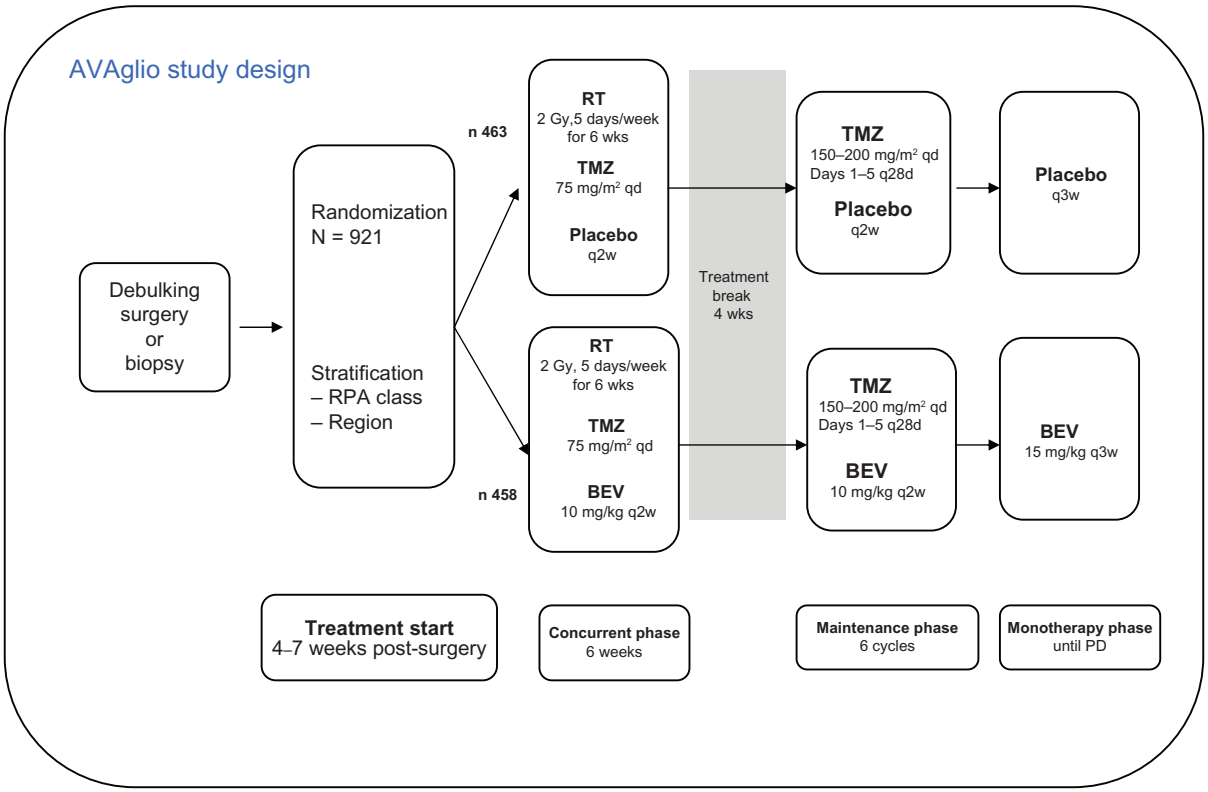

Figure 1. AVAglio study design.
Note: Last patient in March 2011.
Abbreviations: BEV, Bevacizumab; PD, progressive disease; RPA, recursive partitioning analysis; RT, radiotherapy; TMZ, temozolamide; qd, daily; q28d, every 28 days; q2w, every 2 weeks; q3w, every 3 weeks.

tives were investigator assessment of PFS and OS.[53] Secondary objectives included independent review of PFS, 1-year and 2-year survival rates, Quality of Life (QoL) and safety parameters. Patients were well balanced in both arms with 42% of patients having complete resection in the placebo arm and 41 in the bevacizumab arm. Karnofsky performance status (KPS) higher than 90 was seen at about 70% in both arms. Investigator assessment showed a median PFS of 6.2 months in the placebo arm and 10.6 months in the bevacizumab arm [stratified HR: 0.64 (95% CI: 0.55–0.74) $P < 0.0001$ (log-rank test)]. A radiologic central review assessed a median PFS of 4.3 months in placebo arm and 8.4 months in bevacizumab arm [stratified HR: 0.61 (95% CI: 0.53–0.71) $P < 0.0001$ (log-rank test)].[54] At the interim analysis, the OS did not cross the threshold for significance, with 263 events in placebo arm and 254 in bevacizumab arm. Final OS data are expected in October 2013. Interestingly, the time to steroid initiation for patients who did not receive steroids at baseline was 3.7 months in the placebo arm versus 12.3 months in bevacizumab arm [stratified HR: 0.71 (95% CI: 0.57–0.88) $P = 0.0018$ (log-rank test)].

Safety of Bevacizumab in GBM Patients

Bevacizumab treatment is generally well tolerated in patients with GBM. Bevacizumab-related toxicities in GBM patients are comparable to those that have been characterized in other solid cancers. Phase II trials showed the toxicity profile of bevacizumab at 10 mg/kg every 2 weeks in recurrent GBM. Fatigue (45.2% of patients), headache (36.9% of patients), hypertension (29.8% of patients) and thromboembolism (12.5% of patients) were the most common adverse events (AEs) reported when bevacizumab was administered alone in the BRAIN study.[32] A Japanese phase II trial showed the most frequent toxicity side effects to be proteinuria, hypertension, hemorrhage grade 1, pyrexia and seizures in 41.9%, 32.3%, 32.3%, 22.5%, 9.7% of patients, respectively.[55] Grade 3 or greater adverse events were experienced by 27.1% to 46.4% of patients, depending on the study. The most common events were thromboembolic events, hypertension, seizures, fatigue and bowel perforation, affecting 2.4%–12.5%, 4.2%–9.7%, 3.2%–6%, 3.6% and 2.1%–2.5% of patients, respectively.[32–34] Discontinuations related to side effects of bevacizumab were reported in 4.8% of patients and deaths due to AEs were observed in 2.4% of patients in the BRAIN study.[32] However, no discontinuations or deaths related to treatment in the Kreisl et al study were observed.[34] Moreover, severe intracranial hemorrhage, a feared side effect in antiangiogenic therapies, was reported at low frequency rates (<3%).[32–35,55] We must remember that spontaneous intracranial hemorrhage in patients with GBM without bevacizumab is reported approximately 2%–3% of the time. The rates of other serious AEs such as gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome, cardiac failure, and wound-healing complications in GBM studies were low (each having ≤2% incidence).

The dose of bevacizumab may be related to the rate of vascular complications. Bokstein et al, using a dose of 5 mg/kg and irinotecan 125 mg/m^2 every 2 weeks in 20 patients with recurrent glioma, reported lower vascular complication rates: all but 2 cases were no more than grade 2. There were no thrombotic complications or significant bleeding other than epistaxis. In addition, 47.3% of evaluable patients showed an objective radiologic response, median time to progression was 4.7 months, and the 6-month PFS and OS were 25% and 55%, respectively.[56]

The most common AEs (all grades) with the combination of bevacizumab and irinotecan were fatigue (75.9%), diarrhea (74.7%), nausea (67.1%) and constipation (40.5%). Grade 3–4 neutropenia was only 8.9% and lymphopenia was 7.6%.[31,32] The gastrointestinal side effects were mainly due to irinotecan; these side effects may decrease the QoL in these patients, which needs to be considered.

In a series of 25 patients with recurrent GBM and treated with bevacizumab plus fractionated stereotactic RT, there were 3 grade 3 toxicities: gastrointestinal perforation, intratumoral hemorrhage and wound dehiscence.[50]

Hypertension as an AE is generally controlled with antihypertensive medication.[35] A retrospective review of 21 patients treated with bevacizumab and anticoagulation for prevention or management of thromboembolic events found that it was a safe and acceptable treatment, not presenting lobar hemorrhages.[57] Only 3 patients had small areas of hemorrhage and only 1 patient developed symptoms from this lesion.

In a phase II study of bevacizumab and concurrent RT and temozolomide for patients with newly diagnosed GBM, severe adverse events included ischemic stroke, pulmonary embolus, wound breakdown, gastro-intestinal bleeding/perforation, and renal dysfunction. Isolated cases of retinal detachment and optic neuropathy have also been observed,[51] and in 125 patients included in the trial by Vrendenburgh et al, 5 patients had to withdraw from treatment due to pulmonary embolism in 2 cases, central nervous system hemorrhage in 1 case, grade 4 pancytopenia in 1 case and wound dehiscence in 1 case.[52]

Finally, the safety of bevacizumab combined with temozolomide in the standard chemo-irradiation schedule for GBM was assessed in the AVAGLIO phase III study.[54] This trial did not find new bevacizumab-related complications. The most common adverse events in bevacizumab plus temozolomide arm were hypertension, proteinuria, bleeding problems and arterial thromboembolic events (see Table 3). Furthermore, 62.7% of patients under bevacizumab treatment developed grade 3 to 5 compared to 50.1% of temozolomide plus placebo patients, and 24.6% of them discontinued the treatment due to an adverse event, in contrast to 13.2% of the temozolomide plus placebo arm.

Thus, the cumulative data from 11 clinical trials suggest that despite a small risk of life-threatening complications, including intracranial hemorrhage and thromboembolism, therapy that includes bevacizumab is well tolerated, with manageable, class-specific toxicities.

Patient Preference

No studies or patient guides regarding this issue have been published to date. However, data about the QoL and the cognitive status of patients under bevacizumab treatment should be taken into account with regards to the patient's drug preferences. Former small studies showed improvements in outcome measures such as KPS, the Independent Living Score and the Barthel Index, with potential positive effects in the QoL of these patients.[35,40,58,59] Moreover, it was also reported that one of the consequences of bevacizumab therapy was a steroid-sparing effect in a subset of patients.[28,30,32,34,38,39,56,60] It is well known that corticosteroid use has negative effects on neurocognitive

Table 3. Bevacizumab related toxicities in prospective phase II–III studies.

Toxicities	Bevacizumab alone		Bevacizumab plus Irinotecan		Bevacizumab plus Temozolomide plus RT	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Fatigue	45.2	3.6	75.9	8.9	20	0
Headache	36.9	0	32.9	0	NR	0
Hypertension	29.8–39.3	4.2–10–7	21.5–26.6	1.3–3.8	37.5	10.3
Thromboembolism	8.4–12.5	2.4–3.6	16.4	6.3	12.8	11.4
Proteinuria	–41.9	0.6	25	1.3	14	3.7
Pyrexia	22.5	0	25	0	NR	0
Seizures	9.7	3.2–6	14	14	9	0
Bowel perforation	2.1–2.5	2.1–2.5	2.5	2.5	1.7	1.1
Hemorrhage (out of CNS)	27.4–32.3	0–5.3	26.6	1.3	38.2	1.1
Cerebral hemorrhage	2.4–3.6	0–2.4	2.5–3.8	1.3	2.6	1.5
Wound-healing	6	2.4	2.5	1.3	3.7	1.5
Leukoencephalopathy	0.6	0	1.3	0	0	0
Cardiac failure	<2	<2	<2	<2	0.4	0.4
Diarrhea	21.4	1.2	74.7	5.1	1	1
Nausea	15.5	0	67.1	0	NR	NR
Vomiting	6	0	36.7	0	NR	NR
Constipation	14.3	0	40.5	0	NR	NR
Neutropenia	2.4	1.2	15.2	8.9	NR	NR
Lymphopenia	7.1	2.4	16.5	7.6	NR	NR
Hyperglicemia	16.7	<2	13.9	<2	NR	NR
Peripheral edema	13.1	0	17.7	0	NR	NR

function and / or the QoL in healthy subjects and in various diseases states.[61,62] Therefore, it would be expected that a reduction in steroid use would have a positive impact on QoL. This indirect evidence has been confirmed by the preliminary results reported by the AVAGLIO phase III study, where the standard questionnaires of EORTC (QLQ-C30 and BN20) were used to measure QoL. This randomized trial shows that patients treated with bevacizumab achieved a maintained or improved global health status and the communication deficit, physical, social and motor functioning domains were up to 2 times higher, at around 4 months, than those for patients treated only with the standard therapy for the GBM. Moreover, there was also observed to be a significant delay in the need for steroids, and KPS scores of independency were maintained for longer in patients treated with bevacizumab.[54]

Finally, neurocognitive function has not usually been assessed in case series or in phase II bevacizumab trials. Only 2 controlled studies focused on this question have been reported. The phase II BRAIN trial in recurrent GBM, comparing the efficacy of bevacizumab alone or in combination with irinotecan, showed improved or stable neurocognitive function at the time of response or at the 24-week assessment, respectively. However, most patients had poorer performance on all neurocognitive tests at baseline compared with the normative general population scores and did not achieve normalization at follow-up.[63] Another controlled small clinical cohort study found punctuation improvements in 62% of patients treated with bevacizumab and irinotecan.[58] Currently, the cognitive substudy of the AVAGLIO trial is under evaluation.

Place in Therapy, Issues and Conclusions

Bevacizumab has thus far been shown to be active in patients with GBM, with acceptable toxicity. Most serious adverse events, defined as grade 3 or 4, are 5% or less. It seems that bevacizumab improves PFS and OS compared to historical controls in recurrent GBM patients, with the most impressive RR thus far for any such therapy. There are data to support activity of bevacizumab alone in patients with recurrent GBM. However, there is a lack of randomized-controlled trials to provide definitive answers on the true impact of bevacizumab-containing regimens at this point. The EORTC trial 2601 is currently prospectively evaluating bevacizumab versus lomustine (CCNU) versus combination therapy in patients with recurrent GBM, and will likely define the benefit of bevacizumab in comparison to CCNU, the standard of care in Europe.

However, there are other questions to answer about the role of bevacizumab in the treatment of GBM. one question involves the dosage. We do not know the optimal bevacizumab dose. Although Stark-Vance's initial study[27] used bevacizumab in a dose of 5 mg/kg every 2 weeks, most later trials have used 10 mg/kg/ every 2 weeks. A small trial using a dosage of 5 mg/kg of bevacizumab every 2 weeks reported lower vascular complication rates and similar efficacy.[56] In a prospective series from the GEINO group, 40 patients were treated with bevacizumab 5 mg/kg every 2 weeks alone, and after progression the bevacizumab dose was scaled to 10 mg/kg and irinotecan 125 mg/m^2/2w was added.[65] Preliminary results show a RR of 20% and a median PFS of only 2.7 months; nevertheless, an OS of 8 months seems similar to studies that start with bevacizumab 10 mg/kg.

The need to use bevacizumab with chemotherapy and the best partner in the treatment of recurrent GBM is not yet absolutely clarified because a phase II randomized trial did not show differences in OS.[32]

Another uncertainty is the duration of the treatment. A meta-analysis of 5 phase II trials suggested a survival benefit for continuing bevacizumab after bevacizumab failure in recurrent GBM.[64] These findings require validation in a prospective randomized trial of bevacizumab continuation versus non-bevacizumab salvage therapy in patients with recurrent GBM who progress on bevacizumab. The MO 28347 study sponsored by Hoffman-La Roche Ltd., has recently been designed to answer this question.

Another open question is whether progression after bevacizumab treatment is different. It was reported that a number of patients with recurrent malignant glioma treated with bevacizumab developed a diffuse infiltrating disease at the time of progression, particularly those patients who demonstrated radiographic responses,[28] but an evaluation of progression patterns in patients included in the BRAIN study showed that most patients did not experience a change from baseline in radiographic characteristics of the disease.[66]

The results of the double blind phase III AVAGLIO study have shown better PFS when bevacizumab is used in the diagnosis of GBM along with temozolomide and with standard conventional external beam irradiation.[54] If the RTOG study confirms these results, bevacizumab will form part of the standard treatment against GBM after surgery.

Lastly, the main issue regarding bevacizumab treatment is the lack of biomarkers and genetic patterns to identify patients who may benefit from anti-angiogenic agents such as bevacizumab. It is hoped that continued identification of biomarkers and genetic patterns will identify patients who may benefit from anti-angiogenic agents such as bevacizumab, and these studies may also suggest other treatable cellular targets that may be critical to the advancement of treatment for GBM patients.

Future randomized-controlled trials identifying optimal dose, combinations with other therapeutic agents, and length of treatment would be very helpful in optimizing the use of bevacizumab for GBM patients.

Author Contributions

Conceived and designed the experiments by revision: MJG. Analyzed the data: MJG, CM, MR, JB. Wrote the first draft of the manuscript: MJG, CM, MR, JB. Contributed to the writing of the manuscript: MJG, CM, MR, JB. Agree with manuscript results and conclusions: MJG, CM, MR, JB. Jointly developed the structure and arguments for the paper: MJG, CM, MR, JB. Made critical revisions and approved final version: MJG, CM, MR, JB. All authors reviewed and approved of the final manuscript.

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As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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