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RESEARCH **REVIEW ARTICLE**

Bevacizumab for Glioblastoma Multiforme: A Literature Review

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ABSTRACT

BACKGROUND AND AIMS - Glioblastoma multiforme (GBM), a grade IV astrocytoma, is the most common primary brain tumor in adults. Bevacizumab, a humanized anti-vascular endothelial growth factor monoclonal IgG1 antibody, is a Food and Drug Administration-approved agent for treating advanced Glioblastoma multiforme. In this review, we aimed to discuss the therapeutic effects of bevacizumab for Glioblastoma multiforme treatment.

METHODS - We searched Google Scholar, PubMed, and Scopus using the keywords "Glioblastoma multiforme," "GBM," and "Bevacizumab." Two authors screened the records independently to identify relevant studies and classify them according to our outcomes of interest. We have only included articles published after the year 2000.

RESULTS - Bevacizumab selectively binds circulating VEGF, interfering with the role of VEGF in endothelial cell differentiation, sprouting, and capillary formation. Consequently, it inhibits tumor neovascularization and induces the development of normal vascular structures.

CONCLUSIONS - Ultimately, Bevacizumab helps to slow down tumor growth and progression. It promotes the development of normal vascular structures, which can help to improve the overall health of the patient. Overall, its effectiveness in inhibiting tumor neovascularization makes it a valuable addition to the arsenal of anti-cancer drugs available.

KEYWORDS - Antibody, Bevacizumab, Glioblastoma, Monoclonal

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INTRODUCTION

Glioblastoma multiforme (GBM), a grade IV astrocytoma, is the most common primary brain tumor in adults. It is responsible for 45.2% of primary malignant brain and central nervous system tumors. GBM is characterized by mitotic activity and necrosis and typically has a poor prognosis [1]. The median age for GBM presentation is 64 years, and the incidence is insignificantly higher in men than women. GBMs can be classified as primary, which develops without a known precursor, or secondary, where a low-grade tumor progresses over time into GBM [2]. Secondary GBMs usually have less necrosis and a better prognosis [1]. Classical molecular changes in GBM include mutations in genes associated with retinoblastoma protein signaling or rat sarcoma and those encoding p53, phosphoinositide 3-kinase receptor, and tyrosine kinases. Regarding treatment, current research has focused on the molecular aspects that drive a malignant phenotype, such as aberrant signal transduction and angiogenesis, as well as immunotherapy-focused approaches [3].

Angiogenesis (blood vessel formation) plays a significant role in tissue growth and is involved in some diseases, such as inflammation and cancer [4]. Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis in cancer. It is upregulated by multiple mechanisms, including oncogenic expression, numerous growth factors, and hypoxia [5].

Bevacizumab, a humanized anti-VEGF monoclonal IgG1 antibody, is a Food and Drug Administration (FDA)-approved agent for treating advanced GBM. Bevacizumab acts by selectively binding circulating VEGF to prevent VEGF-induced angiogenesis. This ultimately reduces the microvascular extension of tumor blood vessels, limiting the blood supply to the tumor tissues [6]. In 2009, accelerated approval was granted by the USA-FDA for using bevacizumab as monotherapy against recurrent GBM resistant to previous radiotherapy or chemotherapy [7].

This article reviews the therapeutic effects and efficacy of bevacizumab for treating GBM.

METHODS

In this study, we reviewed multiple sources to present the therapeutic effects and efficacy of bevacizumab for treating GBM. Our primary sources were original and review articles about bevacizumab in treating GBM. We searched the Web of Science, PubMed, Cochrane CENTRAL, and Scopus for relevant studies. We have only included articles published after the year 2000.

BEVACIZUMAB FOR THE TREATMENT OF GBM

NEOVASCULARIZATION - Numerous studies have investigated pathways involved in the angiogenesis induced by GBM. These studies have focused on fundamental fibroblasts, placental growth factor, neuropilin-2, macrophage migration inhibitory factor, Delta-like 4, and growth factor erythropoietin. [8]. Five mechanisms of neovascularization in GBMs have been studied: glioblastoma–endothelial cell transdifferentiation, vascular mimicry, vasculogenesis, angiogenesis, and vascular co-option. These mechanisms are intertwined [8].

GBMs express growth factors, most importantly VEGF, and receptors associated with angiogenesis. The progression of low-grade to high-grade gliomas is characterized by increased vascularization. Despite the increase in blood vessels, necrosis occurs within the tumors, increasing oxygen demand. Consequently, VEGF and multiple other factors are highly upregulated to overcome tissue hypoxia, forming new blood vessels. However, glioma cells can also adapt to oxygen-deprived environments [9].

Although hypoxia is an essential cause of neovascularization, there are also non-hypoxic mechanisms, such as p53- and hypoxia-independent VEGF-mediated pathways. In addition, VEGF receptors are upregulated in many human malignancies, not only in GBM, affected by oxygen deprivation, but also in tumors, even in the absence of hypoxia [10].

Although patients with severe malignant gliomas showed an increase in absolute levels of sVEGFR-1, the sVEGFR-1: VEGF-A ratio is 2.6-fold decreased in GBM compared to that in diffuse astrocytomas, indicating that the ensuing increased bioavailability of VEGF-A favors angiogenesis. Additionally, the inhibition of endothelial chemotaxis induced by sVEGFR-1 suggests that sVEGFR-1 could be helpful as an angiogenesis inhibitor in the specific context of human gliomas [11].

Consequently, interfering with tumor vasculature has a promising therapeutic potential. However, it is vital first to identify suitable specific targets. For example, high-level neovascularization in high-grade gliomas is an excellent target because angiogenesis plays a significant role in the growth and survival of these tumors [8].

Antibiotics targeting specific pathways help avoid many undesirable adverse effects, as they are well tolerated compared to those in conven-

tional cancer therapy. In addition, anti-angiogenic therapy may help overcome chemotherapy resistance in the tumor. Unfortunately, resistance to anti-angiogenic treatment can also occur. Resistance includes increased perivascular tumor growth and upregulation of alternative pro-angiogenic pathways [12].

MECHANISM OF ACTION - Bevacizumab is an anti-VEGF monoclonal antibody with several potential mechanisms of action. For example, when this drug inhibits blood vessel growth, newly formed tumor vasculature regresses, and vascular function and tumor blood flow are negatively affected [13]. In addition, bevacizumab exerts pro-apoptotic activity against some cancers [14].

Bevacizumab selectively binds circulating VEGF, interfering with the role of VEGF in endothelial cell differentiation, sprouting, and capillary formation. Consequently, it inhibits tumor neovascularization and induces the development of normal vascular structures. Moreover, it improves excess vascular permeability and decreases intratumoral pressure, allowing the effective distribution of chemotherapy [15]. Figure 1 shows the mechanism of GBM angiogenesis and how Bevacizumab can prevent it.

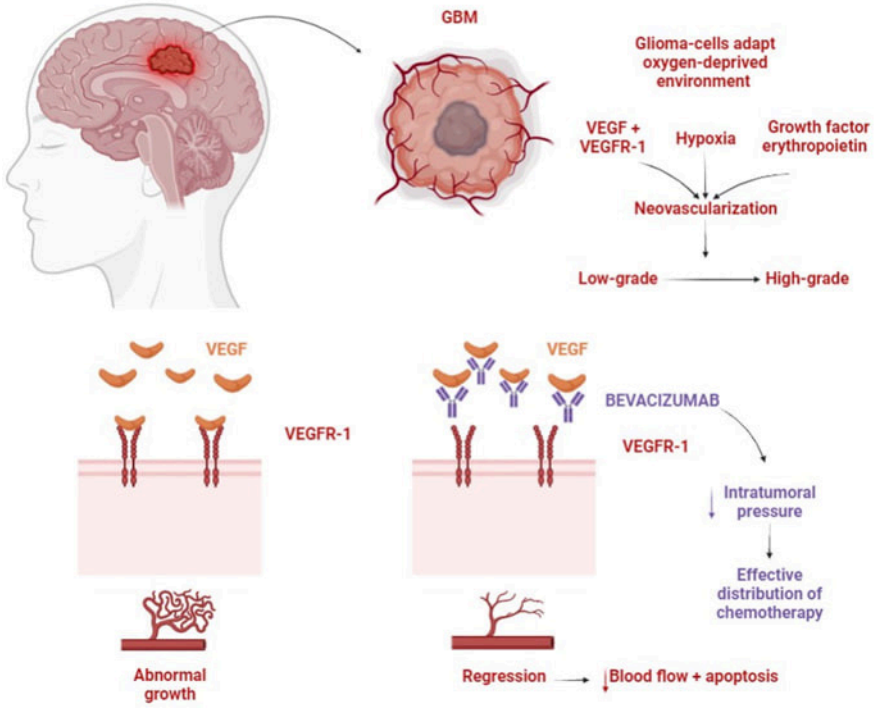
BIOLOGICAL MARKERS - The detailed characterization of GBM molecular signatures enabled a more personalized therapeutic approach and contributed to developing a new generation of anti-GBM therapies [16]. In addition, there has been a greater need for imaging biomarkers to help evaluate individual patient responses to bevacizumab therapy [17]. Table 1 shows predictive markers for bevacizumab.

TREATMENT EFFICACY AND PROGNOSTIC IMPROVEMENT IN GBM

The current standard approach for treating GBM involves surgical resection, followed by concomitant radiotherapy and chemotherapy [1]. GBM is characterized by rapid tumor growth, extensive angiogenesis (formation of new blood vessels), and high invasiveness [1]. VEGF plays a crucial role in promoting angiogenesis, making it an attractive target for anti-cancer therapy [1]. Bevacizumab works by binding to VEGF and inhibiting its interaction with its receptors on endothelial cells, thereby preventing the formation of new blood vessels and reducing tumor growth [1].

In addition to its efficacy, bevacizumab has demonstrated prognostic improvement by improving quality of life and reducing symptoms

Figure 1. Shows the mechanism of GBM angiogenesis and how can Bevacizumab prevent it.



associated with GBM. Patients receiving bevacizumab have reported improved neurological function, reduced corticosteroid use, decreased edema (swelling), and improved overall well-being [1].

Since 2009, major studies on recurrent [18] and newly diagnosed GBM [19,20,21,22] have repeatedly shown that bevacizumab, compared to placebo, has extended progression-free survival (PFS) but did not influence overall survival (OS). However, the degree to which the crossover to bevacizumab at progression in the control groups of these studies contributed to the disparity in PFS and OS is unclear.

However, it is essential to note that despite the initial positive results, the long-term benefits of bevacizumab in GBM treatment still need to be determined. Some studies have shown that while bevacizumab may delay disease progression, it does not significantly extend overall survival. Additionally, there are concerns about potential side effects and the development of resistance to bevacizumab over time [19,20,21,22].

Table 1. Displays the contingency-table analysis for each individual PSQI component in relation to participant characteristics and K10.

Biomarker type	Biomarker name
Genetic	EGFR: is related to poor response to bevacizumab [18].
	MGMT: unmethylated MGMT patients were found to be sensitive to bevacizumab treatment [19].
Imaging	Radiomics: has recently been reported as a prognostic marker for patients with GBM receiving bevacizumab [20].
	Diffusional kurtosis imaging: a significant imaging factor for tumor progression through detecting tumor changes 28 days after therapy with bevacizumab [21].
	Representative imaging markers: include: contrast-enhanced T1-weighted subtraction maps, perfusion maps, relative cerebral blood volume variation, and enhancing tumor volume measurements [22-24].
Others	.Neutrophils and Regular T cells: their existence in venous blood is an indicator of survival during treatment with bevacizumab [25].

Abbreviations: EGFR: epidermal growth factor receptor, MGMT: methylguanine-DNA-methyltransferase.

Bevacizumab Efficacy in recurrent GBM

Regarding recurrent GBM, Bevacizumab as a single-agent therapy has shown significant clinical efficacy in many studies, including a retrospective analysis of 24 patients in 2015 that reported an overall response rate of 20.8% [23]. Additionally, a Japanese study conducted in 2012 demonstrated an objective response rate (ORR) of 28.2% for Bevacizumab in the treatment of recurrent GBM [23]. The median PFS in these studies was 6.4 months/10.5 months and 4.1 months/3.3 months, respectively [24,25].

Interestingly, a meta-analysis of published clinical studies was conducted to evaluate the effectiveness and side effects of angiogenesis inhibitors used alone as salvage therapy in a total of 842 individuals (343, 386, and 81 patients treated with bevacizumab, with other angiogenesis inhibitors, and with thalidomide, respectively) [26]. Compared to other angiogenesis inhibitors, treatment of recurrent GBM with single-agent bevacizumab significantly increased the ORR and 6-month PFS. However, the 1-year OS was similar between the groups. Bevacizumab therapy in recurrent GBM substantially increased the ORR, but not the 1-year OS, relative to thalidomide [26].

In a recent meta-analysis, researchers quantitatively synthesized data from 1,169 patients from seven randomized clinical trials. They concluded that bevacizumab combined with chemotherapy resulted in considerably improved PFS over single-agent therapy in patients with recurrent GBM. They also revealed a considerably higher ORR with the combination than with bevacizumab or chemotherapy alone. Additionally, the groups had no significant difference in OS [27].

Furthermore, Ren et al. studied the effectiveness of lomustine combined with bevacizumab for GBM in a meta-analysis. They reported an effective increase in OS, PFS, and 6-month PFS in patients with recurrent GBM treated with the combination therapy [26]. However, the observed PFS advantage did not translate into an OS advantage over monotherapy alone in another meta-analysis of three randomized clinical trials that included 574 patients [28].

Bevacizumab efficacy in newly diagnosed GBM

From all available data, bevacizumab was examined regarding its advantages and disadvantages among anti-angiogenic drugs for treating high-grade gliomas; however, until 2015, no study had focused on using bevacizumab for primary GBM [29]. A meta-analysis using available eligible trials was performed to assess the effectiveness of bevacizumab in combination with radiotherapy/temozolomide therapy in patients with newly

diagnosed GBM. The results did not indicate improved OS but did show increased PFS with additional bevacizumab [30].

In addition, Eriksson et al. showed that including a multimodal strategy to improve GBM treatment boosted survival in an unselected clinical sample. This was particularly clear in the 2-year survival rate, which increased from 7% in 1995–1996 to 18% in 2010–2015 [29]. However, the minor increase in the median OS (6.9–10.3 months) highlights the need for further advancements in the management of GBM.

Lawrence et al. conducted an extensive study on 15,888 patients with GBM. They revealed that the prognosis of GBM patients gradually improved between 2001 and 2007, but only in patients aged < 70 years [30].

In conclusion, bevacizumab has demonstrated efficacy and prognostic improvement in GBM by inhibiting angiogenesis and reducing tumor growth. It has shown significant improvements in PFS and potential benefits in OS. However, further research is needed to understand its long-term effects fully and to identify optimal patient selection criteria for its use in GBM treatment. Several other studies that also intended to provide verifiable values and exhaustive insights into the effectiveness of bevacizumab and its optimal combination regimens for treating newly diagnosed and recurrent GBM are listed in Tables 2 and 3, respectively.

Dosing and cost-effectiveness

In a retrospective analysis by Gleeson et al., patients were divided into standard-dose (10 mg/kg q2/52 or 15 mg/kg q3/52) or reduced-dose (5 mg/kg q2/52 or 7.5 mg/kg q3/52) bevacizumab treatment groups [31]. The OS was statistically similar (5.97 vs. 5.7 months; hazard ratio 1.11, P-value: 0.584) and clinically insignificant (Δ 0.27 months) among patients with progressive GBM who received standard-dose or reduced-dose bevacizumab therapy. This study showed that reduced-dose bevacizumab has an indistinguishable OS from standard-dose bevacizumab monotherapy and is associated with substantial cost savings [31]. Similarly, another meta-analysis of patients with malignant gliomas treated with bevacizumab regimens showed no significant dose-response efficacy difference between 5 mg/kg and 10–15 mg/kg regarding PFS, OS, or disease response [32].

Criteria

Identifying a subpopulation that primarily benefits from such therapy is crucial. The type of genetic mutation present affects the prognosis and OS after bevacizumab initiation. Rigakos et al.'s retrospective review [33] stated that several publications reported a better prognosis for patients with IDH1 mutations. Patients with IDH1 mutations had approximately 100 weeks longer survival than those with wild-type IDH1. However, the median OS in patients with epidermal growth factor receptor variant III and unmethylated methylguanine-DNA-methyltransferase promoter after initiating bevacizumab was like that of patients with a favorable prognosis [33]. Adverse effects, such as arterial and venous thromboembolic events, are associated with the use of angiogenesis inhibitors. Maurice and Mason's retrospective study evaluated the risk factors and stroke mechanisms in a population of GBM patients who experienced an ischemic cerebral stroke during bevacizumab treatment [34]. Their study highlights the need to evaluate risks and benefits before starting drug administration. Taking the patient's comorbidities and medical history into consideration is significant for identifying the relevant subpopulation that will benefit the most from bevacizumab treatment.

Neoadjuvant vs adjuvant therapy

Neoadjuvant chemotherapy is offered to downstage locally advanced (inoperable) disease and might subsequently eradicate micrometastatic disease better than adjuvant therapy. In addition, it reduces tumor cell shedding during surgery. However, adjuvant therapy is usually administered after primary treatments, such as surgery, to reduce the risk of cancer recurrence and improve long-term survival.

Bevacizumab should not be administered for at least 28 days before permissive surgery and should be withheld for more than 28 days following surgery and complete wound healing [35]. Concomitant bevacizumab and irradiation have a synergistic effect over bevacizumab administration alone. This has been confirmed by many studies in which bevacizumab was reviewed as an effective treatment for radiation-induced brain necrosis secondary to irradiation-induced vascular dysfunction, followed by high levels of VEGF expression. Bevacizumab promotes its effect by alleviating brain edema symptoms and significantly decreases vascularization and tumor volume [36, 37, 38, 39].

The combination of bevacizumab and irradiation emerged as a possible treatment option in a systematic review of 34 studies that compared recurrent high-grade GBM patients receiving re-irradiation therapy (reRT) with or without concomitant bevacizumab therapy. The results illustrated that patients receiving bevacizumab had significantly lower rates of radiation necrosis ($P < 0.001$) than those receiving reRT alone.

Still, no significant increase was found in OS and PFS (P = 0.057, P = 0.99), respectively [40]. The pivotal GENOM 009 study in patients with unresected GBM compared the efficacy of temozolomide plus bevacizumab as neoadjuvant therapy versus that of temozolomide alone [41]. They reported no significant difference between the groups (PFS: 4.8 vs. 2.2 months; OS: 10.6 vs. 7.7 months; P = 0.10). Bevacizumab conferred benefits in terms of tumor shrinkage, and the reduction in neurological deterioration was significant (P = 0.005), albeit at the expense of more significant toxicity (P = 0.06) [42].

Timing of surgery and bevacizumab therapy in neurosurgical patients with recurrent high-grade glioma

Bevacizumab has many significant side effects, such as wound dehiscence, stroke, cardiac failure, bowel perforation, and intracranial hemorrhage [43,44]. Wound dehiscence is a critical surgical issue in patients at increased risk due to decreased angiogenesis. Consequently, reoperations are contraindicated until the antibody (which has a 20-day half-life) has dissipated from the blood [45].

According to the drug manufacturer, it is advised to delay the start of bevacizumab treatment after surgery for at least 4 weeks. Additionally, if neoadjuvant bevacizumab has been discontinued, reoperation can be considered after a 4-week interval. However, neurosurgeons face a severe ethical and practical conundrum with this suggestion. Only a few alternative therapies are effective without requiring reoperation, and the survival of patients with bevacizumab-treated relapses is less than 4 months [46].

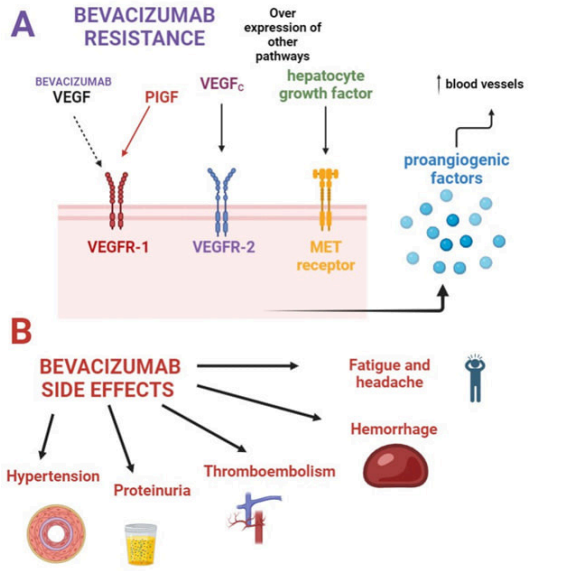
Most newly enrolled participants in clinical immunotherapeutic trials require reoperation to debulk tumors, confirm the histopathological diagnosis, and collect tissue for the study. Given that the size of the GBM can double every 2 weeks, reopening it early could extend a patient's life. Therefore, the ideal window between surgical intervention and adjuvant bevacizumab termination or initiation must be precisely established to enable safe and rapid surgery and postoperative commencement of chemotherapy. Unfortunately, there is no agreement in the literature regarding the ideal interval length, and future research is needed to establish accurate timing recommendations.

Development of resistance

Bevacizumab mainly targets the VEGFA/VEGFR2 pathway and does not affect other pathways, as previously mentioned [47]. Therefore, the main reason for bevacizumab resistance is a modification in the expression of proangiogenic factors and their receptors, other than the VEGFA/VEGFR2 pathway [48].

These proangiogenic factors include the placental growth factor, VEGFB, VEGFC, VEGFD, and basic fibroblast growth factor [49,50,51]. Furthermore, tyrosine kinase receptors, such as VEGFR1, hepatocyte growth factor receptor, and MET are overexpressed [50,51]. This leads to the activation of many pathways, including the PlGF/VEGFR1, hepatocyte growth factor/MET, and VEGFc/VEGFR2 pathways, compensating for the absence of the VEGFA/VEGFR2 pathway, which was blocked by bevacizumab [52,53,54]. Activation of these pathways subsequently leads to the overexpression of metalloproteinases, which are essential for stromal invasion and the expression of proangiogenic factors [55]. Figure 2, Part A, represents the mechanism of the Bevacizumab resistance development.

Figure 2. The mechanism of Bevacizumab resistance development; B) the side effects of Bevacizumab



Targeting different growth factors results in the development of distinct resistance mechanisms, which decreases the drug's efficacy over time. Overcoming these resistance mechanisms by initiating combinational therapy can be beneficial but does not resolve the problem. Targeting intracellular pathways and molecular signaling associated with tumor growth and resistance might be the answer to this question. Furthermore, targeting the transcription of genes responsible for growth and resistance can be beneficial. If there is a way to target the specific promoter sites of the genes responsible for these particular resistance mechanisms, it may be possible to overcome this barrier. Additionally, if a drug

capable of such action can be developed and used in combination with bevacizumab, OS may be expected to increase significantly.

If it is difficult to target gene promoter sites, enhancer sites, and silencer sites in these genes can also be targeted. Most studies in the literature illustrate the use of additional angiogenic inhibitors, but few have suggested targeted gene therapy. Focused clinical trials using this approach could provide hope for overcoming drug resistance.

LIMITATIONS, CONTRAINDICATIONS, AND SAFETY - Although bevacizumab is effective for patients with malignant GBM, much remains unknown regarding its use, such as appropriate combination therapy, treatment duration, radiographic response criteria, and contraindications. These unsolved problems remain under investigation in ongoing clinical trials [56]. Nevertheless, randomized clinical trials have consistently shown that bevacizumab increases PFS but not OS [57]. However, the survival rate after bevacizumab treatment has not been extended for more than 14.5 months, according to clinical trial data [56].

Furthermore, the mechanisms of action and drug resistance are not thoroughly understood, and no clear markers for predicting bevacizumab response have been identified [57]. Furthermore, to boost therapeutic efficacy, different combinations of bevacizumab and other medicines are still under investigation [56].

As a sign of an active anti-tumor effect when treating GBM with bevacizumab, side effects will develop, such as hypertension and proteinuria [57]. However, the absence of these side effects indicates resistance to the mechanism of bevacizumab action [58]. The most common side effects documented in bevacizumab monotherapy have been fatigue, headache, thromboembolism, and seizures, affecting 45.2%, 36.9%, 12.5%, and 9.7% of patients, respectively [58]. In addition, according to a Japanese study, hemorrhage grade 1 and pyrexia are severe side effects associated with this treatment [56]. Figure 2, part B, represents the side effects of Bevacizumab.

Moreover, patients with brain metastases from solid tumors were excluded from receiving bevacizumab use due to a single unanticipated finding in a patient with hepatocellular carcinoma with a history of undiscovered brain metastases who were reported to have a fatal cerebral hemorrhage after the use of bevacizumab [53]. Intracranial hemorrhage is a rare side effect of bevacizumab; however, patients with GBM are already at risk of spontaneous intracranial hemorrhage [56,59].

THE FUTURE: RANIBIZUMAB, A BEVACIZUMAB-DERIVED DRUG - New studies have shifted to developing new techniques for targeting tumor cells in GBM treatment, such as ranibizumab, a drug derived from bevacizumab. Ranibizumab is a humanized monoclonal antibody fragment [50]. It was designed to inhibit the activity of all biologically active isoforms of human VEGF by high-affinity binding to the receptor-binding site of the active forms of VEGFA [55,56]. Thus, they prevent VEGFA from interacting with its receptors, reduce production in endothelial cells, vascular permeability, and formation of new blood vessels [57, 58, 59].

The presence of antibodies in the body may trigger an anaphylactic reaction. It may also affect the pharmacological efficacy, leading to changes in the pharmacokinetics of the medication [56, 57, 58]. The clinical significance of immunoreactivity to ranibizumab remains unclear [59]. However, antibodies to ranibizumab were found to have low titers in ranibizumab-treated patients [45].

Both ranibizumab and bevacizumab have epitopes found in the receptor-binding region of VEGF, and both target VEGF in the same manner [52, 58, 59]. However, ranibizumab lacks a fragment crystallizable region. Consequently, ranibizumab has a smaller molecular size than bevacizumab [59]. Moreover, ranibizumab is manufactured in prokaryotic E. coli and lacks glycosylation sites. In contrast, bevacizumab is manufactured in eukaryotic cell line and is N-glycosylated in its Fc region [60]. Bevacizumab and ranibizumab neutralize VEGF and appear to have long-lasting effects, even when they are no longer active [60]. Owing to the size of ranibizumab, it more easily penetrates the retina and inhibits vessel growth [53,59] and has been proven to be safer than bevacizumab for age-related macular degeneration [53,59].

A 60 ng/mL concentration was the lowest required to achieve VEGF neutralization. Ranibizumab has a 17-fold higher VEGF-binding capacity than bevacizumab [56,57,59]. In ranibizumab clinical trials, the overall incidence of systemic adverse events was modest [35, 58, 59]. Since bevacizumab has a long half-life, it has a higher potential for causing adverse effects [59, 60, 61]. A previous study of patients treated with at least one injection of ranibizumab, or bevacizumab, showed that 12.4% of bevacizumab-treated patients developed systemic adverse effects compared with 1.4% of ranibizumab-treated patients [60]. A retrospective comparative study that investigated the effectiveness of ranibizumab treatment, performed by Chang et al., revealed that ranibizumab fared better than bevacizumab [61]. Although ranibizumab and bevacizumab

share the same structure, there are still several differences between the two medications, as shown in Table 4.

Table 4. Similarities and differences between ranibizumab and bevacizumab

	Ranibizumab (Lucentis)	Bevacizumab (Avastin)
Similarities		
Target	VEGF	VEGF
Type	Monoclonal antibody	Monoclonal antibody
Differences		
Molecular weight	48.39 kDa	149 kDa
Effectiveness	Very strong	Strong
Clearance	Slow	100-fold faster

VEGF, vascular endothelial growth factor

CONCLUSION

In this review, we discussed the therapeutic effects of bevacizumab and its efficacy in treating GBM. Moreover, we attempted to highlight some factors that may maximize the drug's effectiveness at the lowest possible cost. Some aspects were highlighted to maximize the effectiveness of bevacizumab at the lowest possible cost, such as selecting appropriate patient populations, optimizing dosing strategies, and monitoring treatment response. For example, patients with a high baseline VEGF expression and those with a good performance status may benefit more from bevacizumab treatment. Dose optimization can also help to balance the efficacy and toxicity of the drug, and biomarker-guided treatment can help to identify patients who are likely to respond to bevacizumab. The review also mentions the limitations of using bevacizumab, such as the development of drug resistance and the lack of predictive biomarkers. To address these limitations, potential solutions were put forward such as combination therapy with other targeted agents, the use of imaging biomarkers to monitor treatment response, and the development of new predictive biomarkers.

Overall, the review provides a comprehensive overview of the therapeutic effects of bevacizumab in the treatment of GBM, and it highlights some important factors and solutions that can help optimize its use in clinical practice. However, many questions remain unanswered; therefore, further well-designed studies are required to investigate the optimal management of bevacizumab treatment of GBM.

AUTHORS' CONTRIBUTIONS

Ahmed Bassam Mohd: Conceptualization (lead); writing – original draft (lead). Omar Bassam Mohd: Conceptualization (supporting); writing – original draft (equal). Yasmeen Jamal Alabdallat: Software (lead); writing – review and editing (equal). Reem Ayman Ghannam, Abdalrahman Altiti: writing – original draft (lead). Khaled Albakri, Abdulrhman Khaity, Salem Al-Dwairy: writing – review and editing (equal).

STATEMENT OF DATA AVAILABILITY

On reasonable request, the supporting data of this study's findings can be provided by the first author

SUPPLEMENTAL MATERIALS

Table 2. Clinical trials including bevacizumab in treatment of newly diagnosed GBM

First Author (Year)	N	Median Age (Years)	Treatment	Control	PFS,OS respectively	Prior Treatment
Carlson (2015) [1]	Tx: 30 Control: 26	Tx: 56.5 Control: 60.5	Bevacizumab + Hypofractionated-intensity modulated radiotherapy + Temozolomide	Hypofractionated-intensity modulated radiotherapy + Temozolomide	Bevacizumab + Hypofractionated-intensity modulated radiotherapy + Temozolomide: 12.8 months, 16.3 months Hypofractionated-intensity modulated radiotherapy + Temozolomide: 9.4 months, 16.3 months	Biopsy/ surgery
Chauffert (2014) [2]	Tx: 60 Control: 60	Tx: 60.2 Control: 60.9	Bevacizumab + Irinotecan + Radiotherapy + Temozolomide	Radiotherapy + Temozolomide	Bevacizumab + Irinotecan + Radiotherapy + Temozolomide: 7.1 months, 11.1 months Radiotherapy + Temozolomide: 5.2 months, 11.1 months	Biopsy only
Gilbert (2014) [3]	Tx: 312 Control: 309	Tx: 59.0 Control: 57.0	Bevacizumab + Radiotherapy + Temozolomide	Placebo + Radiotherapy + Temozolomide	Bevacizumab + Radiotherapy + Temozolomide: 10.7 months, 15.7 Placebo + Radiotherapy + Temozolomide: 7.3 months, 16.1	Biopsy/ surgery
Chinot (2014) [4]	Tx: 458 Control: 463	Tx: 57.0 Control: 56.0	Bevacizumab + Radiotherapy + Temozolomide	Placebo + Radiotherapy + Temozolomide	Bevacizumab + Radiotherapy + Temozolomide: 10.6 months. 16.8 months Placebo + Radiotherapy: 6.2 months, 16.7 months	Biopsy/ surgery
Balana (2016) [5]	Tx: 49 Control: 53	Tx: 62.9 Control: 62.0	Bevacizumab + Temozolomide	Temozolomide	Bevacizumab + Temozolomide: 4.8 months, 10.6 months Temozolomide: 2.2 months, 7.7 months	Biopsy only

Herrlinger (2016) [6]	Tx: 116 Control: 54	Tx and Control: 56.0	Bevacizumab + Irinotecan + Radiotherapy	Radiotherapy + Temozolomide	Bevacizumab + Irinotecan + Radiotherapy: 9.7 months, 16.6 months Radiotherapy + Temozolomide: 5.99 months, 17.5 months	Biopsy/ surgery
Wirsching (2018) [7]	Tx: 50 Control: 25	Tx: 70 Control: 70	Bevacizumab + Hypofractionated-radiotherapy	Hypofractionated-radiotherapy	Bevacizumab + Hypofractionated-radiotherapy:7.6 months,12.1months Hypofractionated-radiotherapy: 4.7 months, 12.2 months	surgery, steroids

Abbreviations: GBM, glioblastoma multiforme; n, number of patients; Tx, treatment; PFS, progression free survival; OS, overall survival
Note: Clinical trials have been arranged in chronological order according to their starting date.

Table 3. Clinical trials including bevacizumab for the treatment of recurrent GBM

First Author (Year)	N	Median Age (Years)	Treatment	Control	PFS,OS respectively	Prior Treatment
Friedman et al (2009) [1]	Tx: 82 Control: 85	Tx: 57 Control: 54	Bevacizumab + Irinotecan	Bevacizumab		Radiotherapy and temozolomide
Taal et al (2014) [2]	Tx: 50 Control: 46	Tx: 58 Control: 56	Bevacizumab	Lomustine	Bevacizumab: 3 months, 8 months Lomustine: 1 month, 8 months	Chemoradiotherapy with temozolomide
Field et al (2015) [3]	Tx: 60 Control: 62	Tx: 55 Control: 55	Bevacizumab + carboplatin	Bevacizumab	Bevacizumab + carboplatin: 3.5 months, 6.9 months Bevacizumab: 3.5 months, 7.5 months	Radiotherapy and temozolomide
Van den bent et al (2018) [4]	Tx: 78 Control: 77	Tx: 44.6 Control: 43.1	Bevacizumab + Temozolomide	Temozolomide	Bevacizumab + Temozolomide: 6.9, 13.8 Temozolomide: 6.1, 15.0	Radiotherapy or chemotherapy
Brandes et al (2019) [5]	Tx: 61 Control: 62	Tx: 56 Control: 58.5	Lomustine (CCNU) + Bevacizumab	Lomustine (CCNU) + Placebo		Biopsy, surgery
Reardon et al (2020) [6]	Tx: 185 Control: 184	Tx: 55 Control: 55.5	Bevacizumab	Nivolumab	Bevacizumab: 3.5, 10.0 Nivolumab: 1.5, 9.8	Radiotherapy and temozolomide

Abbreviations: GBM, glioblastoma multiforme; n, number of patients; Tx, treatment; PFS, progression free survival; OS, overall survival
Note: Clinical trials have been arranged in chronological order according to their starting date.

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