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Advanced Targeted Therapeutic Strategies for Glioblastoma Multiforme: Bevacizumab and Its Emerging Nanotechnology-Based Interventions

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ABSTRACT

Bevacizumab is an important treatment for glioblastoma multiforme (GBM), especially after surgery, radiation, and chemotherapy, but it has not yet been successfully used to treat recurrent or progressive tumors. Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor A and inhibits neovascularization. Bevacizumab works by cutting off the blood supply to the tumor, thus alleviating symptoms and enhancing quality of life in situations where standard therapies have failed. Nonetheless, the effect of bevacizumab on the overall survival of patients with GBM was modest. Resistance ultimately occurs through the activation of alternative angiogenesis pathways or tumor evolution, including remodeling of the microenvironment and extracellular matrix. In response to these drawbacks, new strategies are under investigation, focusing on drug delivery systems based on nanotechnology. These include bevacizumab-loaded nanoparticles that cross the blood-brain barrier with greater efficiency, allowing for direct drug delivery to the tumor. Synergistic therapies using bevacizumab and classical chemotherapeutic agents or immunomodulatory therapies in these nanoparticle systems have shown promise in improving therapeutic potency by simultaneously targeting multiple tumor pathways or mechanisms, as demonstrated preclinically. Further development of these novel delivery approaches could lead to a more robust therapeutic paradigm for GBM, improving survival and quality of life for patients affected by this complex disease.

Keywords: Glioblastoma, bevacizumab, nanotechnology, tumor resistance

INTRODUCTION

Glioblastoma multiforme (GBM) is a highly aggressive primary malignant brain tumor of the highest grade (1). Standard treatment protocols and conventional immunotherapy are ineffective as they fail to meaningfully improve the long-term survival of GBM patients (2). Bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), has shown some improvement in progression-free survival (PFS) in GBM patients, but due to poor overall survival, there is no standard definition of its effectiveness (3). We discuss the responsiveness of bevacizumab in GBM, the causes of immune escape, and future therapeutic approaches for progressive GBM, including nanotechnology. Currently approved therapeutic strategies and subsequent lines of systemic treatments using emerging scientific advances in targeted therapies will also be discussed.

Characteristic Properties of GBM

GBM is the most aggressive type of malignant brain tumor, and it is characterized by local invasion, extreme treatment resistance, and high lethality (1). Due to its biological characteristics, it is highly invasive and can infiltrate normal adjacent brain tissue via numerous pathways, and almost all patients with this tumor are resistant to conventional therapies (2). The rapidly growing nature of GBM allows

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for a more aggressive invasion, and it can rapidly infiltrate the normal brain tissue that surrounds it, often traveling to sites in the contralateral hemisphere. Changes in cell mobility allow the GBM to travel through brain tissue along the perivascular spaces and white matter tracts (3). In contrast to most cancers, GBM is not associated with classical metastatic spread. Its invasive behavior also seems to trigger major changes in the adjacent connective tissues, which contain a nonspecific fibrous tissue encapsulating the tumor nodule (4). Such extreme heterogeneity at the cellular and molecular levels is one of the main reasons for the rapid spread of GBM (Table 1).

"GBM heterogeneity" refers to the different traits of cancer cells, which can have various genetic profiles and show various responses to treatment in different tumor areas, making it difficult to target them all the same way (5). Transcriptional and mutational profiles characteristic for different tumors and even parts of the same tumor have led to the subdivision of GBM tumors into major subtypes, primarily proneural, classical, and mesenchymal (6-7). In addition, single-cell RNA sequencing (scRNA-seq) identified multiple GBM transcriptional states, such as oligodendrocyte progenitor-like, neural progenitor-like, astrocyte-like, and mesenchymal-like, that can change during tumor evolution (6-7).

The growth of GBM is further supported by the induction of angiogenesis, which provides an ever-present supply of oxygen and nutrients (8). Low oxygen levels in the tumor microenvironment (TME) drive the secretion of angiogenic factors like VEGF from surrounding stroma to sustain angiogenesis and aid the escape or re-entry of tumor cells through the blood stream (9). Mutations in the epidermal growth factor receptor (EGFR) gene, deletions in the phosphatase and tensin homolog (PTEN) tumor suppressor gene, and activation of the PI3K/AKT/mTOR signaling pathway are genetic and molecular changes that promote relentless growth of GBM and invasion to surrounding tissues (10). Furthermore, proteolytic enzymes such as matrix metalloproteinases (MMPs) secreted by GBM cells degrade the extracellular matrix (ECM), which breaks down tissue barriers and aids tumor spread (Figure 1).

Treating GBM is also made more difficult by the blood-brain barrier (BBB) and blood-tumor barrier (BTB). The BBB normally prevents most therapeutic agents from entering the brain, resulting in an anatomically and physiologically immune-privileged site that often impedes therapy with immunotherapies (11). Although the BTB formed around the GBM may be more penetrable than the BBB, this irregular permeability restricts effective drug transport. As a result, this immune-privileged niche can reduce the surveillance of immune activity and promote the escape of GBM from defense via host immunity, further supporting tumor expansion (12-13). In conjunction with the intrinsic cellular heterogeneity of GBM, these barriers render its effective treatment exceedingly difficult (Figure 2).

Table 1. The mechanisms and clinical implications of the spread of GBM

Spread Factor	Mechanism	Clinical Implications
Invasiveness	GBM cells infiltrate surrounding brain tissue	Makes surgical and localized treatment less effective
Glioma Stem Cells	Treatment-resistant stem-like cells drive growth and spread	Leads to high recurrence and treatment resistance
Angiogenesis	Formation of new blood vessels to support tumor growth	Supports sustained tumor growth and distant spread within the brain
Genetic Alternations	Mutations in EGFR,PTEN and PI3K/AKT/mTOR pathways	Drives aggressive proliferation and spread
ECM Degradation	Degradation of extracellular matrix by MMP enzymes	Allows tumor cells to invade adjacent tissues
Immune Evasion	Immune system suppression due to the brain's immune-privileged environment	Limits the body's natural ability to fight the tumor
Tumor Heterogeneity	Genetic diversity among tumor cells enables survival and spread	Results in poor treatment response and recurrence
Resistance to Apoptosis	Resistance to programmed cell death (apoptosis)	Prolongs tumor cell survival and promotes invasion
Tumor Microenvironmental Interaction	GBM interacts with surrounding cells and immune responses to enhance spread	Creates a supportive environment for further invasion and growth

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GBM: Glioblastoma multiforme; EGFR: Epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog; ECM: Extracellular matrix; MMP: Matrix metalloproteinases.

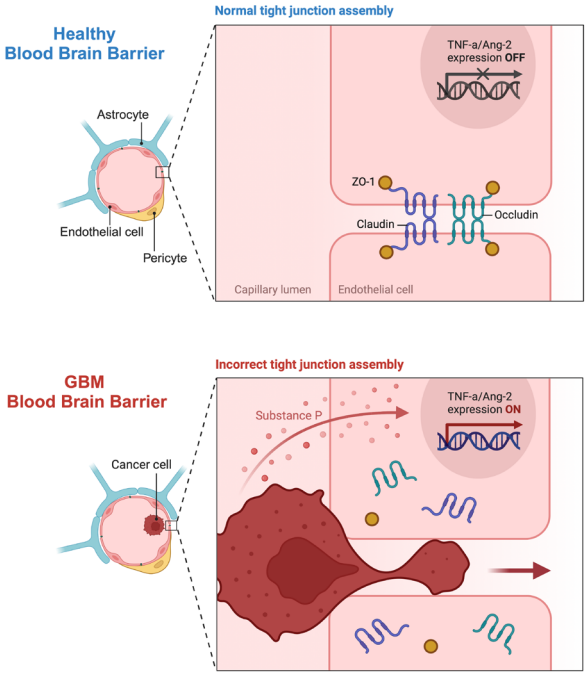

Figure 1. The structure of the BBB in normal brain tissue and the GBM.
The upper panel represents a healthy BBB, which is characterized by normal tight junction assembly between endothelial cells. Tight junction proteins (ZO-1, Claudin and Occludin) maintain the integrity of the barrier and thus prevent unwanted crossing of material from blood to the brain. The synthesis of pro-inflammatory factors such as TNF-α and Ang-2, is inhibited, and tight junction formation is maintained. The lower panel depicts the effect of brain tumors on BBB permeability, depicting the aberrant tight junction assembly. This permeability allows substances such as substance P to infiltrate the brain, as tumor cells disrupt tight junction proteins. The pro-inflammatory factors TNF-α and Ang-2 stimulate barrier disruption, which ultimately promotes tumor cell infiltration and metastasis. This leakiness of a dysfunctional BBB facilitates the transference of cancer cells and toxic elements across the BBB, thereby promoting glioma growth and invasive progression in the brain (Created in https://BioRender.com).

BBB: Blood–brain barrier; GBM: Glioblastoma multiforme; TNF-α: Tumor necrosis factor alpha; Ang-2: Angiotensin-2.

GBM cells create apoptosis-resistance mechanisms that enable cells to survive despite the invasion of neighboring tissues (14). Additionally, GBM cells also affect adjacent cells and the immune system to form a protective niche for unrestricted tumor growth. This variability and evolutionary liability makes it improbable that a single treatment modality can be designed, emphasizing the need for therapies that take into account genetic, cellular, and environmental diversity in GBM (15).

Current Treatment Modalities for GBM

Due to the aggressive properties of GBM and the hindrance caused by BBB in drug penetration, GBM treatment involves a multimodal approach (16). These methods are referred to as the first treatment for GBM, which consists mainly of surgery, radiotherapy, chemotherapy, and targeted therapy (17).

Temozolomide (TMZ) is an oral chemotherapeutic agent that inhibits the replication of cancer cells by acting on their DNA (18). It is usually administered in conjunction with radiotherapy as one of the first lines of standard treatment for GBM. It plays a role in front-line therapy due to its capacity to partially penetrate the BBB, whereby it can affect tumor cells within the brain (19). Nonetheless, TMZ penetrates the barrier incompletely, and its efficacy is limited, whereas GBM is often accompanied by the development of resistance dynamics. Although TMZ is effective for treating newly diagnosed GBM, its long-term effects are often abrogated by cell resistance to drug-mediated cytotoxicity and limited brain penetration (20).

The role of TMZ in PFS and overall survival (OS) in GBM has been disputed for years, especially when it comes to the long-term effects of TMZ on survival (18-20). TMZ has shown efficacy in PFS. Many trials have demonstrated that the combination of concomitant radiation with TMZ is associated with a longer time to progression in patients with newly diagnosed GBM. Nevertheless, the median time to PFS for patients on TMZ is relatively short; typically within the 6–9 month range (18-20). This means that although the drug delays tumor growth for a period, it does not prevent the disease from progressing. Furthermore, the role of TMZ in improving OS is controversial. Although TMZ has been demonstrated to prolong OS compared with other therapeutic regimens, the impact is modest. When TMZ with radiation is used, for example, the median OS usually is on the order of 14–16 months (18-20). The question of whether TMZ is effective against OS remains open, even more so in cases of relapsing GBM after this treatment when the disease frequently develops resistance to the drug.

Bevacizumab, a targeted agent, is capable of inhibiting VEGF, a major force promoting tumor angiogenesis (21). Bevacizumab inhibits the process of angiogenesis by blocking VEGF, limiting tumor blood supply to naturally reduce tumor size and decrease the symptoms of edema. Bevacizumab is mainly used for recurrent GBM after the first-line treatment, such as surgery, radiotherapy, and TMZ, has failed, especially in advanced-stage symptom control, contributing to brain edema or other neurological deficits (22). Bevacizumab leads to a relative prolongation of PFS; however, its effect on OS remains unclear and has been debated in GBM. Eventually, treatment fails because of the inevitable resistance to bevacizumab (21-22). Further studies are needed to elucidate the underlying mechanisms and to develop new methods of drug delivery to enhance efficacy and reduce resistance.

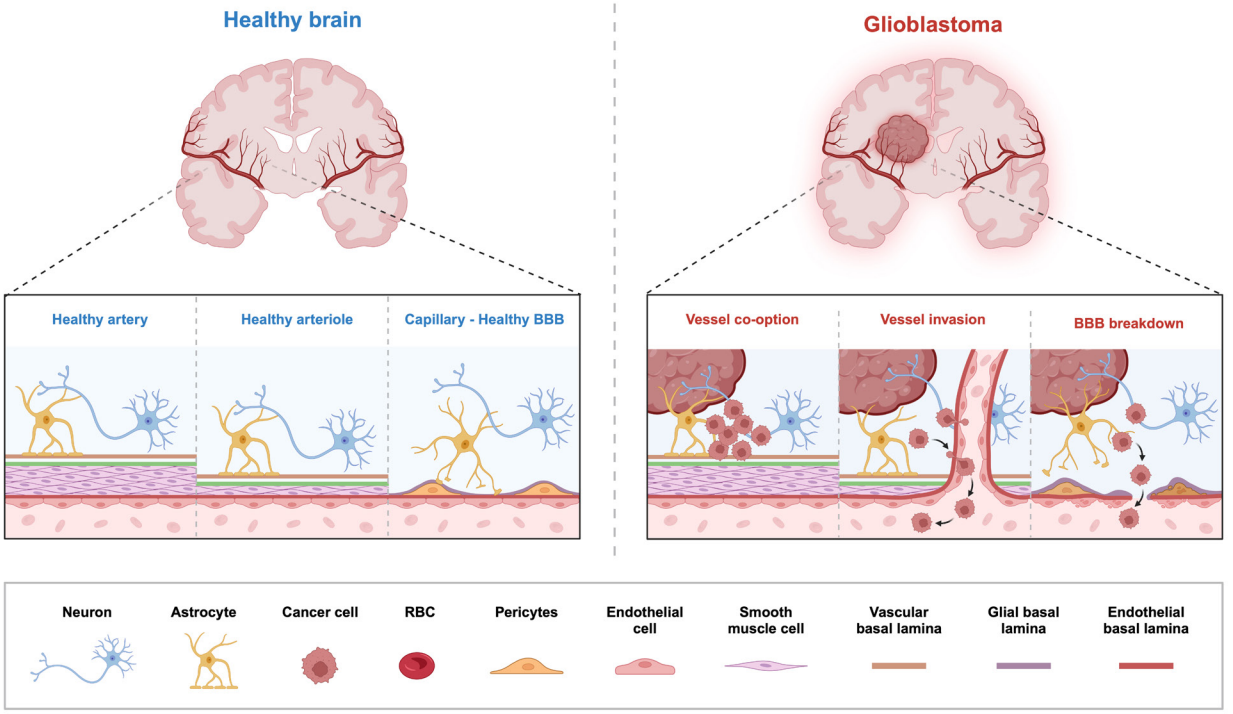

Figure 2. Neuropathological illustration comparing vascular structures in healthy brain versus GBM-invaded brain tissue. The schematic representation illustrates the differences between normal brain vasculature and the pathological vascular microenvironment in GBM. In a normal brain, the BBB provides a protective layer that prevents unwanted components from entering the brain. This barrier involves the cooperation of several key cells, including neurons, astrocytes, pericytes, and endothelial cells. The left column depicts a normal brain with preserved BBB structures where pericytes, astrocytes, and endothelial cells maintain healthy arteries, arterioles, and capillaries supported by neurons. A GBM-invaded brain is depicted on the right panel, with vessel co-option (black arrow), vessel invasion (white arrows), and BBB breakdown as hallmarks of cancer progression. Some of these alterations in pathology enable infiltration into surrounding brain tissue and destruction of the BBB; both allow for expansion and dissemination of GBM. By contrast, in GBM, cancer cells derange this organization via vessel co-option (tumor cells use pre-existing blood vessels), followed by infiltration of tumor cells into the vascular wall, and ultimately BBB disruption. These adaptations allow cancer cells to metastasize, modify blood circulation, and provide nutrients and oxygen to the tumor. BBB dysfunction hampers effective treatment delivery by hindering therapeutic agents from reaching the tumor site, which causes GBM to exhibit an aggressive phenotype and exhibit resistance to conventional therapies (Created in https://BioRender.com).

BBB: Blood–brain barrier; GBM: Glioblastoma multiforme; RBC: Red blood cell.

Bevacizumab as a Targeted Therapeutic Agent

Bevacizumab blocks VEGF-mediated invasion and spread (Figure 2). The importance of these results lies in the possible integration of bevacizumab with other therapies targeting invasion and metastasis. Furthermore, emerging preclinical evidence suggests that bevacizumab may affect tumor metabolism. These results are noteworthy because GBM cells mostly use glucose for energy and often exhibit a glycolytic phenotype, even in oxygen-rich environments (23). Moreover, GBM cells can effectively metabolize lactate (24). Researchers have reported that the antiangiogenic drug bevacizumab worsens hypoxic stress by stopping the growth of new blood vessels and changing how tumor cells use energy. When bevacizumab is mixed with metabolic drugs that stop glycolysis, biological treatment may be more effective (23-24).

Although bevacizumab mainly antagonizes VEGF-A, emerging evidence implicates other pathways in its effects (25). Bevacizumab enhances the tumor microenvironment and inhibits the infiltration of regulatory T cells and myeloid-derived suppressor cells into tumors. While current immunotherapies, like anti-PD-1 and anti-CTLA-4, use counter-immunity (PD-L1 or CTLA-4) to make the "counter-immune" agents less efficient,

if bevacizumab can clear these immune-suppressing cells, they may enhance their effectiveness by allowing more of them to survive (26). In addition, the mobilization of ECM is an important physiological action of bevacizumab. VEGF is an established mediator of ECM degradation and allows tumors to infiltrate normal tissue (27).

Clinical Significance of Bevacizumab in GBM

Bevacizumab is widely used because it effectively reduces peritumoral edema, headache, and seizures caused by high intracranial pressure (27). The FDA has approved bevacizumab for treating recurrent GBM. This approach not only reduced the need for corticosteroids but also likely aided for treating neurological symptoms in a group in which these issues substantially affected their quality of life (28). However, its limited impact on OS constrains the advantages of bevacizumab in enhancing PFS (27-28). In response to this issue, researchers have conducted clinical trials that combine bevacizumab with other medications to enhance its efficacy. Researchers may use immune checkpoint inhibitors such as nivolumab and ipilimumab, combined with bevacizumab, can enhance the presence of $CD8^+$ effector T cells and lymphoid structures inside tumors. This treatment may provide therapeutic effects (29).

Bevacizumab alters the tumor microenvironment and may increase immunotherapy efficiency by promoting immune surveillance and cytotoxicity against tumor cells. This mechanism could further enhance the synergy of combination therapy with anti-PD-L1 agents (27-29). This has also led to clinical trials of the wide range of antiangiogenic combinations that are currently under investigation aiming at targeting certain angiogenic pathways to possibly bypass resistance to anti-VEGF therapies (30). Other pro-angiogenic factors, such as fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), have received attention as possibly having greater importance in stimulating angiogenesis than VEGF alone (27–30). Investigators have also been investigating the use of bevacizumab combined with agents that inhibit the hepatocyte growth factor (HGF) or insulin-like growth factor 1 (IGF1) pathways to optimize treatment. However, the emergence of resistance of some tumor cells to bevacizumab and other targeted therapies is still unknown (27-30). Several recent studies have focused on targeting bevacizumab via nanotechnology to further its site-specific therapeutic use and prolong its therapeutic effect (31). Nanocarriers such as liposomes, polymeric nanoparticles (NPs), and exosome-based systems help increase drug proximity to tumors (32). This might increase the life span of patients without increasing poor PFS or OS rates. To enhance immune activity and limit resistance, the use of checkpoint inhibitors with bevacizumab has been explored (32).

Integrating Bevacizumab with Nanotechnology for GBM Treatment

One of the most utilized nanotechnological approaches is the design of NPs that are denoted as a suitable solution to the hard-line penetration of conventional drugs due to the dual enhancement of passive and active delivery of them to GBM tumor cells (33). The most inspiring point is that intravenously injected NPs can be easily homed specifically to the brain by navigating through the BBB. From the tumor angiogenesis environment, NPs serve as main actors in the multi-targeted intervention of GBM tumor cells, as well as tumor angiogenesis and vessel barriers (34). To form a mononuclear phagocyte system and secrete cytokines, it is a routine process that various inorganic and organic substances are encapsulated onto the surface of NPs, mainly smoothing the phagocytosis of macrophages, elongating the period of the biological circulation of NPs, and enhancing delivery to the brain, improving BBB penetration and permeability (33-34).

Many types of NPs have shown wonderful application in the imaging department, particularly gadolinium, gold NPs, and carbon-based materials, offering MRI, CT, and fluorescence-mediated imaging of GBM (33-34). Furthermore, it is worth noting that the application of cell membrane-camouflaged NPs can surmount the barriers of the BBB and BTB in tumor cells (35).

Recent studies have shown big steps forward in using nanotechnology to make bevacizumab more effective in treating GBM, especially in getting past the BBB, which is a major problem for drugs that are meant to target the brain (Figure 2). Using gold NPs (AuNPs) with bevacizumab makes the BBB more permeable, which helps target tumors and boosts anticancer effects at the same time (36). Bevacizumab-coated NPs concentrate around the tumor, reducing contact with healthy tissue and improving the drug's therapeutic effectiveness (37). Researchers have found that adding bevacizumab to a nanoparticle delivery system makes other drugs work better at stopping the growth of new blood vessels and the immune system's response to them. Graphene quantum dots (GQDs) have the potential to improve drug delivery via photothermal effects (38). This results from their capacity to augment membrane permeability and promote the infiltration of medications into cells. This comprehensive approach may substantially impede tumor progression while minimizing the negative effects often associated with systemic therapies. Ultrasonic technology and nanoparticle therapeutics are being studied together in new clinical studies to determine how they can work better together to pass the BBB.

Initial research suggests that this approach improves drug delivery and alters the tumor microenvironment to promote immune system recognition. This is a notable progression in the immunotherapeutic treatment of GBM (39). Technologies such as biodegradable hydrogel systems and implanted devices that provide bevacizumab locally and continuously may be used. These technologies provide increased concentrations of medication at the tumor location, possibly improving patient outcomes over time and extending PFS (40). These strategies are important for treating GBM because they allow the creation of platforms for multifunctional NPs that can target,

transport, and change the immune system. These are crucial for addressing the complexity and resistance mechanisms of GBM (39-40).

Clinical Trials

Ongoing studies are exploring the existence of biomarkers predictive of clinical response to bevacizumab, which may lead to a more personalized treatment strategy for GBM (41). High VEGF levels, tumor hypoxia, and certain genotypes of FGF have been proposed as biomarkers for predicting the response to treatment with bevacizumab, which allows researchers and clinicians to personalize therapeutic regimens according to individual tumor characteristics to improve efficacy (42). Various combinations of bevacizumab with immune checkpoint inhibitors, as well as molecularly targeted drugs, are currently being investigated in clinical trials to enhance treatment outcomes for GBM (42). Co-therapy with inhibitors of the PI3K/AKT/mTOR pathway, which is frequently altered in GBM, has shown promise in preclinical models, thereby appearing to represent a potential approach for further inhibition of pathophysiological processes enabled by bevacizumab therapy (43). Alternative studies suggest improved responses from combining radiation or agents that inhibit DNA damage repair pathways with bevacizumab to take advantage of the intrinsic sensitivity of GBM cells and minimize other patterns of resistance, a common obstacle in long-term therapy with bevacizumab (44). Additionally, several new drug delivery systems based on nanotechnology have been developed to enhance the efficacy and safety profile of bevacizumab (45). Improvements in nanoparticle design have been reported to enable targetable, locus targeted delivery of therapeutic agents like bevacizumab with reduced systemic exposure and increased tumor vulnerability (46). Nanoparticle platforms capable of crossing the BBB to enable simultaneous delivery of multiple therapies on one platform are also in development. Targeting multiple pathways and conveying better bioactivity of bevacizumab using these platforms can lessen treatment resistance by providing an innovative strategy to overcome the multifactorial nature of GBM.

CONCLUSION

Bevacizumab continues to be a crucial antiangiogenic treatment for GBM, showing improvements in symptomatic and PFS. Given that bevacizumab failed to extend survival, phase II investigations into combination therapies and innovative drug delivery methods are needed. These investigations must focus on non-VEGF-driven pathways that are unaffected by VEGF suppression. For many years, nanotechnology-based delivery methods have provided an effective solution to these issues, allowing targeted and controlled bevacizumab release with minimal systemic adverse effects (47). Adding bevacizumab to immunotherapy and molecularly targeted treatments or improving the nanoparticle delivery system might improve GBM treatment work better (48).

We anticipate that discovery will stimulate significant future molecular research in GBM, perhaps leading us to overcome this fatal disease. We anticipate that the creation of tumor-specific therapy vectors using bevacizumab will enhance the prognosis and survival rates of individuals afflicted with these lethal illnesses in the coming decade (49). This suggests that further research is required to determine the optimal combination of treatment modalities and to identify potential biomarkers that could predict patient outcomes. This may enhance the beneficial effects of bevacizumab in patients (50).

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REFERENCES

1. Lan Z, Li X, Zhang X. Glioblastoma: An update in pathology, molecular mechanisms and biomarkers. Int J Mol Sci 2024; 25(5): 3040.
2. Bou-Gharios J, Noël G, Burckel H. Preclinical and clinical advances to overcome hypoxia in glioblastoma multiforme. Cell Death Dis 2024; 15(7): 503.
3. Aghajani M, Jalilzadeh N, Aghebati-Maleki A, Yari A, Tabnak P, Mardi A, et al. Current approaches in glioblastoma multiforme immunotherapy. Clin Transl Oncol 2024; 26(7): 1584-612.
4. Shahcheraghi SH, Alimardani M, Lotfi M, Uversky VN, Guetchueng ST, Palakurthi SS, et al. Advances in glioblastoma multiforme: Integrating therapy and pathology perspectives. Pathol Res Pract 2024; 257: 155285.
5. Lorimer I. Modeling glioblastoma. eLife 2024; 13: e100824.
6. Wu H, Guo C, Wang C, Xu J, Zheng S, Duan J, et al. Single-cell RNA sequencing reveals tumor heterogeneity, microenvironment, and drug-resistance mechanisms of recurrent glioblastoma. Cancer Sci 2023; 114(6): 2609-21.
7. Tomar MS, Kumar A, Srivastava C, Shrivastava A. Elucidating the mechanisms of Temozolomide resistance in gliomas and the strategies to overcome the resistance. Biochim Biophys Acta Rev Cancer 2021; 1876(2): 188616.
8. Cortes Ballen AI, Amosu M, Ravinder S, Chan J, Derin E, Slika H, et al. Metabolic reprogramming in glioblastoma multiforme: A review of pathways and therapeutic targets. Cells 2024; 13(18): 1574.
9. Sarkar S, Patranabis S. Immunomodulatory signalling networks in glioblastoma multiforme: a comprehensive review of therapeutic approaches. Hum Cell 2024; 37(5): 1355-1377.
10. Barzegar Behrooz A, Talaie Z, Jusheghani F, Łos MJ, Klonisch T, Ghavami S. Wnt and PI3K/Akt/mTOR survival pathways as therapeutic targets in glioblastoma. Int J Mol Sci 2022; 23(3): 1353.

11. Jena L, McErlean E, McCarthy H. Delivery across the blood-brain barrier: nanomedicine for glioblastoma multiforme. Drug Deliv Transl Res 2020; 10(2): 304-18.
12. Song X, Qian H, Yu Y. Nanoparticles mediated the diagnosis and therapy of glioblastoma: bypass or cross the blood-brain barrier. Small 2023; 19(45): e2302613.
13. Pearson JRD, Cuzzubbo S, McArthur S, Durrant LG, Adhikaree J, Tinsley CJ, et al. Immune escape in glioblastoma multiforme and the adaptation of immunotherapies for treatment. Front Immunol 2020; 11: 582106.
14. Tang W, Fan W, Lau J, Deng L, Shen Z, Chen X. Emerging blood-brain-barrier-crossing nanotechnology for brain cancer theranostics. Chem Soc Rev 2019; 48(11): 2967-3014.
15. Kılıç T, Yıldırım Ö, Şahin S, Pamir MN. Glial tümörlerin anjiogenezi. Turk Neurosurg 2005; 15(1): 1-9.
16. Michaelsen SR, Staberg M, Pedersen H, Jensen KE, Majewski W, Broholm H, et al. VEGF-C sustains VEGFR2 activation under bevacizumab therapy and promotes glioblastoma maintenance. Neuro Oncol 2018; 20(11): 1462-74.
17. Diaz RJ, Ali S, Qadir MG, De La Fuente MI, Ivan ME, Komotar RJ. The role of bevacizumab in the treatment of glioblastoma. J Neurooncol 2017; 133(3): 455-67.
18. Arora H, Mammi M, Patel NM, Zyfi D, Dasari HR, Yunusa I, et al. Dexamethasone and overall survival and progression free survival in patients with newly diagnosed glioblastoma: a meta-analysis. J Neurooncol 2024; 166(1): 17-26.
19. Pasupuleti V, Vora L, Prasad R, Nandakumar DN, Khatri DK. Glioblastoma preclinical models: strengths and weaknesses. Biochim Biophys Acta Rev Cancer 2024; 1879(1): 189059.
20. Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: The CheckMate 143 phase 3 randomized clinical trial. JAMA Oncol 2020; 6(7): 1003-10.
21. Tsien CI, Pugh SL, Dicker AP, Raizer JJ, Matuszak MM, Lallana EC, et al. NRG Oncology/RTOG1205: A randomized phase II trial of concurrent bevacizumab and reirradiation versus bevacizumab alone as treatment for recurrent glioblastoma. J Clin Oncol 2023; 41(6): 1285-95.
22. Tamura R, Tanaka T, Ohara K, Miyake K, Morimoto Y, Yamamoto Y, et al. Persistent restoration to the immunosupportive tumor microenvironment in glioblastoma by bevacizumab. Cancer Sci 2019; 110(2): 499-508.
23. De Leo A, Ugolini A, Yu X, Scirocchi F, Scocozza D, Peixoto B, et al. Glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma. Immunity 2024; 57(5): 1105-23.e8.
24. Rashidi A, Billingham LK, Zolp A, Chia TY, Silvers C, Katz JL, et al. Myeloid cell-derived creatine in the hypoxic niche promotes glioblastoma growth. Cell Metab 2024; 36(1): 62-77.e8.
25. Stadlbauer A, Roessler K, Zimmermann M, Buchfelder M, Kleindienst A, Doerfler A, et al. Predicting glioblastoma response to bevacizumab through MRI biomarkers of the tumor microenvironment. Mol Imaging Biol 2019; 21(4): 747-57.
26. Fathi M, Razavi SM, Sojoodi M, Ahmadi A, Ebrahimi F, Namdar A, et al. Targeting the CTLA-4/B7 axes in glioblastoma: Preclinical evidence and clinical interventions. Expert Opin Ther Targets 2022; 26(11): 949-61.
27. de Cristo Soares Alves A, Lavayen V, de Fraga Dias A, Bruinsmann FA, Scholl JN, Cé R, et al. EGFRvIII peptide nanocapsules and bevacizumab nanocapsules: A nose-to-brain multitarget approach against glioblastoma. Nanomedicine (Lond) 2021; 16(20): 1775-90.
28. Cai Q, Li X, Xiong H, Fan H, Gao X, Vemireddy V, et al. Optical blood-brain-tumor barrier modulation expands therapeutic options for glioblastoma treatment. Nat Commun 2023; 14(1): 4934.
29. Mauldin IS, Jo J, Wages NA, Yogendran LV, Mahmutovic A, Young SJ, et al. Proliferating CD8+ T cell infiltrates are associated with improved survival in glioblastoma. Cells 2021; 10(12): 3378.
30. Jimenez-Pascual A, Mitchell K, Siebzehnrubl FA, Lathia JD. FGF2: A novel druggable target for glioblastoma? Expert Opin Ther Targets 2020; 24(4): 311-8.
31. Singh RR, Mondal I, Janjua T, Popat A, Kulshreshtha R. Engineered smart materials for RNA based molecular therapy to treat glioblastoma. Bioact Mater 2023; 33: 396-423.
32. Wiwatchaitawee K, Quarterman JC, Geary SM, Salem AK. Enhancement of therapies for glioblastoma (GBM) using nanoparticle-based delivery systems. AAPS PharmSciTech 2021; 22(2): 71.
33. Ruiz-Garcia H, Ramirez-Loera C, Malouff TD, Seneviratne DS, Palmer JD, Trifiletti DM. Novel strategies for nanoparticle-based radiosensitization in glioblastoma. Int J Mol Sci 2021; 22(18): 9673.
34. Lakshmi BA, Kim YJ. Modernistic and emerging developments of nanotechnology in glioblastoma-targeted theranostic applications. Int J Mol Sci 2022; 23(3): 1641.
35. Jena L, McErlean E, McCarthy H. Delivery across the blood-brain barrier: Nanomedicine for glioblastoma multiforme. Drug Deliv Transl Res 2020; 10(2): 304-18.
36. She L, Su L, Liu C. Bevacizumab combined with re-irradiation in recurrent glioblastoma. Front Oncol 2022; 12: 961014.
37. Uddin MS, Mamun AA, Alghamdi BS, Tewari D, Jeandet P, Sarwar MS, et al. Epigenetics of glioblastoma multiforme: From molecular mechanisms to therapeutic approaches. Semin Cancer Biol 2022; 83: 100-20.
38. Cui X, Huo D, Wang Q, Wang Y, Liu X, Zhao K, et al. RUNX1/NPM1/H3K4me3 complex contributes to extracellular matrix remodeling via enhancing FOSL2 transcriptional activation in glioblastoma. Cell Death Dis 2024; 15(1): 98.
39. Mahmoud AB, Ajina R, Aref S, Darwish M, Alsayb M, Taher M, et al. Advances in immunotherapy for glioblastoma multiforme. Front Immunol 2022; 13: 944452.
40. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2023; 41(32): 4945-52.
41. Collado J, Boland L, Ahrendsen JT, Miska J, Lee-Chang C. Understanding the glioblastoma tumor microenvironment: leveraging the extracellular matrix to increase immunotherapy efficacy. Front Immunol 2024; 15: 1336476.
42. Chamarthy S, Mekala JR. Functional importance of glucose transporters and chromatin epigenetic factors in glioblastoma multiforme (GBM): possible therapeutics. Metab Brain Dis 2023; 38(5): 1441-69.
43. Abdi F, Arkan E, Eidizadeh M, Valipour E, Naseriyeh T, Gamizgy YH, et al. The possibility of angiogenesis inhibition in cutaneous melanoma by bevacizumab-loaded lipid-chitosan nanoparticles. Drug Deliv Transl Res 2023; 13(2): 568-79.
44. Khan MA, Kalsoom S, Ayub AR, Ilyas M, Hassan N, Irshad K, et al. Host-guest coupling to potentially increase the bio-accessibility of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea by nanocarrier graphyne for brain tumor therapy, a comprehensive quantum mechanics study. J Mol Graph Model 2023; 123: 108517.
45. Tensaouti F, Desmoulin F, Gilhodes J, Roques M, Ken S, Lotterie JA, et al. Is pre-radiotherapy metabolic heterogeneity of glioblastoma predictive of progression-free survival? Radiother Oncol 2023; 183: 109665.

46. Liang HT, Mizumoto M, Ishikawa E, Matsuda M, Tanaka K, Kohzuki H, et al. Peritumoral edema status of glioblastoma identifies patients reaching long-term disease control with specific progression patterns after tumor resection and high-dose proton boost. J Cancer Res Clin Oncol 2021; 147(12): 3503-16.
47. Brown CE, Rodriguez A, Palmer J, Ostberg JR, Naranjo A, Wagner JR, et al. Off-the-shelf, steroid-resistant, IL13Rα2-specific CAR T cells for treatment of glioblastoma. Neuro Oncol 2022; 24(8): 1318-30.
48. Jo J, Wen PY. Antiangiogenic therapy of high-grade gliomas. Prog Neurol Surg 2018; 31: 180-99.
49. Kim MM, Umemura Y, Leung D. Bevacizumab and glioblastoma: Past, present, and future directions. Cancer J 2018; 24(4): 180-6.
50. Carvalho B, Lopes JM, Silva R, Peixoto J, Leitão D, Soares P, et al. The role of c-Met and VEGFR2 in glioblastoma resistance to bevacizumab. Sci Rep 2021; 11: 6067.