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# Glioblastoma Multiforme: A Therapeutic Review

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*Abstract*— **Glioblastoma multiforme (GBM) is one of the most common forms of malignant brain cancer. Despite advancements in technology and treatment over the past century, GBM remains largely incurable. Standard approaches for treatment include surgery and combinations of radiotherapy and chemotherapy, but factors such as the highly selective blood-brain barrier have made treating GBM and other brain diseases extremely difficult. However, immunotherapy or "personalized medicine" integrated with chemotherapy or radiotherapy may become the future for targeting GBM tumors and other brain diseases. This review evaluates the mechanisms and efficacy of standard drugs such as temozolomide and bevacizumab, as well as novel advancements in the field, such as nano-mediated drug delivery systems (NDDS) and the rise of immunology as a basis for treating GBM.**

## I. Introduction

Accounting for more than 78% of brain cancers [1] and causing almost 15,000 deaths every year, glioblastoma multiforme (GBM) is one of the most common and aggressive malignant tumor forms in the central nervous system. GBM is characterized as a high-grade intra-axial tumor because it interferes with brain tissue [1]. Tumors are categorized as "low-grade" or "high-grade" depending on their invasiveness and growth rate [2], with low-grade cancers growing more slowly with less likelihood of metastasizing, or spreading to other sites of the body, than high-grade cancers [1]. GBM develops in glial cells, cells that protect neural tissue, causing a toxic buildup of glutamate, an excitatory neurotransmitter for cell signaling [3]. The excess glutamate kills surrounding neurons, creating brain space for the tumor to expand [4].

A variety of factors are taken into consideration when determining treatment, which may include varying combinations of surgery, radiation, and chemotherapy. Currently only two drugs, temozolomide and bevacizumab, are FDA-approved to treat GBM [5]. Unfortunately, these two chemotherapy drugs have had very limited impact on GBM patient survival rates [6]. Developing alternative and targeted therapies has posed a challenge as glioma tumor cells are protected by the blood-brain barrier (BBB), which is a highly selective semipermeable membrane that acts to protect the brain from pathogens and infections. Due to the barrier's highly selective permeability, many therapies are unable to cross this boundary [7]. This review will discuss traditional treatments and potentially new technology for the treatment of GBM.

## II. Traditional Treatments

One class of the oldest chemotherapy drugs used for GBM and other cancer forms is alkylating agents, which are able to permeate the BBB [8], making them an optimal choice for GBM treatment. Alkylating agents are used in cancer therapies due to their ability to prevent cells from replicating by inflicting damage to the cell's DNA [9]. Temozolomide (TMZ) is a typical alkylating agent used for GBM therapy, usually in conjunction with radiotherapy. The drug methylates DNA guanine bases [10], which results in alkylation of the DNA and DNA damage. Subsequently, this triggers apoptosis of malignant cells [11]. However, some tumor cells can become resistant to TMZ's effects, especially if the tumor cells have mutated and contain the gene MGMT that allows the cancerous cells to repair the DNA damage, preventing apoptosis and continuing the uncontrolled proliferation of the damaged cells [12]. Though TMZ-based chemotherapy demonstrates a comparable improvement in the treatment of patients who have high-grade gliomas, the median increase in survival for patients with GBM is only 2.5 months [13]. Recent studies also indicate that 60-75% of patients with GBM derive no benefit in regards to increased lifespan and quality of life from treatment with TMZ, demonstrating that the drug is only a modestly effective chemotherapy [13]. Additionally, 15-20% of patients who were treated with TMZ developed significant toxicity [14] and side effects such as amnesia and paralysis [15]. While TMZ is a widely-used drug, there is a significant need for chemotherapy or treatment with higher efficacy and safety.

Failure in treating GBM with TMZ chemotherapy led to the development of monoclonal antibodies and the introduction of targeted immunotherapies. Monoclonal antibodies have been used in therapy processes because of their high affinity for specific proteins involved in brain tumors and other cancers [16]. In 2004, the FDA approved bevacizumab (BEV), which inhibits angiogenesis, the development of new blood vessels, by neutralizing and blocking vascular endothelial growth factor (VEGF), a signaling protein that guides new vessel formation [18]. By targeting tumor growth mechanisms and inhibiting cell growth and division, BEV is able to block oncogenic signaling. Researchers have shown that glioma cells express and secrete VEGF, which has a positive correlation with increased tumor strength and aggressiveness. Since vascular proliferation is a hallmark of glioblastomas, [19], [20], BEV and its VEGF targeting mechanisms have been introduced for GBM.

With regards to GBM, bevacizumab slows tumor growth, but it does not cure the actual tumor itself or prolong overall patient survival time [16]. Additionally, rebound phenomena such as tumor recurrence and regrowth are often observed after discontinuation of BEV therapy [21]. Adverse side effects, such as hypertension and proteinuria are also associated with BEV usage [22]. While BEV has been shown to improve the quality of life for patients and has slight efficacy in recurrent GBM [23], [24], it is still only modestly

effective in treating GBM overall. With the need for more effective treatment, the basic mechanism of bevacizumab as a monoclonal antibody has led to the development of new immunotherapies and advanced technology systems in treating GBM.

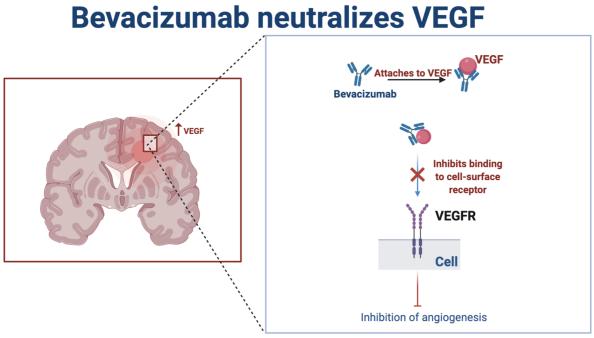


Figure 1: Bevacizumab is a monoclonal antibody that inhibits angiogenesis, the process by which new blood vessels form. It does so by blocking vascular endothelial growth factor (VEGF), a signaling protein that guides new vessel formation and is expressed in glioma cells. It has led to the development of new immunotherapies and advanced alternative treatment options, such as a vaccine targeting VEGF receptors in neurofibromatosis type 2 [62].

## III. Novel Treatment Options

Though traditional drugs have had some limited success in treating GBM, nanotherapeutic drug delivery systems (NDDSs) and nanocarriers, transport vehicles for drugs, are rising in popularity as new alternative targeted cancer treatments. Compared to traditional drugs, NDDSs have been shown to have increased advantages when it comes to treating cancers, such as improved stability, enhanced permeability, and highly accurate targeting [25], [26]. Additionally, they have been shown to overcome cancer-related drug resistance by targeting resistance mechanisms including defective programmed cell death and overexpression of transporters [27]. Using NDDSs for treatment of brain cancer has become a promising alternative, as it is more effective at transporting chemotherapeutics across the BBB than traditional therapies and has minimal side effects on healthy, surrounding tissue [28], [29]. Dp44mt (Di-2-pyridyl ketone-4, 4-dimethyl-3-thiosemicarbazone) is a novel glioma-targeted nano-therapeutic that has been found to specifically target its toxicity towards glioma cells with no impact on the surrounding healthy tissue [28], [29]. When tested in mice, the Dp44mt nanoparticles reduced tumor growth by 62%. Other chemotherapies, such as TMZ and doxorubicin only reduced tumor growth by 16% [27], [30]–[32]. This may lead to better prognosis, and Dp44mt may serve as a more effective treatment for GBM in humans.

Attached to the nanocarrier, Dp44mt has a glioma-targeted ligand to Interleukin-13 (IL-13), which is found on gliomas [28]. In experimental studies, researchers found that Dp44mt's conjugation with IL-13 receptors on the tumor enhanced glioma cell uptake of the nanocarrier and allowed for more successful permeation of the BBB [28]. Dp44mt is an iron chelator, which extracts excess iron from cells. Though iron is not the underlying cause of many diseases, it does play a role in the rate of disease progression through facilitation of cellular growth and proliferation [33]. For cancer cells, the chelator removes the iron they need for maintaining basic cellular functions, thus starving them [34]. Dp44mt, with the use of a nanocarrier, is the first instance of testing a nano-therapeutic system on brain tumors; it has yielded successful results, as this chelator has been able to overcome multidrug resistance, a common trait of high-grade tumors that renders them immune to chemotherapies [35].

While the drug is still undergoing numerous trials before reaching FDA consideration for approval, certain components of the drug, such as the nanoparticles used to create the carrier, have already been approved [29], [36].

Though a novel form of targeted therapy, nanocarriers and nanotherapeutic drug delivery systems hold promise for the future of cancer therapies. However, as this is still a technology undergoing preliminary testing, the drug's success in animal models may not translate completely to patients, and side effects are still unknown in humans. With the uncertainty surrounding this new technology combined with the low efficacy and adverse side effects of traditional treatments, research has found focus on personalized immunotherapy.

## IV. Rise of Personalized Immunotherapies

Vaccines are among the most standard forms of immunotherapy for bacteria and viruses. Now, vaccines are on the rise to treat diseases such as Alzheimer's and cancer [37], [38]. Some vaccines that prevent certain viral infections such as human papillomavirus (HPV) and hepatitis B have been modified to serve as cancer vaccines [37]. Due to this repurposing, vaccine therapy for GBM has risen in popularity with the study and development of vaccines in three primary categories: peptide, heat-shock, and cell-based [38]–[41]. Currently, a recent vaccine study for human epidermal growth factor receptor 2 (HER2)-positive breast cancer moved forward after successful results in preventing cancer reformation [42]. In addition to being expressed in breast cancer, upregulated expression of HER2 has been identified in GBM, and could potentially be an immunotherapy target [43]. With the preliminary success of the HER2 vaccine for breast cancer, it could potentially be used as an immunotherapy for GBM as well.

Several current Phase I and Phase II trials for GBM studying immunotherapies have shown tumor reduction and lifespan expansion, as 20% of patients in the study survived from four to five years, which is unusual considering the high fatality of GBM [44]. Compared to other forms of treatment, vaccine immunotherapies are compelling because they have minimal toxicity and can induce a highly patient-personalized anti-tumor response that may be key to eradicating GBM [40].

Additionally, as each vaccine is highly unique to each patient's immune system, it aligns with the upcoming

concept of "personalized medicine" [45], [47]. Personalized medicine is more effective than standard medication as treatment is tailored to the genes of each specific person [45], which has been shown to have high efficacy in cancers such as breast cancer [46], [48]. It may make GBM, one of the most malignant human tumors, manageable for patients while reducing side effects and increasing quality of life [48]. However, vaccine therapy does face some challenges, as surgical removal or biopsy of the tumor may be necessary in order to identify pathology and prepare the vaccine accordingly [49]. Furthermore, because each vaccine is individualized to each patient, this treatment method may not be affordable for all patients. However, as more advances in technology development and existing trials continue, manufacturers may find a cheaper way to create these vaccines. Though it may be an expensive treatment as of now, the precision of personalized medicine can improve the overall quality of life after therapy compared to other treatments, and the results outweigh the cost.

mRNA vaccines have also shown promise in regard to cancer immunotherapy. After vaccination, vehicle-loaded mRNA vaccines express tumor antigens in antigen-presenting cells (APCs), causing APC activation and stimulation of the innate and adaptive immune system [50]. mRNA cancer vaccines hold high promise over other vaccine forms due to their specific toxicity to tumor cells, increased safety, and cost-effectiveness [50], [51]. However, mRNA vaccines have had limitations such as instability in their ability to break down and inefficient delivery in vivo to tumor cells [52]. Nucleotide modifications and other alterations have been investigated to overcome these challenges, and numerous studies are underway [53]. There also is potential in repurposing treatments, such as the COVID-19 vaccine, to treat GBM. Combinations of mRNA vaccines with other immunotherapies may also increase the anti-tumor immune response. With the recent FDA approval of mRNA vaccines for COVID-19 and promising results of other mRNA cancer vaccines against aggressive solid tumors [51], mRNA vaccines may be a potential immunotherapy treatment for GBM.

Though mainstream therapies have had limited success and other forms of immunotherapies are still undergoing trials, the development of chimeric antigen reporter (CAR) T-cell therapy has also shown promise in treating GBM [54]. The treatment relies on using the patients' collected and genetically engineered cells targeting specific tumor-associated antigens [55]. These cells are harvested from the patient, modified to target particular proteins that the tumor expresses, then injected into the patient to destroy the tumor cells [56]. Once the CAR construct binds to the intended target antigen, the T cells are activated, prompting a cytokine release [57]. CAR T has been approved for use in other cancers, such as acute lymphoblastic leukemia and non-Hodgkin's lymphoma [59]. Complete remission rates for patients with leukemia undergoing CAR T therapy have been as high as 68%-93%, indicating the treatment's high efficacy and potential [59], [60]. The approach used in these other cancers is now being applied to treating GBM [59]. There has been evidence that CAR T cells injected directly into the brain tumor tissue or spinal fluid may cause positive responses in patients [60], though a clinical trial is still underway for results to be validated.

The efficacy of CAR T therapy is still yet to be determined in GBM, as only preliminary studies of CAR T in GBM have been conducted. Therefore, it is essential to continue studying CAR T in the context of GBM since prior cancer studies have shown CAR T's effectiveness as a treatment option. Its application to GBM is still limited due to the lack of identified tumor-specific antigens expressed in the disease [61]. However, further advances in CAR T, such as multitargeting CAR T therapy, may be effective. Targets such as HER2, IL-13, and EGFRvIII have been identified as antigens involved in GBM, but there are numerous other antigens that have yet to be explored [55].

## V. Conclusion

GBM has been one of the solid tumor cancers that are the most difficult to treat, despite advances in recent technology and medicine. Current standards of care, such as TMZ and radiotherapy, have had limited success in treating patients, often resulting in a myriad of side effects that can be fatal, as well as a significant decrease in the quality of life for patients. As GBM is notoriously difficult to treat due to its high aggressiveness, there is a significant need for treatments with higher efficacy and safety.

Immunotherapy has emerged as a promising choice for treatment, alongside the concept of "personalized medicine." With numerous treatments under development or undergoing studies and trials, immunotherapies such as vaccines for GBM and CAR T therapy have shown positive results in efficacy, as well as reduced side effects.

This review discussed standard forms of treatment and introduced a new perspective regarding the rise of novel immunotherapies for use in GBM, including vaccines and CAR T. With their revolutionary success in treating other diseases, these therapies have significant potential for GBM. While this review does not have an exhaustive list of therapies, it provides insight into novel therapeutics, building off of the standard treatments currently available.

Based on the direction that these immunotherapies are taking, there is a significant likelihood that future clinical trials will place a greater emphasis on efficacy, safety, immune system mechanisms, and drug resistance prevention. With this, the future of GBM may be combinations of CAR T therapy, vaccines, and other modes of standard treatment, such as chemotherapy, radiation, surgery, etc., making the modern concept of "personalized medicine" a reality.

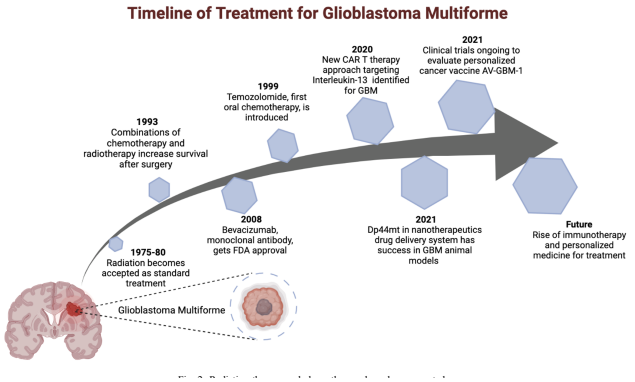


Figure 2: Radiation therapy and chemotherapy have been accepted as traditional forms of treatment for GBM but are still not sufficient. The rise of immunotherapy and "personalized medicine" have led to the development of potential new technology for the treatment of GBM, many of which are undergoing clinical trials and testing.

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