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REVIEW

Status and Prospects of Glioblastoma Multiforme Treatments

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive and common primary brain cancer in adults. Its standard-of-care therapy encompasses surgical resection, radiotherapy, and chemotherapy. Although this combination therapy somewhat extends patient survival, its efficacy remains limited, and the recurrence rate remains high. In recent years, novel therapeutic approaches for the treatment of GBM have emerged: (i) tumor-treating fields delivering nonionizing low-intensity alternating electric fields to disrupt mitosis; (ii) molecular targeted therapies that inhibit specific gene mutations or signaling pathways; (iii) immunotherapy that activates the patient's own immune system to fight this cancer; (iv) proton therapy, which, with its precise radiation dose distribution, minimizes damage to the normal brain parenchyma surrounding the GBM; (v) oncolytic virus therapy to selectively infect and lyse GBM cells; (vi) the use of nanoparticle carriers for targeted drug delivery to increase therapeutic efficacy and reduce side effects; (vii) phototherapy; and (viii) sonodynamic therapy. The purpose of this narrative is to review both standard-of-care and novel contemporary approaches to this devastating cancer. In the future, with further advancements in multiomics

Abbreviations: 5-ALA, 5-aminolevulinic acid; AIE, aggregation-induced emission; Akt, the collective name of a set of three serine/threonine-specific protein kinases.; BBB, blood–brain barrier; BIC, bis-chloroethylnitrosourea, irinotecan, and cisplatin; BICC, BIC and combretastatin; BNPDs, boron nitride NPs; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell; CDKs, cyclin-dependent kinases; Ce6, chlorin e6; cGAS-STING, cyclic GMP-AMP synthase—stimulator of interferon genes; cPDT, conventional PDT; CPNs, conjugated polymer nanoparticles; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAMPs, damage-associated molecular patterns; DCV, dendritic cell vaccine; DOX, doxorubicin; DSPE-PEG, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol); EANO, European Association of Neuro-Oncology; EGFR, epidermal growth factor receptor; EGFRvIII, EGFR, variant III; EPHA3, ephrin type-A receptor 3; FDA, Food and Drug Administration; FNPs, functionalized nanoparticles; GBM, glioblastoma multiforme; GM-CSF, granulocyte macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HIFs, hypoxia-inducible factors; HLA, human leukocyte antigen; HM, hybrid membrane; HMGB1, high-mobility group protein B1; Hsp, heat-shock protein; IDH, isocitrate dehydrogenase; IL, interleukin; MGMT, O6-methylguanine-DNA methyltransferase; mPDT, metronomic PDT; mTOR, mechanistic target of rapamycin; NIR, near-infrared; NPs, nanoparticles; OS, overall survival; PD-1, programmed cell death receptor 1; PDGFRA, platelet-derived growth factor receptor A; PDK1, pyruvate dehydrogenase kinase 1; PD-L1, programmed cell death receptor 1 ligand; PDT, photodynamic therapy; PDX, patient-derived xenograft; PEG, polyethylene glycol; PEG-PHB, poly(ethylene glycol)-poly(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acrylate); PEtOz-SS-PCL, poly(2-ethyl-2-oxazoline)-b-poly(e-caprolactone); PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PLGA, poly(lactic-co-glycolic acid); poly-ICLC, two long duplexed strands of polyinosine and polycytidine complexedwith poly-L-lysine and carboxymethylcellulose; PTAs, photothermal transduction agents; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PTT, photothermal therapy; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; SDT, sonodynamic therapy; TAA, tumor-associated antigen; TBE, TMZ butyl ester; TERT, telomerase reverse transcriptase; TIM-3, T-cell immunoglobulin and mucin domain-3; TME, tumor microenvironment; TMZ, temozolomide; TNTs, tunneling nanotubes; TP5, thymopentin; TPP, triphenylphosphorus; TSA, tumor-specific antigen; TTFields, tumor-treating fields; TUMAPs, tumor-associated peptides; T-VEC, talimogene laherparepvec; VGEF, vascular endothelial growth factor.

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technologies, artificial intelligence, and novel biomaterials, GBM treatment should move toward more personalized, precise, and comprehensive approaches, offering patients more effective treatment options.

1 | Introduction

Glioma is a blanket term for a group of brain neoplasms originating from glial cells. A subset of gliomas that originate from astrocytes are termed astrocytomas, which are classified as low (I and II) or high (II and IV) grade, with the latter class being considered malignant. Among them, glioblastoma multiforme (GBM), or simply glioblastoma, is the most malignant type and has been recently reclassified as a subset of astrocytoma grade IV expressing the wild-type enzyme isocitrate dehydrogenase (IDH) (Weller et al. 2021). GBM accounts for 48% of all primary malignant brain neoplasms (Tan et al. 2020), is highly invasive, and has a high proliferative capacity (Louis et al. 2021). The prognosis for GBM patients is poor, with a median survival period typically less than two years, whereas the five-year survival rate is less than 10% (Sun et al. 2023). The quality of life of GBM patients is severely impacted. Physically, patients often suffer from symptoms such as headaches, nausea, vomiting, and seizures, which not only reduce physical comfort but also further weaken their physical functions (Park and Park 2022). As the disease progresses, patients may develop cognitive impairments and limb dysfunction, significantly affecting their ability to perform daily activities and social interactions (Bosma et al. 2007). Psychologically, when diagnosed with a malignant neoplasm and enduring the treatment process, patients often experience tremendous stress, leading to anxiety, depression, and hopelessness (Taphoorn and Klein 2004). Given the high degree of malignancy, high mortality rate, and significant impact on patients' quality of life, it is crucial to conduct in-depth research into the current treatment landscape of GBM.

GBM pathological characteristics are notable, with GBM cells exhibiting significant atypia, varying sizes and shapes of nuclei, deep chromatin staining, and frequent mitotic figures. The infiltration of GBM cells from a single solid tumor mass into adjacent brain tissue is the most common (80%–99.5%) clinical presentation of GBM (Scherer 1938), whereas multifocal GBMs represent 0.5%–20% of all clinical cases (Patil et al. 2012). Both scenarios indicate the invasive nature of this cancer (Zagzag et al. 2008; Robert and Wastie 2008). The tumor often contains areas of necrosis and hemorrhage, with GBM cells around necrotic foci arranged in a palisade pattern, which is a typical pathological feature of GBM (Alifieris and Trafalis 2015). Under a microscope, tumor cells show diffuse infiltration and growth, with unclear boundaries between the tumor and surrounding normal brain tissue, penetrating deeply into brain tissue such as tree roots, and making complete surgical resection extremely difficult (Rodríguez-Mendoza et al. 2024).

The pathogenesis of GBM is complex and involves abnormal changes in multiple genes and signaling pathways, as discussed in detail elsewhere (Weller et al. 2024). Here, we limit the discussion to a subset of genetic changes (Figure 1). Amplification and overexpression of the epidermal growth factor receptor (EGFR) gene and its active mutant variant III, EGFRvIII, are common in GBM (An et al. 2018). The amplification of the EGFR oncogene is present in ~45% of GBMs, and most of them (~97%) overexpress EGFR (Shinojima et al. 2003), a receptor tyrosine kinase, which leads to excessive activation of downstream signaling pathways such as the phosphoinositide 3-kinase (PI3K)/Akt (the collective name of a set of three serine/threonine-specific protein kinases)/mTOR (mechanistic target of rapamycin) pathways, promoting the proliferation, survival, and migration of GBM cells (An et al. 2018). Specifically, mTOR promotes the progression of cells from the G1 phase to the S phase by regulating the levels of specific cyclins and thus the activity of cyclin-dependent kinases (CDKs) (Proud 2010). This is counteracted by P21, a cyclin-dependent kinase inhibitor capable of inhibiting all cyclin/CDK complexes (Xiong et al. 1993). This P21 kinase is associated with linking DNA damage to cell cycle arrest (Bunz et al. 1998; Waldman et al. 1995), as it represents a major target of p53, a crucial tumor suppressor protein, the activity of which plays a major role in maintaining genomic stability and preventing cancer.

Most of the overexpressed EGFR genes (~65%) were wild-type EGFR. In ~45% of GBM patients with and ~8% without amplification of EGFR, the EGFRvIII mutant is overexpressed (Shinojima et al. 2003). EGFRvIII lacks the extracellular ligand-binding domain and is constitutively active (Wong et al. 1992). In a preclinical mouse model with xenografting of human GBM biopsy materials, wild-type EGFR overexpression promoted GBM invasion without angiogenesis. Moreover, EGFRvIII overexpression generated more aggressive GBM growth with angiogenesis; EGFRvIII activated the nonreceptor tyrosine kinase c-Src, the activity of which led to increased secretion of vascular endothelial growth factor (VEGF) from these GBMs and angiogenesis (Eskilsson et al. 2016).

Loss or mutation of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) tumor suppressor gene is also common; loss of PTEN function disrupts the intracellular signal balance, further enhancing the activity of the PI3K/Akt pathway and allowing GBM cells to evade growth inhibition and apoptosis signals (Hashemi et al. 2023). The type 1 insulin-like growth factor receptor can promote the survival of GBM cells through activation of the PI3K/Akt/mTOR pathway (Zhang et al. 2018). Mutations in the tumor suppressor genes p53 (Fang et al. 2024) and IDH1/2 (Turcan et al. 2018) are closely related to the development and progression of GBM. IDH1/2 mutation leads to changes in enzyme activity, converting α-ketoglutarate to the carcinogenic metabolite D-2-hydroxyglutarate. This metabolite inhibits histone lysine demethylases and ten-eleven translocation methylcytosine dioxygenases. The latter inhibition leads to genome-wide hypermethylation and manifests as a cytosine–phosphate–guanine island methylator phenotype, thereby abnormally regulating gene expression and promoting tumor stem cell characteristics and invasiveness (Ozair et al. 2023). In addition, IDH mutations are associated with sensitivity to temozolomide (TMZ). O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, which results in the loss of the MGMT protein, which is a DNA repair enzyme that counteracts TMZ-induced DNA damage, can serve as a putative predictive marker for chemotherapy (Weller 2011).

Hepatocyte growth factor receptor, encoded by the MET gene, can be abnormally activated in GBM. HGF/MET signaling

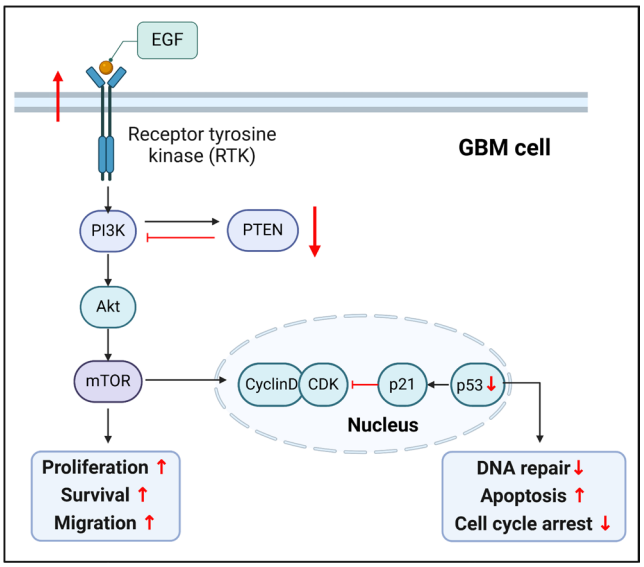

FIGURE 1 | Genetic alterations in GBM. Epidermal growth factor (EGF) is a potent mitogenic factor that acts by binding with high affinity to the cell surface epidermal growth factor receptor (EGFR). EGFR is a receptor tyrosine kinase (RTK), and approximately 45% of GBM patients overexpress this protein. Activation of EGFR promotes GBM cell proliferation and migration by stimulating downstream signaling cascades of the PI3K/Akt/mTOR pathway. Additionally, loss or mutation of the PTEN gene, which is a tumor suppressor gene, disrupts the intracellular signal balance, further enhancing the activity of the PI3K/Akt/mTOR pathway and allowing cancer cells to evade growth inhibition. Moreover, the expression of p53 is abnormal in GBM patients, and the degradation of p53 can lead to increased apoptosis and decreased cell cycle arrest, and DNA repair. See additional details in the text. The downward and upward arrows indicate decreases or increases in the expression/level and/or function of proteins, respectively. The black and red blunt arrows within the pathways represent promoting and inhibiting actions, respectively. The figure was made via *bioRENDER*. Akt, the collective name of a set of three serine/threonine-specific protein kinases; CDK4/6, cyclin-dependent kinases 4/6; EGF, epidermal growth factor; GBM, glioblastoma multiforme; mTOR, mechanistic target of rapamycin; PI3K, phosphatidyl-inositol-3-kinase; and PTEN, enzyme phosphatase and tensin homolog deleted on chromosome 10.

promotes the epithelial-to-mesenchymal transition, a process that underlies the ability of cancer cells to invade (Lee et al. 2014). MET overexpression promotes the survival of cancer stem cell-like cells, leading to chemotherapy resistance in GBM (Al-Ghabkari et al. 2024).

The incidence of telomerase reverse (TERT) promoter mutations (mainly C228T and C250T) in primary GBM is high, ranging from ~39 to 74% (see (Chen et al. 2025) and references within). These mutations play a role in malignant transformation via telomerase activation and endow GBM cells with unlimited proliferation ability (Powter et al. 2021; Fan et al. 2019).

Indeed, genetic changes have led to the molecular classification of GBM into proneural, neural, classical, and mesenchymal subtypes with aberrations and gene expression of platelet-derived growth factor receptor A (PDGFRA, also termed CD140a)/IDH1, EGFR, and neurofibromin 1, each of which defines the proneural, classical, and mesenchymal subtypes, respectively (Verhaak et al. 2010). Notably, however, the European Association of Neuro-Oncology (EANO) suggests the term "IDH-mutant GBM" as obsolete, classifying this subpopulation of cancers as b*ona fide* astrocytoma IV, whereas the subset of wild-type IDH astrocytoma IV is classified as *bona fide* GBM (Weller et al. 2021). Nonetheless, these genetic alterations form a complex molecular network that collectively drives the malignant biological behavior of GBMs.

In addition to GBM cells, immunosuppressive cells (such as tumor-associated macrophages) and cytokine networks can also promote tumor progression (Khan et al. 2023; Lin, Liu, et al. 2024). Indeed, various immune cells (B and T lymphocytes, bone marrow-derived macrophages, and microglia) are associated with GBM molecular subtypes, providing guidance for the design of immunotherapeutic approaches (Martinez-Lage et al. 2019).

2 | Standard-of-Care Treatment for GBM

2.1 | Surgical Treatment

Surgical treatment plays a crucial role in the comprehensive management of GBM and is a key component of initial therapy. The primary goal is to remove as much cancerous tissue as possible while ensuring patient safety and preserving neurological functions (Sanai et al. 2011). In the surgical treatment of GBM, craniotomy is the classic surgical approach. However, craniotomy has certain limitations; owing to significant surgical trauma, patients may experience noticeable postoperative pain around the incision site along with redness and swelling. The recovery time is relatively long, and there is a risk of complications such as brain retraction injury (Andrews and Bringas 1993), infection, and bleeding (Fernández-de Thomas et al. 2025).

Minimally invasive surgery, which includes neuroendoscopic surgery and stereotactic surgery (Andrews and Bringas 1993), has emerged in recent years with advancements in medical technology. The expanded endoscopic endonasal approach can avoid craniotomy and brain retraction and reduce the incidence rate of neurovascular damage (Dehdashti et al. 2009). Neuroendoscopic approaches might play a leading role in better defining the prognosis and optimally tailoring management protocols for GBM (Iacoangeli et al. 2012). Stereotactic surgery uses stereotaxis to precisely locate the cancerous mass/tumor position and then uses methods such as puncture to deliver surgical instruments to the resection site (Seliem et al. 2003). This technique provides precise targeting and minimal damage to surrounding tissues, and when associated with brain mapping (Sales et al. 2022), it is suitable for tumors in special locations, such as those in critical brain functional areas (e.g., motor and language) or deep brain loci (Lovo et al. 2021).

2.2 | Radiotherapy

Radiotherapy is another crucial component of standard-of-care treatment for GBM. Its mechanism of action is based primarily on the biological effects of high-energy ionizing radiation on cells. When high-energy radiation, such as X-rays or γ-rays,

interacts with cells, it can cause damage to the cell's DNA either directly or indirectly (Ravanat et al. 2014). Direct action involves the energy from the radiation directly breaking the chemical bonds of the DNA molecules, leading to double-strand or single-strand breaks. Indirect action occurs when radiation interacts with water molecules within the cell, generating many free radicals (Ravanat et al. 2014). These highly reactive oxygen species (ROS) can attack DNA molecules, causing various forms of damage, including base damage and strand breaks. If DNA damage cannot be effectively repaired, the cell initiates apoptosis, thereby achieving the goal of killing cancer cells. However, not only cancer cells incur damage. The radiosensitivity of cells depends on their regenerative/proliferative ability. Cells that regenerate/proliferate quickly (such as lymphocytes in the blood) are more sensitive. Furthermore, the cell cycle phase matters, with proliferating cells in the G2 (without time to repair before cell division) and M phases being the most sensitive (Pawlik and Keyomarsi 2004). Thus, it is important to restrict ionization as much as possible to cancer cells and spare healthy cells.

Despite the crucial role of radiotherapy in the treatment of GBM, resistance to radiation therapy remains a significant clinical challenge that needs to be addressed. The mechanisms underlying GBM resistance to radiotherapy are complex and involve multiple biological processes. One of the key factors contributing to this resistance is the hypoxic microenvironment within the tumor. In GBM, rapid tumor growth often outpaces angiogenesis, leading to insufficient blood supply and the formation of hypoxic regions within the tumor. Hypoxia-inducible factors (HIFs), particularly HIF-1α, are upregulated under these hypoxic conditions (Bae et al. 2021). HIF-1α further regulates the expression of various downstream genes, including pyruvate dehydrogenase kinase 1 (PDK1). Upregulation of PDK1 alters glucose metabolism by inhibiting the activity of pyruvate dehydrogenase, preventing pyruvate from entering the mitochondria for aerobic oxidation and instead promoting its metabolism through glycolysis, resulting in the production of large amounts of lactate (Shi et al. 2023). This metabolic shift not only provides energy for tumor cells but also contributes to their resistance to radiotherapy. The acidic microenvironment generated by glycolysis affects the intracellular pH and inhibits the DNA damage repair mechanisms induced by radiotherapy, thereby reducing the sensitivity of cancer cells to radiation (Xu et al. 2005). Additionally, enhanced DNA damage repair mechanisms within cancer cells and the presence of cancer stem cells, also referred to as brain tumor-initiating cells, are closely related to GBM resistance to radiotherapy. Cancer stem cells possess self-renewal and multilineage differentiation capabilities, increasing their resistance to both radiotherapy and chemotherapy. These cells can survive radiotherapy and proliferate, leading to GBM recurrence (Shi et al. 2023).

2.3 | Chemotherapy

Chemotherapy plays a crucial role in the comprehensive treatment of GBM and is the third component of standard-of-care therapeutic approaches. TMZ is currently the most commonly used chemical drug for treating GBM in clinical settings (Stylli 2020). It belongs to the second generation of alkylating agents. TMZ has a unique mechanism of action; its small molecular size and good lipophilicity allow it to effectively cross the blood–brain barrier (BBB), achieving up to 40% plasma concentration within the central nervous system. Among GBM chemotherapy protocols, concurrent chemoradiotherapy and adjuvant chemotherapy are two common treatment modalities. Stupp et al. reported that a treatment regimen combining concurrent chemoradiotherapy (radiotherapy with TMZ) followed by TMZ adjuvant chemotherapy increased the median overall survival (OS) of GBM patients to 14.6 months compared with 12.1 months with radiotherapy alone; it also increased the two-year survival rate from 10.4% to 26.5% (Stupp et al. 2005). These results underscore the significant value of concurrent chemoradiotherapy in the treatment of GBM.

Despite the significant role of chemotherapy in the treatment of GBM, several formidable challenges remain. One of the primary obstacles is the presence of the BBB (Zheng et al. 2021), which is composed of brain capillary endothelial cells with tight junctions. The BBB acts as a specialized barrier, serving as a semipermeable "membrane" that effectively blocks harmful substances from entering brain tissue, thereby protecting the normal function of the central nervous system (Xu et al. 2005). However, this barrier also makes it difficult for many chemotherapy drugs to penetrate, preventing them from reaching effective therapeutic concentrations at the cancer site. Drug properties such as molecular size, charge, and lipophilicity limit the ability of most chemical drugs to cross the BBB. Many large-molecule chemotherapy drugs cannot pass through the tight junctions between endothelial cells, whereas hydrophilic drugs struggle to traverse the lipid bilayer of cell membranes (Pardridge 2005). Studies have shown that only a few small, lipophilic chemotherapy drugs can partially penetrate the BBB, but their permeability rates are relatively low (Pardridge 2003). As a result, most chemotherapy drugs achieve much lower concentrations in the brain than in other parts of the body, rendering them ineffective against GBM cells.

Drug resistance is another major challenge faced by chemotherapy in GBM treatment. The mechanisms underlying GBM cell resistance to chemotherapy are complex and involve multiple biological processes. The overexpression of drug efflux pumps is one of the key reasons for resistance. P-glycoprotein (Munoz et al. 2015) and multidrug resistance-associated proteins (Chen et al. 1990) on the surface of cancer cells can actively pump chemotherapy drugs out of the cells, reducing intracellular drug concentrations and preventing the drugs from exerting their effects. In resistant GBM cells, the expression levels of P-glycoprotein are significantly elevated, enhancing the efflux of drugs such as TMZ and thereby increasing GBM cell tolerance to these agents (Munoz et al. 2013). Enhanced DNA damage repair mechanisms within cancer cells also contribute to drug resistance (Rodriguez-Hernandez et al. 2014). When chemical drugs damage the DNA of cells, intracellular DNA repair proteins, such as MGMT, quickly initiate repair processes to fix damaged DNA. MGMT specifically removes the methylation caused by TMZ at the O6 position of guanine, thereby reducing the toxicity of TMZ to GBM cells (Silber et al. 2012), allowing these cancer cells to evade the cytotoxic effects of chemotherapy. Additionally, resistance to apoptosis (Ge et al. 2018) and abnormal cell cycle regulation in cancer cells are closely related to chemotherapy resistance (Zhang et al. 2019). These intertwined

resistance mechanisms continuously increase the tolerance of GBM cells to chemotherapy drugs, significantly reducing the efficacy of chemotherapy.

3 | Emerging Treatment Methods for GBM

3.1 | Tumor-Treating Fields

Tumor-treating fields (TTFields) have emerged as promising therapeutic modalities for GBM, offering a noninvasive approach to disrupt cancer cell division. Here, a portable device with an electrode placed on the skin near the tumor targets cancer cells while sparing most nearby healthy cells. TTFields utilize low-intensity (1–3 V/cm), intermediate-frequency (100–300 Hz) alternating/sinusoidal electric fields to interfere with the mitotic process, ultimately leading to cancer cell death (Kirson et al. 2007; Li et al. 2023). Compared with TMZ therapy alone, the pivotal EF-14 human phase III clinical trial demonstrated that combining TTFields with maintenance TMZ chemotherapy significantly improved the progression-free survival (PFS) and OS of newly diagnosed GBM patients. The median OS increased from 16.0 to 20.9 months, and the 5-year survival rate increased from 5% to 13% (Stupp et al. 2017). Because of these findings, TTFields received approval from the United States and the Chinese Food and Drug Administration (FDA) for both newly diagnosed and recurrent GBMs. Despite its efficacy, challenges such as patient compliance, skin irritation from device use, and the need for continuous treatment remain (Toms et al. 2019).

3.2 | Molecular Targeted Therapy

Molecular targeted therapy represents an emerging strategy for the treatment of GBM, with a unique mechanism of action. It primarily targets specific abnormal molecules within GBM cells, which often play crucial roles in the development and progression of this cancer. These molecules are involved in key biological processes such as cell proliferation, apoptosis, migration, and angiogenesis (Touat et al. 2017). By using specific drugs to precisely target these abnormal molecules, molecular targeted therapy aims to block their aberrant signaling pathways, thereby inhibiting cancer cell growth and proliferation and inducing apoptosis (Touat et al. 2017). Unlike traditional chemotherapy, molecular targeted therapy offers greater specificity, allowing for more precise targeting of cancer cells while minimizing damage to normal cells and reducing side effects.

In the treatment of GBM, bevacizumab is a commonly used drug that targets VEGF. This growth factor plays a crucial role in the growth and development of GBM by promoting tumor angiogenesis, providing cancer cells with sufficient nutrients and oxygen to support their rapid growth and invasion (Hicklin and Ellis 2005). Bevacizumab, a humanized monoclonal antibody against VEGF, blocks the interaction of VEGF with its receptors, thereby inhibiting tumor angiogenesis (Khasraw and Lassman 2010). This mechanism significantly reduces cancer growth, invasiveness, and metastasis by removing adequate blood supply to the cancerous tumor (Hanahan and Folkman 1996). Notably, GBM metastases are rare, with a frequency of ~0.44% (Robert and Wastie 2008). Numerous clinical studies have shown that bevacizumab has some efficacy in GBM treatment, significantly prolonging PFS in patients (Gruber et al. 2009). In particular, for recurrent GBM patients, bevacizumab treatment has shown some initial radiographic success (Li, Ali, et al. 2017) and extends PFS compared with traditional treatments. However, bevacizumab also has limitations; it does not significantly extend OS, as GBMs progress within a few months and can cause adverse reactions such as hypertension, bleeding, and thrombosis, which limits its clinical application to some extent (Gilbert et al. 2014).

In addition to bevacizumab, other targeted drugs are used and researched in GBM treatment. For example, drugs that target EGFR, such as gefitinib (N.R.G. Oncology 2003) and erlotinib (Yung et al. 2010), have been developed. As mentioned earlier, EGFR is often overexpressed or mutated in GBM cells, leading to abnormal activation of downstream signaling pathways and promoting tumor cell proliferation, survival, and migration (Figure 1). These targeted drugs specifically bind to EGFR, inhibiting its tyrosine kinase activity and blocking downstream signaling, thus suppressing cancer cell growth (Fleming et al. 1992). Novel agents, such as PD 0332991, which is designed to selectively inhibit CDK4 and CDK6 within the EGFR downstream pathway in the cell nucleus, have demonstrated strong anti-GBM efficacy (Michaud et al. 2010) and have been subsequently evaluated in a human phase II clinical trial. In a preclinical mouse model, it was proven to be highly effective in suppressing the growth of intracranial human GBM xenograft tumors, including those that had recurred after initial therapy with TMZ (Michaud et al. 2010). Within the EGFR cytosolic downstream pathway, the pan-class I PI3K inhibitor buparlisib has been evaluated in a human phase II clinical trial. It has shown efficacy in combination with bevacizumab (Massacesi et al. 2016), but monotherapy has a limited effect on GBM patients. Owing to the molecular heterogeneity of GBMs, different patients respond differently to these targeted therapies, and some may develop resistance, affecting treatment outcomes.

Combining targeted therapy with traditional chemotherapy is an important strategy in GBM treatment, aiming to leverage the strengths of both approaches to enhance therapeutic efficacy. This combination therapy offers multiple advantages (Kesari et al. 2005). Mechanistically, chemotherapy drugs can disrupt cancer cell DNA structure, leading to cell death, whereas targeted drugs can inhibit cancer cell resistance, increasing the sensitivity of cancer cells to chemotherapy drugs and thereby increasing the effectiveness of chemotherapy. Hata et al. analyzed the clinical records of 120 GBM patients and reported an improvement in the median OS for patients treated with the combination of TMZ and bevacizumab (22.1 months) compared with patients treated with TMZ alone (14.9 months) (Hata et al. 2020). Prados et al. analyzed 65 patients newly diagnosed with GBM or gliosarcoma. Patients receiving the combination of erlotinib and TMZ during and following radiotherapy had a better median OS (19.3 months) than control patients did (14.1 months) (Prados et al. 2009). The combination of thalidomide, which has antiangiogenic activity, and TMZ in patients with GBM was more effective than thalidomide alone with respect to median survival times of 103 weeks and 63 weeks, respectively (Baumann et al. 2004). David et al. reported that a combination of irinotecan/CPT-11, a topoisomerase I inhibitor

aimed at interrupting DNA replication in cancer cells, and celecoxib, a nonsteroidal anti-inflammatory agent that acts as a selective cyclooxygenase-2 inhibitor and may stop cancer growth by causing apoptosis independent of Cox-2 (Jendrossek 2013), resulted in radiographic improvements in patients with recurrent GBM (Reardon et al. 2005). Notably, however, celecoxib has dose-dependent adverse cardiovascular effects (Cotter and Wooltorton 2005).

3.3 | Immunotherapy

Immunotherapy has emerged as a promising new approach for the treatment of GBM (Tan et al. 2020). One of the key approaches in immunotherapy is the use of immune checkpoint inhibitors, which work by intervening in critical regulatory points within the immune system (Figures 2 and 3, Box 2). Under normal physiological conditions, T cells in the immune system express immune checkpoint proteins such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death receptor 1 (PD-1) along with their ligand (PD-L1) (Topalian et al. 2015). These proteins regulate T-cell activity to prevent excessive activation of the immune system, which can damage healthy tissues. However, during cancer development, malignant cells exploit these immune checkpoint mechanisms by overexpressing ligands, such as PD-L1, which bind to PD-1 on the surface of T cells, transmitting inhibitory signals that deactivate T cells (Wu and Wang 2024). Immune checkpoint inhibitors specifically block the interaction between these checkpoint proteins and their ligands, thereby increasing the inhibition of T cells and reactivating their anticancer activity. In the treatment of GBM, research on the application of immune checkpoint inhibitors has yielded promising results. The CheckMate 143 human clinical trial (Reardon et al. 2020), which focused on recurrent GBM patients, enrolled 153 patients who were randomly assigned to receive nivolumab, a monoclonal antibody against PD-L1, or bevacizumab. Although there was no significant difference in OS or PFS between the nivolumab and bevacizumab treatment groups, the nivolumab group demonstrated a lower incidence of adverse events, suggesting that nivolumab offers a safety advantage when treating recurrent GBM (Reardon et al. 2020). Another human clinical trial, CheckMate 548, involving 716 GBM patients, evaluated nivolumab vs. placebo in combination with radiotherapy and TMZ. There was no significant difference in OS or PFS between the nivolumab group and the placebo group, but the latter group had a lower incidence of adverse events (Lim et al. 2022). Immune checkpoint inhibitors face additional challenges in GBM treatment. Owing to the highly immunosuppressive microenvironment characteristic of GBM, some patients exhibit poor responses to these inhibitors, leading to limited treatment efficacy (Razavi et al. 2016).

Chimeric antigen receptor T-cell (CAR-T) therapy is another significant type of immunotherapy that involves the genetic engineering of an individual patient's own T cells to express chimeric antigen receptors (CARs). These CARs can specifically recognize antigens on the surface of cancer cells (Zhu, Zhang, et al. 2021). Antigens can be classified as tumor-specific antigens (TSAs), which are endogenously present only on cancer cells but not on normal cells, or as tumor-associated antigens (TAAs), which are present on both cancer cells and some healthy cells but are enriched in cancer cells and successfully targeted (Okarvi and AlJammaz 2019). In GBM, EGFRvIII and interleukin (IL)-13Rα2 (IL-13Rα2), which are TSAs, and human epidermal growth factor receptor 2 (HER2), which is a TAA, have been successfully used to enable T cells to precisely target and activate their cytotoxic functions against this cancer (Figure 2) (Huang et al. 2020). The first three human clinical trials targeting these antigens in GBMs demonstrated safety guidelines for the use of CAR-T cells (Migliorini et al. 2018). In a clinical trial/case study of an adult patient with recurrent multifocal GBM, treatment with CAR-T cells that specifically targeted IL-13Rα2 led to complete regression of intracranial and spinal tumors (Brown et al. 2016). In a HER2 clinical study enrolling 7 pediatric and 10 adult GBM patients, an objective radiographic response

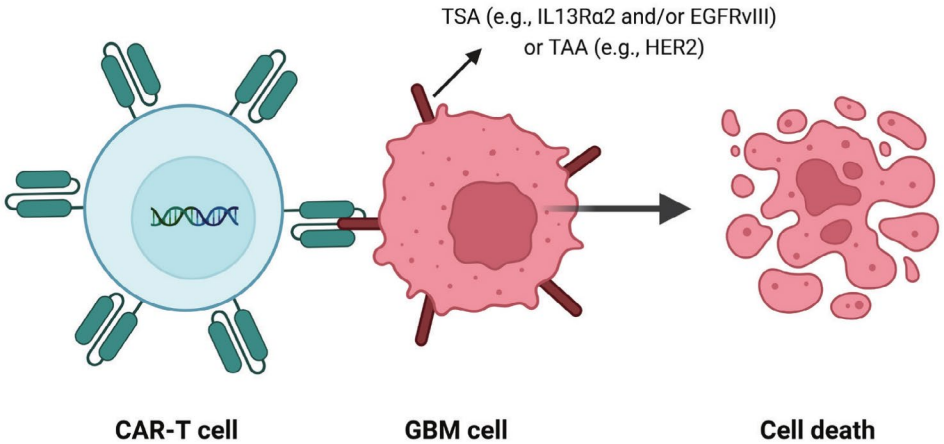

FIGURE 2 | CAR T-cell therapy. Autologous normal T cells can be modified to express chimeric receptors for tumor-specific antigens (e.g., EGFRvIII and IL13Rα2) and/or tumor-associated antigens (e.g., HER2). These CAR-T cells bind to cancer cells that express these antigens and kill them. See additional details in the text. The figure was made via *bioRENDER*. CAR-T cells, chimeric antigen receptor T cells; EGFRvIII, epidermal growth factor receptor variant III; HER2, human epidermal growth factor receptor 2; IL13Rα2, interleukin 13 receptor alpha 2; TAA, tumor-associated antigen; TSA, tumor-specific antigen.

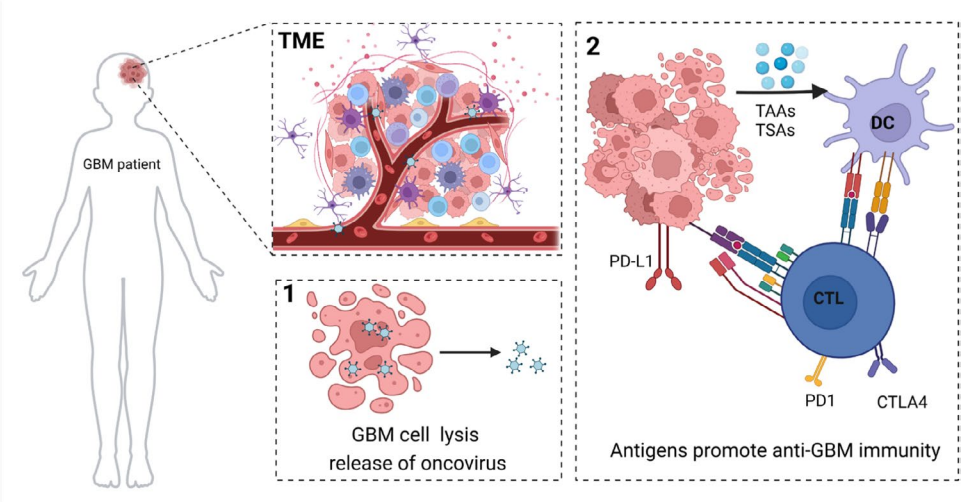

FIGURE 3 | Oncolytic viroimmunotherapy for GBM patients. Box TME. Angiogenesis creates a tumor microenvironment (TME) with blood vessels grossly pervious to macromolecules, as plasma proteins can leak from blood vessels at their interface with the GBM. This allows viruses to reach GBM cells. Box 1. Oncolytic viruses infect GBM cells but not healthy neural cells. Once inside cancer cells, these viruses replicate extensively and eventually cause cancer cells to burst open (cell lysis) and die. The released progeny viruses can then infect neighboring cancer cells, resulting in a cascading amplification effect. Box 2. When cancer cells are lysed, they release tumor-specific and/or tumor-associated antigens that are absorbed and processed by antigen-presenting cells. This leads to the activation of T cells and other immune cells and triggers a systemic anticancer immune response, turning immunologically "cold" tumors into "hot" tumors, enhancing the body's ability to recognize and kill cancer cells. For clarity, the names/abbreviations of drawn interactive intercellular recognition molecules are denoted only if they are mentioned in the text. See additional details in the text. The figure was made via *bioRENDER*. CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DC, dendritic cell; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand; TAA, tumor-associated antigen; TME: Tumor microenvironment; and TSA, tumor-specific antigen.

was observed in one patient, whereas an additional 5 patients experienced disease stabilization for more than 24 months after CAR-T-cell therapy (Ahmed et al. 2017). A clinical trial involving 10 recurrent GBM patients treated with EGFRvIII-targeted CAR-T cells reported no objective radiographic response, whereas one patient had stable disease for over 18 months (O'Rourke et al. 2017). Recently, two human clinical studies published on the same day reported the use of bivalent CAR-T cells, which simultaneously target GBM cells expressing one TAA and one TSA. One study involving three recurrent GBM patients briefly reported the use of bivalent CAR-T cells, termed CARv3-TEAM-E, which target both wild-type EGFR (TAA) and EGFRvIII (TSA). This CAR-T-cell treatment had satisfactory safety. Within days of single-intervention delivery of CAR-T cells, remarkable radiographic regression of GBM tumors was detected in two of the three patients (Choi et al. 2024). Another clinical study reported interim results obtained for six recurrent multifocal GBM patients enrolled in a phase I clinical trial. These patients received intrathecal delivery (into the subarachnoid space) of bivalent CAR-T cells targeting EGFR (TAA) and IL13Rα2 (TSA). This study demonstrated the preliminary safety of bivalent cells. The authors also reported the presence and activity of these bivalent CAR-T cells in situ, the latter of which was determined via the detection of cytokine release in the cerebrospinal fluid. However, there was no objective radiographic response in any of the patients (Bagley et al. 2024). Both bivalent CAR-T-cell studies in humans require a larger cohort and longer follow-up time to further assess the use of bivalent CAR-T cells in the treatment of GBM. Taken together, CAR-T-cell therapy for GBM has achieved modest success but also faces several challenges. Specifically, the presence of the BBB makes it difficult for CAR-T cells to reach the GBM site effectively, limiting their therapeutic efficacy (O'Rourke et al. 2017). Additionally, the expansion and persistence of CAR-T cells in the body need further improvement to ensure that their anticancer activity can be sustained over time.

Dendritic cell vaccines (DCVs) leverage the powerful antigen-presenting capabilities of dendritic cells to activate the body's anticancer immune response. Dendritic cells are the most potent professional antigen-presenting cells in the body and are capable of capturing, processing, and presenting cancer antigens to activate T cells, thereby initiating specific immune responses (Joffre et al. 2012). The preparation of DCVs typically involves collecting dendritic cells from the patient, incubating them with cancer antigens in vitro to load them with these antigens, and then reinfusing them back into the patient. These antigen-loaded dendritic cells can activate T cells, promoting their differentiation into effector T cells that recognize and kill cancer cells (Datsi and Sorg 2021). In the context of GBM treatment, a randomized human phase II clinical trial with 41 newly diagnosed and recurrent GBM patients reported that DCV significantly prolonged OS and PFS compared with a placebo injection of normal saline (Yao et al. 2018). In an additional randomized human phase II clinical trial with 34 newly diagnosed GBM patients, 18 patients in the control group underwent three-pronged standard-of-care therapy (surgery, radio- and chemotherapy), while 16 patients additionally received adjuvant DCV; the median OS (31.9 months) of the DCV group was significantly improved compared with that of the control group (15 months) (Cho et al. 2012). Notably, the efficacy of DCVs is influenced by various factors, including the choice of cancer antigens, the quality and quantity of dendritic cells, and the patient's immune

status (Datsi and Sorg 2021). Optimizing the preparation and application of DCVs to enhance their therapeutic effects remains a key focus of current research.

Peptide vaccines, consisting of 8–30 amino acids, have been used in GBM treatment. Rindopepimut (code name CXD-10) is a GBM vaccine consisting of a specific EGFRvIII peptide sequence conjugated to the immunomodulatory keyhole limpet hemocyanin, which elicits a cytotoxic T lymphocyte immune response against TSA-presenting cells, such as GBM cells. In a human phase II multicenter clinical trial, 65 patients with newly diagnosed EGFRvIII-positive GBMs were first treated with standard-of-care therapy (surgery, radiation, and TMZ treatment), followed by CXD-10 vaccination and adjuvant TMZ therapy. There was a promising median OS of 21.8 months (Schuster et al. 2015). However, in a follow-up human phase III international randomized double-blind clinical trial involving 745 EGFRvIII-positive GBM patients, rindopepimut did not increase survival (Weller et al. 2017).

IMA950 (code name C94211) is a multipeptide vaccine designed to treat GBM. It is composed of a cocktail of eleven tumor-associated peptides (TUMAPs) cognate to TAAs displayed on the surface of the majority of GBMs, the full list of which is available elsewhere (Rampling et al. 2016). TUMAPs activate specific CD8 cytotoxic and CD4 helper T cells, which in turn find GBM cells expressing cognate peptide sequences on their surface TAAs. The vast majority of GBMs express at least two of the targeted TAAs. Thus, the use of peptide vaccines provides redundancy and increases the likelihood of activated T cells mounting a GBM-specific and multiclonal, broad response to kill cancerous cells.

In a human phase I clinical trial, newly diagnosed GBM patients who received only surgical resection were enrolled in this two-cohort study (Rampling et al. 2016). One cohort of patients (cohort 1) received the IMA950 vaccine along with granulocyte macrophage colony-stimulating factor (GM-CSF), an adjuvant with immunostimulatory effects (Choi et al. 2008; Parmiani et al. 2007), for 24 weeks, starting 1–2 weeks prior to combined chemo-/TMZ- and radiotherapy, whereas the other cohort started receiving vaccine-adjuvant treatment one week after chemoradiotherapy (Rampling et al. 2016). Two primary points, TUMAP-specific peripheral CD8+ T-cell immune responses and PFS, were used. Most of the patients who could be evaluated (36 of 40, i.e., 90%) showed antigen-specific peripheral CD8 T-cell immune responses to a single TUMAP, whereas half of them (20 of 40, i.e., 50%) were multi-TUMAP responders. PFSs of 74% and 31% at 6 and 9 months, respectively, were recorded, along with a median OS of 15.3 months (Rampling et al. 2016). As this was a nonrandomized design, the two-cohort design offers an assessment of the administration schedule for future IMA950 studies and developments, but not of efficacy between the cohorts. However, chemoradiotherapy seemingly interfered with the maintenance of CD8+ T-cell immune responses, since Cohort 1 patients had lower durability of TUMAP responses. Nonetheless, this human phase I clinical trial demonstrated the safety of the IAM950 vaccine, with data encouraging its further development. Notably, in this trial, as well as in the subsequent trial discussed below, all patients had human leukocyte antigen (HLA)-A*02 serotype-positive GBMs, which was an inclusion requirement, as 9 out of the 11 peptides in the IMA950 vaccine are restricted to HLA-A*02 (Rampling et al. 2016).

A subsequent human clinical trial, along with a post hoc study, assessed the use of the IMA950 vaccine combined with the adjuvant poly-ICLC (US brand Hiltonol, Oncovir Inc.), a double-stranded RNA viral mimic, which is a humoral and cellular immunostimulator comprising two long duplexed strands of polyinosine and polycytidine complexed with poly-L-lysine and carboxymethylcellulose (Migliorini et al. 2019; Boydell et al. 2019). In a human phase I/II clinical trial, 16 patients with newly diagnosed GBM who had already received standard-of-care (surgery, radiotherapy, and TMZ chemotherapy) received the IMA950 vaccine combined with poly-ICLC (Migliorini et al. 2019). The primary endpoints of the trial were safety, which was fulfilled, and the immunogenicity of the vaccination; for the latter, CD8 T-cell responses to single or multiple TUMAPs in GBM patients (62.5% and 31.2%, respectively) were comparable, albeit somewhat lower than those in the above trial, in which IMA950 was combined with GM-CSF (Rampling et al. 2016). However, the median OS was 19 months for GBM patients, which was longer than that reported in the IMA950/MG-CSF study. As a corollary to the IMA950/poly-ICLC trial (Migliorini et al. 2019), a post hoc clinical study was implemented to assess the potential benefits of IMA950/poly-ICLC for subsequent bevacizumab therapy (Boydell et al. 2019). Here, 16 patients (14 with GBM and 2 with astrocytoma III), who were vaccinated with IMA950 and adjuvant poly-ICLC, along with 40 nonvaccinated patients (35 with GBM and 5 with astrocytoma III), received bevacizumab therapy. The primary endpoints were PFS, with 2.6 months for vaccinated patients and 4.2 months for nonvaccinated patients, and median OS, with 7.8 months and 10.0 months, respectively. Thus, there is no benefit of IMA950/poly-ICLC vaccination for subsequent bevacizumab therapy. The additional use of poly-ICLC has been reviewed elsewhere (De Waele et al. 2021).

Despite the potential of immunotherapy in the treatment of GBM, the presence of the BBB poses a significant challenge. In addition, GBM is generally regarded as an immunologically cold tumor in which the local immunosuppressive tumor microenvironment (TME) is thought to confer resistance to T-cell infiltration (Agliardi et al. 2021). GBM tumors contain various types of cancer-promoting immunosuppressive cells and factors that collectively form a complex network that suppresses the ability of the immune system to recognize and kill tumor cells (Caverzán, Beaugé, et al. 2023); these cells in the GBM immune microenvironment can be used for therapeutic approaches. Tumor-associated macrophages are highly infiltrative in GBM tissue and exhibit multiple phenotypes (Graeber et al. 2002). Among them, M2-type macrophages possess immunosuppressive functions, secreting cytokines such as interleukin-10 and transforming growth factor-β (Yang et al. 2018; Chen et al. 2021). These cytokines inhibit T-cell activation and proliferation, promoting immune evasion by tumor cells. Regulatory T cells are also significantly increased in GBM, where they suppress effector T-cell function through the secretion of inhibitory cytokines and direct contact, thereby reducing the ability of the immune system to attack cancer cells (Dey et al. 2015). GBM cells can also express various immunosuppressive molecules, such as PD-L1 and indoleamine 2,3-dioxygenase, which further inhibit T-cell

activity, allowing cancer cells to evade immune surveillance (Wainwright et al. 2014). In GBM patients, the expression level of PD-L1 in tumor tissues is closely related to prognosis; patients with high PD-L1 expression tend to have poorer responses to immunotherapy and shorter survival periods (Nduom et al. 2016).

3.4 | Proton Therapy

Proton therapy is a highly precise form of radiation treatment that uses high-energy proton beams to target cancers (Chambrelant et al. 2021). This technique leverages the unique physical properties of protons, which are positively charged particles. When a proton beam enters human tissue, it loses energy slowly until it reaches a specific depth, where it suddenly releases a large amount of energy, forming a sharp dose peak known as the Bragg peak. By precisely controlling the energy and angle of the proton beam, the Bragg peak can be positioned accurately within the cancer tumor tissue, delivering a high dose of radiation to the tumor while minimizing damage to surrounding healthy tissue (Sejpal et al. 2011). Unlike X-rays or γ-rays, which are used in traditional radiotherapy and continuously lose energy as they penetrate the body and inevitably irradiate normal tissues along their path, the precise dose distribution of proton therapy minimizes collateral damage, making it particularly advantageous for treating tumors such as GBM.

Several clinical studies have shown that proton therapy can somewhat prolong GBM patient survival (Xu et al. 2023). For example, in one clinical study, 26 GBM patients were treated with proton therapy, whereas the other 26 received conventional radiotherapy. The results indicated that the median OS for proton therapy was 28.3 months, whereas it was 21.2 months for conventional radiotherapy (Matsuda et al. 2023). Patients in the proton therapy group experienced greater post-treatment quality of life, with lower rates of radiation-induced complications such as radiation necrosis and cognitive dysfunction (Matsuda et al. 2023). However, proton therapy faces significant challenges, primarily due to the high cost of equipment, construction, and maintenance. These factors result in relatively high treatment costs, limiting their widespread adoption. Despite these challenges, the precision and potential benefits of proton therapy make it an important option for GBM treatment, especially for patients seeking to minimize side effects and improve their quality of life.

3.5 | Oncolytic Virus Therapy

Oncolytic virus therapy is an emerging cancer treatment strategy that can induce immune responses and thus can also be considered immunotherapeutic, but it has a unique mechanism of action (Rius-Rocabert et al. 2020) (Figure 3). Angiogenesis creates a GBM tumor microenvironment with leaky blood vessels, whereby the tumor-BBB is grossly permeable to macromolecules, as plasma proteins can leak from blood vessels at their interface with the GBM (Watkins et al. 2014). This leaky tumor-BBB likely allows viruses to reach GBM cells within the tumor. Oncolytic virus therapy uses genetically engineered or naturally occurring oncolytic viruses that selectively replicate within cancer cells and exert oncolytic effects while causing minimal damage to normal cells (Santos Apolonio et al. 2021). Once inside cancer cells, these viruses exploit various cellular mechanisms to replicate extensively. As viruses proliferate, they eventually cause cancer cells to die as cells burst open (cell lysis), releasing newly formed virions, which can then infect neighboring cancer cells, creating a cascading amplification effect (Lang et al. 2018). Additionally, oncolytic viruses can activate the body's immune system. When cancer cells are lysed, they release TSAs and TAAs (Russell and Barber 2018), which are taken up and processed by antigen-presenting cells, leading to the activation of T cells and other immune cells, thereby triggering a systemic antitumor/cancer immune response and enhancing the body's ability to recognize and kill cancer cells (Ma et al. 2023). In 2015, the U.S. Food and Drug Administration approved the first therapeutic oncolytic virus, talimogene laherparepvec (T-VEC), for the local (direct intratumoral injection) treatment of unresectable metastatic melanoma (Andtbacka et al. 2015). T-VEC is designed to selectively replicate within cancer cells and express GM-CSF (Poh 2016). Once liberated by cells, this cytokine promotes the recruitment and activation of immune cells, improving the efficacy of viro-immunotherapy.

Experimental GBM virotherapy in a preclinical model of a nude mouse bearing a GBM tumor formed by a human GBM cell line was initiated in 1991 (Martuza et al. 1991). Specifically, Martuza et al. generated a thymidine kinase-negative mutant of HSV-1 that was attenuated for neurovirulence. In cell culture, this virus killed human U87MG and T98G GBM cell lines in a dose-dependent manner, as did short-term (2 passages) cultured cells acutely isolated from two GBM patients. In an in vivo preclinical model, subcutaneous or subrenal capsule injection of U87 cells in nude mice resulted in the formation of ectopic GBM tumors. Intratumoral inoculation with the virus, but not with the vehicle, led to inhibition of GBM tumor growth. U87 cells were injected into the right frontal lobe to generate ectopic GBM tumors. Survival of these ectopic GBM-bearing mice was extended when GBMs were intratumorally inoculated with this genetically altered virus, indicating the promise of virotherapy for GBM treatment.

As a systematic historic outlook on the development of oncolytic HSV therapy for GBM is available elsewhere (Erickson et al. 2025), here, we briefly discuss two recently published clinical trials. In a human phase II clinical trial, G47Δ, a triple-mutated oncolytic HSV-1, was repeatedly administered intratumorally to residual or recurrent supratentorial GBMs in 19 adult patients who had undergone prior radiotherapy and TMZ. This clinical trial fulfilled not only the primary endpoint after G47Δ therapy initiation, as the 1-year survival rate was 84.2%, but also the secondary endpoints, as the median OS and PFS were 20.2 months and 4.7 months, respectively; the study also showed a good safety profile (Todo et al. 2022). In a human phase I clinical trial, 41 patients with recurrent GBM received an intratumoral injection of CAN-3110, a genetically modified oncolytic HSV-1 with preferential GBM replication. This treatment was safe and elicited enhanced anticancer immunity, as evidenced by an increase in T cells in the TME (Ling et al. 2023).

HSV-1 is not the only oncolytic virus used for GBM; rather, adeno- and vaccinia viruses have also been used. DNX-2401 (tasadenoturev) is a replication-competent oncolytic adenovirus.

In a human phase I clinical study, 37 patients with recurrent malignant glioma (based on histology, 33 GBMs, 2 gliosarcomas, and 2 anaplastic astrocytomas) were treated with DNX-201. Patients were divided into two groups. The first group of 25 patients received a single intratumoral injection with dose escalation, which determined safety, i.e., fulfilled the primary endpoint; five patients (20%) survived 3 years post-treatment. The second group of 12 patients received an intratumoral injection through a permanently implanted catheter, followed by surgical resection of the entire GBM tumor after 2 weeks to investigate the mechanism of action. Histopathology of resected GBMs revealed direct virus-induced oncolytic effects, along with an anticancer immune response, seen as tumor infiltration by immune $CD8^+$ and T-bet^+ cells and downregulation of transmembrane protein T-cell immunoglobulin and mucin domain-3 (TIM-3, which normally downregulates Th1 responses (Zhang and Shan 2014)); the latter was corroborated by radiographic signs of inflammation. Glioma stem cells cultured from the GBM surgical resection of 2 patients from the second group were analyzed for damage-associated molecular patterns (DAMPs): high-mobility group protein B1 (HMGB1), heat-shock protein (Hsp)90a, Hsp70, and ATP. DAMPs were elevated in cultured glioma stem cells following DNX-2401 infection but not mock infection, revealing the induction of immunogenic cell death in cancer cells after DNX-2401 treatment (Lang et al. 2018). Thus, treatment with DNX-2401 has direct oncolytic effects on GBMs, followed by an indirect, immune-mediated anti-GBM response.

A phase I/II clinical study for GBM patients is currently ongoing (Transgene 2017), in which patients are treated with the vaccinia virus TG6002 (Foloppe et al. 2019). This virus is highly attenuated in normal cells, yet it displays cancer-selective replication and cancer cell-killing ability.

As discussed above, oncolytic viruses selectively infect and directly lyse cancer cells. Its efficacy, however, depends on the "bystander effect," which refers to the phenomenon of initially uninfected cancer cells being (in)directly killed. The traditional bystander effect is achieved mainly by (i) secondary infection, whereby postlysis-released virions can infect nearby cancer cells; (ii) activating anticancer immune responses (Lin et al. 2023); and (iii) inducing the death of adjacent cancer cells by transmitting apoptotic signals through gap junctions (Asklund et al. 2003) or exosomes (Friesen et al. 2024). However, the bystander effect has significant limitations, including (i) the obstruction of virus diffusion efficiency by physical barriers in the TME (such as matrix fibrosis); (ii) weakened T-cell activity by the immunosuppressive TME; and (iii) tumor heterogeneity, whereby some cells have low, or even lack, expression of virus receptors, making them unable to infect (Lawler et al. 2017).

In recent years, the discovery of tunneling nanotubes (TNTs) has provided a new perspective for enhancing the bystander effect of oncolytic viruses. TNTs are nanoscale membrane channels composed of filamentous actin that are used for intercellular communication and have the ability to efficiently transport viral particles, mitochondria, nucleic acids, and signaling molecules (Melwani and Pandey 2023). Compared with traditional extracellular diffusion, TNTs can allow virus particles to bypass the extracellular matrix barrier and undergo long-distance transmission, thus expanding the range of infection and killing (Ady et al. 2016); TNTs could be especially suitable for bypassing the BBB in brain cancer. TNTs are highly active in GBM cells (Pinto et al. 2021), which may provide a "hidden channel" for oncolytic viruses and enhance their ability to infect distant cancer cells. TNTs can also deliver TAAs or DAMPs to immune cells to activate anticancer immune responses (Zhu, Shi, and You 2021) and thus transform "cold cancers" into "hot cancers". In addition, TNTs may transmit proapoptotic signals or virus-induced stress molecules (such as mitochondrial DNA or DAMPs) (Rustom et al. 2004), further amplifying the effects of oncolytic viruses.

Although oncolytic virus therapy has achieved some preliminary success in GBM treatment, several challenges remain. One key challenge is ensuring the safety of viral vectors, which require that oncolytic viruses replicate specifically within GBM cells to avoid damaging normal tissue. In addition, the BBB may limit the delivery of viral vectors, considerably compromising their oncolytic efficacy (Martikainen and Essand 2019). Addressing these challenges is essential for optimizing the application of oncolytic virus therapy in GBM and maximizing its potential benefits for patients.

3.6 | Nanoparticle Therapeutic Carriers

Nanoparticle therapeutic carriers are passively targeted to tumors through enhanced BBB permeability and cell retention effects; they are suitable vehicles for the delivery of chemotherapeutics in cancer treatment (Li, Baiyang, et al. 2017). Researchers often prefer biodegradable polymers, such as polyethylene glycol (PEG) (Knop et al. 2010) or poly(lactic-co-glycolic acid) (PLGA) (Illum 2000) as carrier materials because of their excellent biocompatibility and degradability.

Li et al. tailored the size of micelles by the structure of the copolymer poly(2-ethyl-2-oxazoline)-b-poly(e-caprolactone) (PEtOz-SS-PCL) to encapsulate the chemotherapeutic drug doxorubicin (DOX) (Li, Baiyang, et al. 2017). These micelles rapidly release their cargos when situated in a reductive intracellular environment, such as that of cancer cells. Specifically, the NADH/NAD^+ ratio is elevated in cancer cells because (i) the Warburg effect, as mitochondrial respiration consumes less NADH, and (ii) the overexpression of NRF2, a transcription factor that regulates the expression of antioxidant proteins and leads to an increase in the NADH/NAD^+ ratio (Luo et al. 2024). To test the delivery of micellar cargo in vivo, the authors used an experimental model of nude mice with entopic tumors formed by injected C6 cells, which were historically and clonally isolated from N-nitrosomethylurea-induced malignant gliomas formed in the rat brain (Benda et al. 1968). In vivo imaging revealed that following intravenous injection, DOX-laden PEtOz-SS-PCL micelles accumulated in C6 tumors, and the release of DOX hampered C6 tumor growth (Li, Baiyang, et al. 2017). However, whether this approach can be translated for use in human GBMs remains elusive.

Tseng et al. used an experimental model of entopic C6 glioma-bearing rats to test the effects of chemotherapeutics released interstitially from two types of PLGA nanofibers. One type, BIC/PLGA, has PLGA nanofibers laden with a cocktail of three chemotherapeutics (BIC): bis-chloroethylnitrosourea (an

alkylating agent), irinotecan (a topoisomerase I inhibitor), and cisplatin (an alkylating agent). The other type of BICC/PLGA had an additional load of combretastatin (a tubulin-binding natural phenol). These loaded nanofiber-forming membranes were placed onto the brain surface of C6 glioma-bearing rats, where the released cargos caused a reduction in tumor progression at the end of BICC/PLGA nanofiber treatment and significantly increased survival rates compared with those of controls (Tseng et al. 2016). It remains to be seen whether this approach is applicable in human GBMs.

An additional approach for the use of nanoparticles in the treatment of GBM is to employ biomimetics or biomimicry. For example, Siqi et al. used an antibody against the TAA Ephrin type-A receptor 3 (EPHA3) (Janes et al. 2014) to functionalize PLGA nanoparticles laden with the chemotherapy drug TMZ butyl ester (TBE) (Chu et al. 2018). These functionalized nanoparticles (FNPs) were preferentially internalized over nonfunctionalized nanoparticles by cultured C6 glioma cells. The FNPs had a cytotoxic effect on these cancer cells, presumably due to the sustained release of TBE over 48 h, as detected in vitro. In an experimental rat model, after the nasal delivery of FNPs to rats entopically grafted with C6 cells to bear C6 gliomas, in vivo imaging revealed the accumulation of FNPs in gliomas, which resulted in significantly increased apoptosis compared with that in gliomas in rats treated with nonfunctionalized (no anti-EPHA3) and/or unladen (no TBE) PLGA nanoparticles. Additionally, these FNPs prolonged the median survival time of glioma-bearing rats by 1.37-fold, indicating that the functionalization of these nanoparticles may serve to noninvasively deliver TMZ, the most commonly used chemotherapeutic drug in the treatment of GBM. Of course, the prerequisite to such a scenario requires prior success in future human GBM clinical trials.

Finally, biomimetic nanoparticles have been tested for use in human GBMs. Gboxin is a cationic oxidative phosphorylation (i.e., mitochondrial ATP synthase) inhibitor that hampers human GBM cell growth but not that of normal astrocytes (Shi et al. 2019). Normal astrocytes possess a functionally active mitochondrial permeability transition pore (Reyes and Parpura 2008; Reyes et al. 2011) that expels cationic gboxin, so the activity of the pore enables the resistance of astrocytes to the cytotoxic effect of gboxin, which kills GBM cells that have weak pore activity (Shi et al. 2019). Compared with vehicle injection, intraperitoneal gboxin treatment in an experimental model of ectopic/flank mouse GBM cell allografts or human GBM patient-derived xenograft (PDX) cell grafts resulted in reduced tumor volume and cellular density; allografted mice had prolonged survival. In a preclinical model, brain intraparenchymal catheterization to circumvent the poor BBB permeability of gboxin and deliver it as the site of entopic implantation of human GBM PDX cells in mouse brains resulted in decreased cellular density and proliferation of PDX cells and GBM marker expression, with no signs of health deficits in treated mice (Shi et al. 2019).

The further clinical application of gboxin is limited by its poor BBB permeability and targeted delivery, which could be remedied via a biomimetic approach. Zuo et al. generated cell-specific biomimetic agent(s), referred to as "nanomedicine," with an inner core and an outer shell (Zou et al. 2023). The inner core is a conglomerate of nanoparticles (NPs) composed of a ROS-responsive polymer, poly(ethylene glycol)-poly(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acrylate) (PEG-PHB); the polymer's biological degradation products can be readily eliminated from the body. NPs can be loaded with gboxin (NPs@G), which is released from the inner core upon encountering intracellular ROS, the levels of which are elevated in cancer cells and are ~90% in mitochondria, where gboxin exerts inhibitory effects on oxidative phosphorylation. The two-tier targeting of NPs@G, first to GBM cells and then to mitochondria, was achieved by enwrapping the inner core with the outer shell, a hybrid membrane (HM) obtained by the fusion of isolated patches of mitochondrial membranes (containing both the inner and outer membranes) and cancer cell membranes (likely a mixture of the plasma membrane and endomembranes). This HM-NP@G nanomedicine was further "personalized," as HMs were prepared from two different human GBMs, the U87MG cell line and patient-derived X01 GBM stem cells. This noninvasive targeting of gboxin to mitochondria is mediated by mitofusin. In cell cultures, HM-NP@G inhibited the proliferation of both U87MG and X01 cells and was cytotoxic to these cells through apoptosis while sparing normal astrocytes. In vivo, HM-NP@G crossed the BBB by reducing the strength of the tight junctions between endothelial cells. In a preclinical model, this medicine increased the survival time of nude mice bearing U87MG or X01 endocranial tumors, not only compared with those of sham-treated animals but also those treated with TMZ. These promising findings await validation in clinical trials enrolling patients suffering from this devastating cancer.

3.7 | Phototherapy

In recent years, phototherapy has provided a promising approach for treating GBM. This approach mainly involves photodynamic therapy (PDT) and photothermal therapy (PTT).

3.7.1 | Photodynamic Therapy

PDT uses photosensitizers to generate ROS upon irradiation with specific wavelengths of light to kill cancer cells (Cesca et al. 2025); thus, it requires oxygen. 5-Aminolevulinic acid (5-ALA, i.e., Gleolan; Photonamic GmbH & Co. KG), which has been approved by the United States FDA for intraoperative fluorescence-guided surgery (Hadjipanayis and Stummer 2019), also has good feasibility and safety as a PDT sensitizer for intraoperative add-on therapy of GBM when delivered immediately after surgical resection (Vermandel et al. 2021); this approach may decrease the risk of GBM recurrence, as it targets residual GBM cells within and/or near the resection cavity. Notably, 5-ALA also responds to ultrasound stimulation by producing ROS and can be used as a sonosensitizer (Ohmura et al. 2011) for sonodynamic therapy (see below, heading 8).

The delivery of photosensitizers requires improvements. They can be experimentally delivered to the GBM via laden nanoparticles as carriers; these composite materials can be delivered directly or by syngeneic immune cells. Thus, neutrophils loaded with photosensitizers attached to nanoparticles have been used for experimental anti-GBM PDT in animals (Wen et al. 2025). Nanoparticles made out of hexagonal boron nitride, also known

as white graphene, were co-functionalized with PEG to provide aqueous solubility and with DOX to facilitate cell membrane partitioning and hence promote cell uptake, presumably via endocytosis. The photosensitizer chlorin e6 (Ce6) was directly attached to functionalized boron nitride nanoparticles, forming BNPD-Ce6, which was loaded into mouse neutrophils (BNPD-Ce6@NE). As an experimental model of GBM, the authors used mouse GL261 glioma cells (originally induced by highly carcinogenic methylcholanthrene), the intracranial tumors of which resemble ependymoblastomas in histology, but display many characteristics of GBM phenotypes (Szatmári et al. 2006). In cell culture experiments, BNPD-Ce6@NE readily released BNPD-Ce6 when it was taken up by cocultured GL261 cells. Upon exposure to light, BNPD-Ce6 generates ROS and causes cytotoxicity (Wen et al. 2025). In an in vivo experimental model, intravenously applied BNPD-Ce6@NE invaded intracranial tumors formed by the implantation of GL261 cells in mice. PDT treatment of these GL261 tumors resulted in significant tumor cell damage as per histology and markedly improved survival when the animals received BNPD-Ce6@NE but not BNPD-Ce6 alone. Taken together, these data indicate that biomimicry, i.e., neutrophils, can be used for GBM-targeted delivery of photosensitizer-laden nanoparticles to successfully implement experimental anti-GBM PDT in an animal model (Wen et al. 2025). This approach awaits further testing of its feasibility in preclinical models of human GBM-bearing mice as well as GBM patients.

As has been the case for the delivery of photosensitizer-laden nanoparticles to the GBM via neutrophils, direct delivery of such nanoparticles is also possible. In an experimental study, Chen et al. (Chen et al. 2024) generated nanoparticles containing triphenylphosphorus (TPP) to target covalently linked Ce6 to mitochondria. For the delivery of TPP-Ce6 through the blood–brain barrier and into cancer cells from the extracellular space, they utilized a cellular copper transport system. Specifically, TPP-Ce6 self-assembled with Cu^{2+} and thymopentin (TP5) to obtain TCe6@Cu/TP5 nanoparticles, which accumulated in GL261 cancer cells entopically implanted in CB57BL/6 mice. TCe6@Cu/TP5 in the mitochondria of GL261 cells caused two-pronged organelle impairment by (i) causing cuproptosis and (ii) oxidative damage due to the accumulation of ROS upon PDT. This impairment led to degradation of the immunosuppressant PD-L1 and activation of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, an innate component of the immune system, in cancer cells. The resulting anticancer immunity was further enhanced by TP5, which promoted the differentiation of dendritic cells and T lymphocytes. These findings illustrate the power of a multimodal approach in anti-GBM therapy in an experimental animal model, whereby PDT is combined with the induction of cuproptosis and boosting of the innate immune response. As above, this approach awaits further testing in preclinical models and clinical trials.

As with any emergent therapy, PDT is undergoing refinements in its regimen. Caverzán et al. compared the efficacy of conventional PDT (cPDT) using high irradiance in a relatively short period (2–8 min) with that of metronomic PDT (mPDT), whereby a lower radiant flux was used over an ~5-fold longer period of time (Caverzán, Oliveda, et al. 2023); however, the same light dose was used in both regimens. The authors synthesized photosensitizer-conjugated polymer nanoparticles (CPNs), which they used in light regimen testing. In cell culture experiments, the CPN-loaded (by uptake) cells of individual human GBM cell lines, U87-MG, T98G, and M059K, suffered from greater cytotoxicity when they received mPDT than when they received cPDT. Further investigation using individual U87-MG and T98G cell lines revealed differential effects of light regimens, whereby mPDT caused sustained intracellular ROS production and apoptotic death, whereas cPDT caused a transient burst of ROS production and necrosis. GBM U87-MG cells were more efficient at taking up CPNs than cocultured macrophages were, which emulated tumor-associated cancer-promoting M2 immune cells of the TME. Both cell types experienced PDT-induced cytotoxicity. However, following PDT, there was a shift from the M2 phenotype to the M1 phenotype, the latter being anticancerous, and this shift was more prominent in the mPDT regime, which was also more effective than cPDT in killing GBM cells but also macrophages. On the basis of these findings, the efficiency of mPDT alone was further tested in vivo. Indeed, in an experimental GBM ectopic graft mouse model in which U87-MG cells formed tumors in the flanks of nude mice, intravenous or intratumoral injections of CPN followed by mPDT inhibited tumor growth, which was more pronounced with intratumoral CPN injections (Caverzán, Oliveda, et al. 2023). Taken together, the use of CNP photosensitizers combined with mPDT represents a promising experimental approach for treating GBM. However, successful testing of this methodology using a preclinical model of mice bearing (entopic/orthotopic) impanation of human GBM cells in their brains, particularly those not of human cell lines but rather human PDXs, has to occur prior to the implementation of this approach in human clinical trial settings.

3.7.2 | Photothermal Therapy

PTT converts electromagnetic irradiation into thermal energy through photothermal transduction agents (PTAs). These agents accumulate in cancer cells but not in normal tissue. When exposed to light, PTAs generate heat-induced cell death. Nonmetallic PTAs in the form of nanoparticles, which penetrate the blood–brain barrier and preferentially accumulate in GBM tissue, are of special interest (Gawel et al. 2024), as is near-infrared I–b (NIR–Ib)/NIR–II irradiation (900–1880 nm), which is particularly suitable because of its deep penetration through the skull and low scattering and absorption in biological tissue (Lai et al. 2019; Lin, Sun, et al. 2024). Thus, the purpose of the PTT approach is to damage PTA-loaded GBM cells while sparing PTA-lacking normal brain tissue. Owing to comprehensive reviews focused on this topic available elsewhere (e.g., (Gawel et al. 2024)), we only briefly outline two experimental studies utilizing PTT in GBM in the context of its TME, as it pertains to macrophages and microglia.

Lai et al. used 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol) (DSPE-PEG), a phospholipid–polymer conjugate (commonly used for drug delivery), along with the infrared IR-792 dye (used as a PTA) to generate self-assembled nanoparticles. The biomimicry of these nanoparticles was obtained by coating their surface with the macrophage plasmalemma; the resulting product was abbreviated/termed MDINPs.

It should be noted, however, that IR-792 has a high intersystem crossing rate (Al-Aqmar et al. 2020) and can act as a photosensitizer (Buddhiraju et al. 2023); however, see the thermal imaging data presented in this study below. Nonetheless, DSPE-PEG allows MDINPs to cross the BBB, while the presence of the macrophage plasmalemma ensures specific targeting of GBM cells; in particular, U87 cells expressing luciferase (U87L) presented increased MDINP uptake. In an experimental model in which U87L tumors formed in the flanks of nude mice, MDINPs delivered intravenously accumulated in the tumors. The efficacy of PTT of MDINP-loaded GBM tumors was confirmed by thermal imaging, whereas the luciferase luminescence of ectopic GBMs reportedly retarded the growth of these tumors (Lai et al. 2019); PTT treatment of GBM tumors in mice that received MDINPs also led to increased animal survival. These data indicate the experimental value of the multidisciplinary approach in the treatment of GBM, whereby polymer chemistry ensures drug delivery across the BBB. Furthermore, nanoparticle self-assembly with a PTA provides efficient PPT, whereas biomimicry via the use of a macrophage plasmalemma coating layer of the nanoparticles provides GBM tumor specificity for the therapeutic approach.

The cells of the TME also include microglia, whose exosomes can be used as therapeutic tools (Dai et al. 2024). Lin et al. prepared exosomes shed by BV2 mouse microglia engineered to express immune checkpoint blockade molecules, i.e., anti-LAG3 inhibitory antibodies (Lin, Sun, et al. 2024). Specifically, LAG3 is an immune checkpoint protein that is overexpressed in T cells of the GBM TME, causing T-cell exhaustion and an overall immunosuppressive TME (Ye et al. 2019). These anti-LAG3 exosomes were fused with nanoparticles composed of DSPE-PEG and a so-called aggregation-induced emission (AIE) (Qu et al. 2022) PTA, denoted Fs, to form hybrid exosome-nanoparticles termed EE@F-NPs (Lin, Sun, et al. 2024). The EE@F-NP composite material crossed the BBB and specifically accumulated in GBM tumors in an experimental model of mouse-bearing orthotopic GBM tumors formed from mouse GL261 cells. LAG3 inhibition reversed T-cell exhaustion, thus allowing the innate immune system response to GBM. It also promoted tumor necrosis factor-α release from T cells, which reduced the expression of Hsps in GBM cells, increasing their susceptibility to PPT. Indeed, NIR-II PPT via EE@F-NPs in an experimental model of mouse-bearing orthotopic GL261 tumors caused GBM cell death and infiltration of the TME with cytotoxic CD8+ T cells and thus liberation from immunosuppression in the TME. This combined photothermal and immune checkpoint inhibition therapy significantly increased the survival time of GBM tumor-bearing mice (Lin, Sun, et al. 2024).

The prospect for the use of biomimicry combined with PPT, as presented in the two above experimental studies, in the clinical management of GBM awaits experiments in a more realistic, preclinical model of mice bearing human PDX GBM tumors in their brains and human clinical trials.

3.8 | Sonodynamic Therapy

Sonodynamic therapy (SDT) is a noninvasive treatment for solid cancers in which focused ultrasound can activate so-called sonosensitizers, which selectively accumulate in cancer cells. When exposed to ultrasound in the cellular milieu, sonosensitizers produce radicals, which cause cell death (Nowak et al. 2022). We noted previously that, e.g., 5-ALA could serve as a PTA and/or sonosensitizer. Thus, hybrid approaches such as photoenhanced SDT, albeit with the use of titanium boride nanosheets, have been successfully attempted in a preclinical model of entopic U87 tumor-bearing nude mice (Xu et al. 2024); this study additionally used macrophage membranes to generate a biomimetic sonosensitizer, a strategy we already discussed above. Similar to the above-discussed engineered exosome approach for PDT, the use of macrophage exosomes for SDT has been successful in a preclinical model of entopic U87 tumor-bearing nude mice (Wu et al. 2022).

In contrast to PDT/PTT, SDT provides deeper tissue penetration and negligible radiation damage to normal tissue, so it should be no surprise that several human trials have reported the use of this technology to treat GBMs; as these trials and preclinical models of GBM SDT have been reviewed elsewhere (Mehta et al. 2023), we only briefly overview recent human trials here.

Since 2021, three clinical trials have been completed, with one ongoing clinical trial. These trials utilized two different sonosensitizers, 5-ALA or SONALA-001, with focused ultrasound activation in an attempt to cause cytotoxicity in high-grade gliomas (2 trials, one with 5-ALA and the other with SONALA-001), GBMs (1 trial with 5-ALA) and recurrent GBMs (1 trial with SONALA-001) (details are available in table 5 of Mehta et al. (2023)). SONALA-001 (a SonALAsense product) is a proprietary United States FDA-approved intravenous ALA formulation; when activated by ultrasound, its metabolite protoporphyrin X induces tumor cell death (Syed et al. 2024). These trials have aimed to test the effects of SDP-mediated activation of porphyrin-based sonosensitizers on cancerous gliomas and GBMs; the full reports of these trials are expected soon.

4 | Concluding Remarks

GBM poses a severe threat to patient health and has long been a significant challenge in the medical field (Nizamutdinov et al. 2018). Traditional treatment methods include surgery, radiation therapy, and chemotherapy, each with its own set of challenges and advancements (Schaff and Mellinghoff 2023). Surgical treatment aims to maximally and safely remove tumor tissue. The application of advanced technologies, such as neuronavigation, intraoperative magnetic resonance imaging, and fluorescence-guided surgery, has improved the precision and safety of surgical procedures (Roberts et al. 2011). However, due to the infiltrative growth characteristics of GBM, complete tumor resection is often difficult, and residual cancer cells can easily lead to recurrence. Radiation therapy uses high-energy rays to kill cancer cells. Techniques such as intensity-modulated radiation therapy, stereotactic radiosurgery, and proton-heavy ion therapy have continuously evolved, improving local tumor control while minimizing damage to normal tissues (Xu et al. 2023). Nevertheless, cancer resistance limits the effectiveness of radiotherapy for GBM. Factors such as a hypoxic microenvironment, enhanced DNA damage repair mechanisms, and the presence of cancer stem cells make it challenging for radiotherapy to completely eradicate cancer cells (Bae et al. 2021; Shi

et al. 2023). TMZ is the most commonly used chemotherapeutic drug in GBM treatment (Gondi and Mehta 2015). Concurrent chemo-radiotherapy and adjuvant chemotherapy play crucial roles in managing this disease (Lee et al. 2013). However, the BBB presents a significant obstacle, making it difficult for chemotherapy drugs to reach effective concentrations within the tumor. Additionally, drug resistance significantly limits the efficacy of chemotherapy. The overexpression of drug efflux pumps, enhanced DNA damage repair mechanisms, and resistance to apoptosis contribute to the development of resistance in cancer cells to chemotherapy agents (Munoz et al. 2015; Eisele and Weller 2013). In summary, while the above traditional standard-of-care treatments have made progress in improving outcomes for GBM patients, significant challenges remain.

Emerging treatments offer new hope for the management of GBM. These innovative approaches address various aspects of tumor biology and treatment limitations, providing potential improvements over traditional therapies. Molecular targeted therapy focuses on specific abnormal molecules in cancer cells. For example, bevacizumab targets VEGF to inhibit tumor angiogenesis (Zhang et al. 2012). This approach aims to block the formation of new blood vessels that tumors need to grow, thereby starving cancer cells of nutrients and oxygen (Jain et al. 2007). When combined with traditional chemotherapy, it can improve treatment outcomes (van Linde et al. 2015). Immunotherapy encompasses several strategies, including immune checkpoint inhibitors, CAR-T-cell therapy, and dendritic cell vaccines (Yasinjan et al. 2023). While these methods have demonstrated therapeutic potential in some patients, their effectiveness is limited by the presence of the BBB and the immunosuppressive microenvironment characteristic of GBM. Immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors, aim to increase the ability of the immune system to recognize and attack cancer cells (Korman et al. 2022). CAR-T-cell therapy involves genetically engineering T cells to target specific antigens on cancer cells (Chen and Yang 2017), whereas dendritic cell vaccines use dendritic cells to present cancer antigens to T cells, activating a robust anticancer immune response (Bregy et al. 2013). Proton therapy utilizes the unique physical properties of protons to deliver precise radiation doses to cancerous tumors, minimizing damage to surrounding healthy tissue. This method can increase patient survival by increasing cancer control rates with fewer side effects. However, the high cost of proton therapy equipment limits its widespread adoption. The ability to concentrate radiation at the cancer tumor site while sparing normal tissue makes proton therapy particularly advantageous for treating brain neoplasms such as GBM (Xu et al. 2023). Oncolytic virus therapy involves the use of viruses that selectively replicate within cancer cells and induce their lysis (Qi et al. 2022) while also stimulating the immune system to attack residual cancer cells (Qi et al. 2022). This immunostimulatory ability of oncolytic viruses in the GBM microenvironment is likely to turn the "cold" immune microenvironment into a "hot" one (Martikainen and Essand 2019). Moreover, as excellent gene delivery vehicles, oncolytic viruses can introduce specific therapeutic genes (including tumor-suppressor genes, immunostimulatory genes, and antiangiogenic genes) and produce their protein products in situ in cancer cells prior to lysis (Loskog 2015). Although promising, this approach still faces challenges related to viral vector safety and targeting efficiency. Ensuring that the virus only replicates in cancer cells and not in normal tissues is crucial for maximizing efficacy and minimizing side effects. Nanoparticle therapeutic carriers represent a cutting-edge strategy that has unique advantages in overcoming the BBB and achieving targeted combination therapy (Li, Baiyang, et al. 2017). This approach leverages advanced materials and biological principles to improve drug delivery and treatment precision. Nanoparticle therapeutic carriers can mimic natural substances to increase drug transport and efficacy (Zhao et al. 2020). Despite their potential, nanoparticle therapeutics are still in the research and development phase, with ongoing studies aimed mainly at optimizing their preclinical applications. Finally, the sonodynamic approach provides a promising noninvasive treatment for GBM, with much needed deep tissue penetration along with negligible radiation damage to normal tissue. This is unlike phototherapy, the advantage of which, however, is a finer focal application. Taken together, the above emerging therapies hold significant promise for improving GBM treatment.

With the advancement of technology, the application of artificial intelligence and big data technology in GBM treatment also has enormous potential. This includes the use of machine learning and deep learning (Zhu et al. 2024) for the former application and the use of big clinical imaging (Di Salle et al. 2024) and genetic data (Ceccarelli et al. 2016) of GBM patients, which can be analyzed to establish accurate prediction models for the treatment response and prognosis of patients (Gomaa et al. 2024). In addition, on the basis of genomics (*Nature* 2008), proteomics, and metabolomics data (Wang et al. 2021), comprehensive molecular feature analysis provides personalized treatment for GBM. The treatment of GBM is complex and requires multiple treatment methods and the continuous exploration of new treatment strategies. In the future, basic research should be conducted to gain a deeper understanding of the pathogenesis and biological characteristics of GBM, providing theoretical support for the development of more effective treatment methods. Moreover, it is important to focus on clinical research, optimize treatment plans, improve treatment outcomes, and enhance patient prognosis and quality of life.

Author Contributions

Xue Yang: conceptualization, writing – original draft, visualization, software. **Shibing Wang:** conceptualization, writing – review and editing, supervision. **Vedrana Montana:** writing – review and editing. **Xiangmin Tong:** conceptualization, writing – review and editing, supervision. **Vladimir Parpura:** funding acquisition, conceptualization, resources, supervision, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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