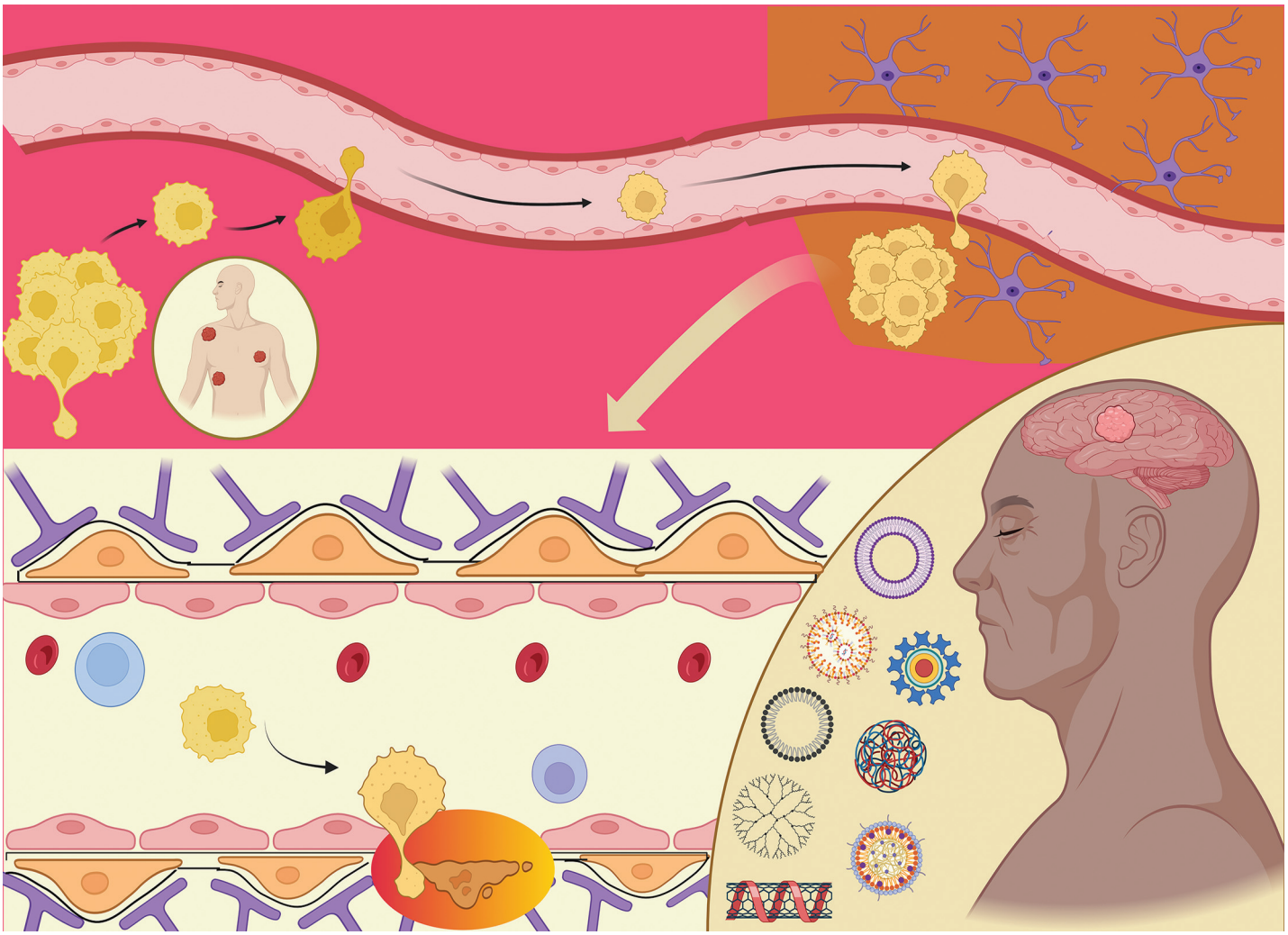

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Comprehensive review on glioblastoma: nanotechnology, immunotherapy and combined therapeutic approaches

The review highlights the intersection of cutting-edge nanocarriers based drug delivery, surface modification of nanocarriers, immunotherapeutic interventions, and combined therapeutic approaches, which are critical for advancing glioblastoma treatment

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Comprehensive review on glioblastoma: nanotechnology, immunotherapy and combined therapeutic approaches

Ashish Dhiman, Yagni Shah, Dhwani Rana and Kalpna Garkhal *

Glioblastoma multiforme (GBM) is the most dangerous type of brain cancer because of spontaneous microvascular growth, which leads to damage to nearby brain tissues. GBM affects a huge population across the globe and current therapies for GBM have not proven fruitful in past decades due to poor clinical prognosis. The slow progression of GBM makes it difficult to track during diagnosis for treatment. Thus, there is a need to develop some cutting-edge drug delivery platforms, which could overcome the challenges faced in the delivery of current therapeutic drugs. Nanotechnology has been an emerging paradigm to unravel promising drug therapies, be they immunotherapy or combination therapy. The surface modification of nanocarriers led to significant improvements in therapeutic aspects of GBM. The surface-modified entities could be monoclonal antibodies, functional peptides, growth inhibitors, folic acid, transferrin, or lectins. Immunotherapeutic interventions, such as vaccines, oncolytic virotherapy, immune checkpoint inhibitors, and CAR T-cell and N-k cell therapies, are rising as a treatment model for GBM. Future research must elaborate on remedies that can encounter problems with current treatment. However, numerous research studies are underway to explore new treatments. The current review reveals potential future therapies to challenge the issues faced in the treatment of GBM. Nanotechnology-based drug carriers, surface modification of nanocarriers for enhanced drug delivery to GBM and immunotherapeutic approaches are enlisted. The review also discusses multi-modal approaches to tackle resistance and others issues related to monotherapy.

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1. Introduction

Over recent decades, there has been a tremendous increase in the number of cancers of the central nervous system (CNS) and many cases are brain cancers. Glioblastoma multiforme (GBM) is particularly prevalent in Europe and North America, where around 50% of primary brain tumors are reported to be GBM.[1] According to data from the Central Brain Tumor Registry of the United States (CBTRUS) from 2013 to 2017, GBM represents nearly 60% of malignant brain and CNS tumors, making it the most prevalent primary brain tumor.[2] GBM primarily affects individuals who are 45–75 years old and it makes up nearly 15% of all brain malignancies. The limited availability of treatment options has led to an urgent requirement for effective therapies for GBM. The current standard treatment for glioblastoma involves resection of the maximum amount of tumor (surgery is possible in 50% to 70% of patients, based on geographical area)[3] but chemotherapy (such as a carmustine implant: Gliadel® wafer from Eisai/Arbor) may also be considered in the United States and Japan. Finally, the "Stupp protocol"—radiation adjuvant chemotherapy with temozolomide (TMZ) (Temodal® from Merck) plus radiation is implemented. The effectiveness of the first-line treatment is assessed by evaluating the overall condition of the patient, and their biological status for methylguanine-DNA-methyltransferase (MGMT) and EGFRvIII genes.[4] However, first-line therapy does not prevent systemic relapse and improves survival rate only at a very low rate.[5,6]

A partially completed clinical study depicted the median survival rate of radiotherapy (RT) plus temozolomide (TMZ) as 14.6 months compared to 12.1 months for RT alone. The overall survival rate for 5 years for RT plus TMZ was 9.8%, while for RT it was 1.9%. Currently, the only known risk factor for the formation of GBM is contact with highly ionizing radiation.[7] It has been reported that individuals with asthma or other allergic disorders are less likely to develop GBM. Furthermore, there is a relationship between a lower risk of GBM and genes that increase the risk of asthma. Numerous scientific studies have indicated that the use of NSAIDs (non-

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steroidal anti-inflammatory drugs) may be negatively correlated with the development of GBM. The GICC (Glioma International Case-Control) Study reported environmental and genetic variables influencing the risk of developing GBM. It involves the collection of data in the form of questionnaires with a common protocol from various countries and different sites.[8] The study suggested that daily consumption of aspirin for more than 6 months leads to a 38% reduction in the threat of glioma. Another study evaluated GBM risks in 600 frequency-matched controls in Houston metropolitan area between 2001 and 2006 among 325 cases.[9] The study demonstrated that routinely consuming NSAIDs was associated with a 33% decreased risk of GBM.[10] According to several theories, the malignant phenotype in GBM is influenced by the human cytomegalovirus. Valganciclovir was administered as an adjuvant therapy to 50 GBM patients in limited research conducted at Karolinska University Hospital. After two years, the survival rate was 62%, but the rate in modern controls with a similar illness stage, surgical resection grade, and baseline treatment was only 18% ($P < 0.001$). In future, larger randomised research studies should be conducted to validate these encouraging results.[11] Although tremendous progress has been made in the treatment of GBM, conventional treatments like surgery, radiation, and chemotherapy still have drawbacks, such as low tumour penetration, resistance, and serious side effects. These challenges have encouraged research into cutting-edge tactics like immunotherapy and nanotechnology. By leveraging nanotechnology-based drug delivery systems and the body's immune response, these emerging approaches aim to overcome existing barriers and offer improved therapeutic outcomes.

This comprehensive review aims to jointly cover evolving drug delivery approaches of nanotechnology, surface modification of nanocarriers, and immunotherapeutic interventions as a newer paradigm for GBM treatment. Current treatments followed for GBM are also discussed in the review to gain a better understanding of them along with emerging therapies. Additionally, it highlights the multi-drug and combination treatments models to overcome the challenges encountered during monotherapy. A discussion on treatment affordability and addressing pediatric GBM is also covered. Furthermore, future prospects with insights into listed drug delivery strategies are discussed.

2. Current treatments for GBM

2.1 Chemotherapy drugs

Patients who have no visible cancer but who are at high risk of recurrence frequently receive chemotherapy in an adjuvant setting. The effect of chemotherapy is increased in this case because the overall tumor load is low. Additionally, due to tumor heterogeneity, drug resistance and less hypoxia, the tumor has the highest proliferation with more vascular supply, and the remaining tumor cells should be most susceptible to chemotherapy. The adjuvant chemotherapy for GBM depends on different factors, such as the effect of a drug on the patient, diagnostic period, chances of recurrence and the patient's age.[12] Adjuvant chemotherapy has been proven to decrease patient mortality rates for solid tumors, including breast and colon cancers. The mostly commonly used first-line treatment is temozolomide (TMZ). The prodrug TMZ functions by converting to monomethyl triazene 5-(3-methyl-1-triazeno) imidazole-4-carboxamide.[13] The biological effects of TMZ are caused by methylation at guanine's O6 position,[14] which results in mutations that eventually evade the mismatch repair (MMR) system. The MMR triggers a signaling pathway by breaking double and single bonds in DNA. The triggered signaling pathway regulates apoptosis, cell cycle check points and G2-M cell cycle arrest.[15] Tumor cells with *O*6-methylguanine-


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Table 1 Drugs commercialized/under development for GBM treatment based on immunological, pharmacological or metabolic modes of action[17]

Mechanism of treatment	Drugs	Mode of action
Anti-angiogenic	Panobinostat, altiratinib, avastin (bevacizumab)	targets VEGF (vascular endothelial growth factor)
	Trebanaib	Targets TAEC
	SapC-DOPS, VB-111	Targets tumor-associated vasculature
	Enzastaurin	Disruption of protein kinase
	Crenolanib, AZD2171, tandutinib (MLN516, CT53518)	Inhibits PDGFR
	TCA2317	Inhibits Aurora-A
Triggers cell apoptosis (kinase inhibitor)	GDC-0084	Inhibits PI3K and mTor
Gene therapy	TOCA511 + TOCAFC	Triggers cytotoxicity
Molecular targeting	Mibefradil, temzolomide (temodar), gliadel	Modifies DNA function
	ANG1005	Blocks mitosis by targeting tubulin
	Afatinib	Inhibits epidermal growth factor receptor
	CBL0137 (curaxins)	Deactivates NK-kB
GBM stem cell inhibition	ICT-107 (DC cells)	Targets stem cells
Oncolytic virotherapy	ParvOryx	Oncolytic parvovirus
miRNA inhibition	TargoMiR	Targets miRNA
Active immunotherapy (vaccine)	Rindopepimut, SurVaxM	Acts as peptide vaccine
	ICT-107 (DC cells), prophage (HSPPC-96), gliovac, IMA950, DCVax-L	Autologous vaccine
Antibody-based immunotherapy	Depatix-M, asunercept	Targets EGFR
	MEDI-575, MEDI-3617	Targets PDGFR
Checkpoint inhibition-based immunotherapy	NOX-A12	Neutralizes CXCL12 pathway
	INdoximod	IDO inhibitor
Nanotherapy	Nanocell	Enhanced doxorubicin tumor delivery

DNA-methyltransferase (MGMT) methylation are more likely to respond to the cytotoxic effects of TMZ than those with functional MGMT.[16] Table 1 shows the chemotherapy drugs currently available in the market or under clinical trials along with other treatment options.[17]

2.2 Function of angiogenesis in GBM

Targeting of the proangiogenic signalling networks has resulted in the increased secretion of proangiogenic growth elements, including VEGF, which is responsible for the substantial tumor vascularization that is observed in GBM. The findings of the randomised, multicenter, open-label phase II BRAIN study had an impact on the US FDA's (Food and Drug Administration) decision to accelerate the approval process for bevacizumab in 2009 for the treatment of recurrent GBM. It was determined that a combination of bevacizumab plus irinotecan was more effective than bevacizumab monotherapy.[18] Progression-free survival (PFS) and objective response rate (ORR) were the primary objectives of the trial. At six months, the PFS for bevacizumab alone was 42.6%, while that for PFS for bevacizumab + irinotecan was 50.3%, with corresponding ORRs of 28.2% and 37.8%. However, the combination of beva-

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cizumab plus irinotecan had a median overall survival (mOS) of 8.7 months, while bevacizumab alone had an mOS of 9.2 months. Grade 3 adverse effects were more common in the combination group (65.8%) compared to bevacizumab alone (46.4%), with convulsions, neutropenia, and fatigue being notable.[19] The combination treatment with bevacizumab for recurrent GBM did not improve OS or PFS compared to bevacizumab alone. Lomustine and bevacizumab together were also investigated. The OS as primary outcome was determined to be 9 months. The combination of bevacizumab and lomustine yielded an mOS of 12 months, whereas bevacizumab or lomustine alone each resulted in an mOS of 8 months. Additionally, the combination raised the 6-month PFS to 42%. The research included a number of participants with grade 4 or grade 3 thrombocytopenia.[20]

Nonetheless, a "pseudo-response" may indicate a rise in PFS, and the event can be characterized by contrast enhancement as a result of normal vascular permeability.[21] In contrast, either FLAIR or *T*2-weighted imaging showed that the non-enhancing portion of the tumor had grown. FLAIR/T2 hyperintensity is taken into account by the Response Assessment in Neuro-Oncology criteria as a stand-in for the non-enhancing component of the tumor.[22] In a phase III trial, a VEGFR-targeting multi-kinase inhibitor, cediranib, did not significantly improve PFS when used alone or in combination with lomustine compared to lomustine alone, as assessed by post-contrast *T*1-weighted MRI reviews. In a phase III randomized trial, cediranib, a multi-kinase inhibitor targeting VEGFR, did not demonstrate a substantial enhancement in PFS. This was observed in both the group receiving cediranib alone and the group receiving cediranib combined with lomustine, as compared to lomustine alone. Independent or local inspection of *T*1-weighted MRI scans after contrast was used as the basis for the assessment.[23] Aflibercept, a fusion protein created through recombinant methods, targets both placental growth factor and VEGF. However, it displayed minimal effectiveness when used alone in unselected subjects with recurrent malignant glioma during a phase II evaluation.[24] Lastly, the NCCN now recommends regorafenib, an oral multikinase inhibitor, for the management of relapsed GBM following TMZ and radiation.[25] In a recent phase 2 trial, this medication showed strong clinical activity and outperformed lomustine alone.[26]

2.3 Tumor treating field (TTF)

TTF is a non-invasive antimitotic treatment that the Optune® device administers *via* an alternating electric field. Preclinical research suggests TTF can disrupt microtubule formation, leading to mitotic arrest and cell death. Additionally, during cytokinesis, it prompts the dielectrophoretic migration of polar molecules. According to preclinical research, TTF can change the way microtubules form, which can result in mitotic arrest and mortality. It further triggers the dielectrophoretic movement of polar molecules during cytokinesis. PFS and OS greatly increased among people with newly diagnosed GBM when Optune® with TMZ was administered rather than chemotherapy alone, as observed in phase III EF-14 research. Higher levels of compliance were associated with enhanced clinical results. Compared to chemotherapy alone, the use of TTF with TMZ greatly increased mOS (20.9 *vs.* 16.0 months, respectively; $P < 0.001$).[27] Two extensive phase III studies demonstrated the clinical tolerability and efficacy of TTF in GBM, and these findings have been confirmed in real-world scenarios. Minimal adverse effects (local or systemic) are linked to TTF. One drawback of TTF is that it needs to be worn constantly with very little break. This invariably results in significant lifestyle adjustments, and the entire monthly therapy expenditure comes to over $21 000.[28] Although TTF has demonstrated clinical benefit, using it in GBM patients is linked to a number of drawbacks and side effects, including a notably greater incidence of localized skin toxicity.[27] After gaining regulatory authorization, the National Comprehensive Cancer Network (NCCN) guidelines recommended TTF and TMZ for the treatment of individuals with recurrent (category 2B) and newly diagnosed (category 1) glioblastoma.[25] When used in combination with TTF, the treatment approaches offer significant therapeutic benefits in preventing further toxicity in brain cancer patients and may also be beneficial for individuals with other solid tumor types. Stupp and coworkers conducted randomised clinical trials on TTFs for the treatment of glioblastoma. In a trial of 695 GBM patients (median age 56, 68% men), adding TTFs to temozolomide significantly improved outcomes compared to TMZ alone. Median progression-free survival (mPFS) was 6.7 *vs.* 4.0 months (HR 0.63, $P < 0.001$), and overall survival was 20.9 *vs.* 16.0 months (HR 0.63, $P < 0.001$). Systemic adverse events occurred in 48% (TTF group) *vs.* 44%, with 52% experiencing mild to moderate skin toxicity from transducer arrays. These findings confirm earlier interim results, showing that TTF enhances survival with manageable side effects.[29] Lu and coworkers conducted a retrospective study and evaluated the outcomes in 48 recurrent glioblastoma (rGBM) patients treated with TTFs and salvage chemotherapies, comparing a triple-drug regimen of TMZ, bevacizumab (BEV), and irinotecan (IRI) (TBI + T, $N = 18$) with BEV-based chemotherapies (BBC + T, $N = 30$). TBI + T patients had an mOS of 18.9 months and progression-free survival (PFS) of 10.7 months, compared to 11.8 and 4.7 months for BBC + T. The OS difference (14.7 months, $P < 0.05$) was more pronounced than PFS (1.5 months). TBI + T was well tolerated, with grade III hypertension (38.9%) and leukopenia (22.2%) as common side effects. Findings suggest TBI + T may improve rGBM outcomes, warranting larger prospective studies.[30] Rominiyi and coworkers conducted a clinical trial and this pilot study demonstrated that TTF combined with lomustine (CCNU) and TMZ in *O*6-methylguanine-DNA methyltransferase-methylated newly diagnosed glioblastoma (MGMTm ndGBM) was safe, feasible, and associated with improved survival, with an mPFS of 20 months. Skin irritation (37–50%) and hematotoxicity rates were reported to be consistent with previous trials, and high TTF compliance (83%) was achieved. Synergistic effects between TTFs and systemic therapy were observed, with minimal distant tumor recurrence recorded. Histological changes, such as giant cell emergence,

were noted, suggesting potential therapeutic impact. Larger prospective studies were recommended to validate these findings. Song and coworkers conducted clinical trials on ten patients, eight males and two females, with a median age of 61 years and a median Karnofsky performance score (KPS) of 90. A median follow-up of 7.9 months was documented, with nine patients having unmethylated MGMT promoters and one methylated. Chemoradiation and TTF were completed by all patients without interruptions, and scalp dose constraints were met. Skin toxicity (grade 1 or 2) was observed in 80% of patients[29] and resolved with topical treatments. An mPFS of 6.9 months was achieved, and further randomized trials were recommended.[31] In clinical trials conducted by Bokstein and coworkers, ten patients were enrolled in a single-center trial between April and December 2017, with a median age of 60.2 years and a median KPS of 90.0. Tumor resection was performed in five patients, while the others had a biopsy. Skin toxicity (grades 1–2) related to TTF was observed in 80% of patients, with no increase in RT- or TMZ-related toxicity. Three patients experienced serious adverse events (unrelated to TTFs). The mPFS was 8.9 months and mOS was not reached. Further investigation of concurrent TTF/RT/TMZ treatment was recommended.[32]

2.4 Surgical treatment

Gross-total resection is currently the guiding principle of glioblastoma surgery, and the results seem promising despite the lack of randomized trials.[33] Regardless of the molecular composition of the tumor or the patient's age, maximal excision increases survival.[34] Stereotactic biopsy is the preferred technique for both molecular assessment and histological confirmation of the tumor when resection is not recommended. Prospective research evaluated the efficacy of 5-aminolevulinic acid combined with fluorescence-guided surgery in improving 6-month PFS (46 *vs.* 28.3%).[35] Gleolan® (5-aminolevulinic acid) was approved by the US FDA in 2017 as an imaging agent for patients indicated with grade III or IV glioma.[36] The routine use of diffusion-tensor fiber evaluation and functional MRI can lead to safer therapies and fewer postoperative sequelae. To ascertain the scope of the intervention, postoperative contrast-enhanced MRI must be carried out within 48 h of excision. The most drastic resection of the focus is conducted in the event of a recurrence, especially if the patient is young, has a good functional status (high Karnofsky performance score), or more than six months have passed since the intervention. Currently, there are no data pertaining to the surgical treatment of recurrent glioblastoma from ongoing randomized clinical trials.[37]

The present treatment for GBM-affected patients is mainly composed of maximum surgical resection of tumor, chemotherapy and radiation therapy. A pictorial summary of the timeline for USFDA-approved treatments with their survival rates is shown in Fig. 1. Treatments considered standard like TMZ sometimes do not work due to *O*6-methylguanine-DNA methyltransferase expression. Radiation therapy kills tumour cells by breaking double strands of DNA. A drawback of radiotherapy in brain tumors is secondary gliomas and the recurrence of tumors. Relapse is also possible after maximal surgi-

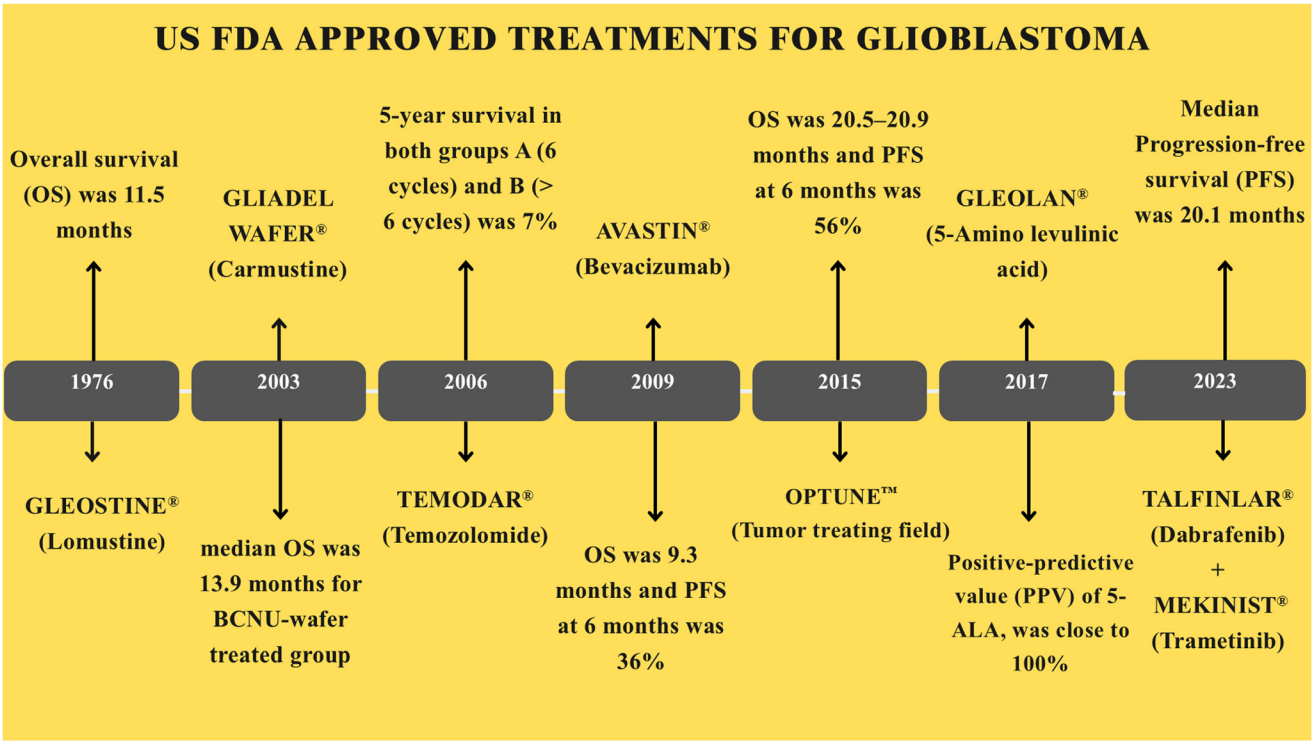

Fig. 1 Summary of timeline for treatments approved by the US FDA with survival rates for glioblastoma.[27,36,38–42]

cal resection of a tumor. Therefore, there is a need for new treatments that can address the limitations of current therapies. Nanotechnology-based nanocarriers and their surface modification could emerge as a substitute for current drug delivery strategies as desired results are obtained in various research projects. Additionally, they offer several benefits, such as prolonged blood circulation, better drug encapsulation, sustained and continuous drug release, and decreased dose frequency. Immunotherapeutic approaches can also target brain tumors and have proven fruitful in meeting recent treatment requirements. These approaches can tackle drug resistance and tumor heterogeneity related issues encountered during GBM treatment. Synergistic drug combinations or multi-drug therapy also help in GBM treatment with raised efficacy, and minimal toxicity.

3. Emerging nanotechnology-based cargos for drug delivery to GBM

3.1. Nanoparticles

Nanoparticles (NPs) are versatile carriers that are ultrafine particles (1–1000 nm) and they are emerging as an excellent drug delivery tool for targeted cancer therapy. Due to their unique benefits, which include an enhanced penetration and retention (EPR) effect, decreased toxicity, increased stability, and accurate targeting, nanoparticles have the potential to be used in the treatment of cancer. Nanoparticles encapsulate antitumor moieties and prevent destabilisation in a tumor microenvironment.[43]

3.1.1. Liposomes. The word liposomes is made up of two Greek words, "lipos" and "soma", meaning "fat" and "structure", respectively. Thus, a liposome refers to a structure constituted of fats with the possibility of encapsulation. These are spherical vesicular systems made using cholesterol, a phospholipid that can simulate lipidic bilayer membranes. These vesicular systems have enhanced biopharmaceutical properties, such as co-localization of therapeutics and enhanced kinetic profiling. Many researchers have formulated liposome-based targeting for glioma. Kim and coworkers formulated temozolomide (TMZ, a DNA alkylating agent) liposomes functionalized with CD133 monoclonal antibody and angiopep-2 for GSC (glioma stem cell) and blood–brain barrier (BBB) targeting. It was observed in preclinical human-GSC-induced nude BALB/c (U87-MG) mice that TMZ-functionalized liposomes gave survival rate of 49.2 days in comparison to TMZ alone of 23.3 days when administered an IV injection on every 3rd day continued for 15 days of treatment.[44] In another study, TMZ coloaded with JQ1 (a bromodomain inhibitor) in liposomes with surface decoration of transferrin was studied in two glioma-induced preclinical models: U87-MG- and GL261-induced C57/BL6 mouse models. Daily IV administration of functionalized coloaded liposomes enhanced the survival rate in comparison to a single drug. Furthermore, these novel liposomes have reduced systemic side effects compared with both drugs. Thus, these studies prove the effective delivery of liposomes in glioblastoma treatment.[45] Charest and coworkers separately formulated liposomal cisplatin and oxaliplatin and compared their anticancer potential with free oxaliplatin and cisplatin in an F98-glioma-induced preclinical mouse model. It was observed that intracarotid infusion of liposomal cisplatin and oxaliplatin enhanced the survival rate from 13 to 29 and 21 to 30 days, respectively, compared with free cisplatin and oxaliplatin.[46] In another study, cilengitide encapsulation was undertaken in magnetic liposomes intended for theranostic purposes under external magnetic stimuli. The survival rate of these modified liposomes was found to be >2 times higher: approximately 60 days compared to 25 days for free cilengitide.[47] Lakkadwala and coworkers developed a co-administration and co-targeting approach for enhanced brain delivery by dual anticancer moieties: DOX and erlotinib in dual-functionalized liposomes, *i.e.*, transferrin and penetratin (cell-penetrating moiety) peptide. In this study, 6 days of treatment were given with IV administration every 2 days in a U87-MG-induced mouse model. The survival rate of the liposomal preclinical model was 36 days in comparison to 25 days with free dual-drug administration.[48] Similarly, Serwer and coworkers developed a topotecan liposomal formulation and studied it in three preclinical glioma-induced models and compared the mean survival time with the free drug group. The liposomal formulation demonstrated a promising improvement in brain tumor survival.[49] In 2012, Verreault and coworkers studied mean survival with irinotecan-loaded liposomes in Rag2M-bearing glioma tumor mice in comparison to free irinotecan and demonstrated enhanced efficacy.[50] But in 2015, a similar group formulated liposomes co-loaded with irinotecan and TMZ and studied the survival in glioma-bearing mice model in comparison to free drugs. After IV administration, it was observed that the mean survival time was 222% higher compared to liposomes with free co-administration of both drugs and 280% higher than with irinotecan alone.[51] Similar studies were also carried out by Noble and coworkers with administration of irinotecan liposomes and comparison of mean survival rate with free irinotecan.[52] Later, Louis and coworkers studied the preclinical administration of irinotecan liposomes *via* the three routes of IV, intranasal (IN), and convection-enhanced delivery (CED) and compared the mean survival rate. The multiple IV-administered shots showed the same overall survival benefit when compared to single CED therapy. When nanoliposomal irinotecan was combined with nanoliposomal chemotherapy, it significantly enhanced the survival rate of mice with brainstem tumors.[53] Furthermore, this study laid down a strong concept of proof for preclinical studies in relation to clinical trial NCT03086616. A list of the advantages of various treatment strategies along with current treatment options for GBM is given in Table 2.

Lu and coworkers formulated dual-responsive, co-administered liposomes of irinotecan and cetuximab. Surface modification was done with iron and citric acid as thermo-magnetic-responsive liposomes. Preclinical survival studies were conducted in an U87-MG-induced mouse model *via* IV administration and compared with the free drug. The mean survival

Table 2 Advantages of various treatment strategies along with current treatment options for GBM

Current treatment	Nanotechnology-based cargos	Immunotherapeutic approaches	Multi-drug/combination treatment
✓ Surgical excision provides immediate removal of tumor	✓ Increased permeation across the BBB	✓ Circumvent immune evasion	✓ Multiple regimens could be prepared from novel drugs
✓ Chemotherapy with the oral administration of TMZ can cross the blood–brain barrier and aid in tumor treatment	✓ Reduced off-target effects	✓ Personalized vaccine therapy based on unique antigen profile	✓ Decreased side effects *via* lower doses
✓ TTF uses an alternative electronic field as non-invasive treatment in patients and offers prolonged survival	✓ Low dose frequency	✓ Localized targeting	✓ Increased patient overall survival
✓ SRS (stereotactic radiosurgery) and IMRT (intensity-modulated radiation therapy) allow precise targeting of cancerous cells without affecting the healthy tissues	✓ Ability to overcome drug resistance	✓ Ability to use in conjunction with other therapies	✓ Reduced drug resistance development
	✓ Enhanced EPR effect	✓ Sustained immune activity against tumor	✓ Ideal dosing methods
	✓ Non-invasive or minimally invasive delivery	✓ Cytokine and oncolytic virotherapy aids in immune system activation and modulation	✓ Targets redundant pathways of tumor cells
	✓ Uniform and sustained drug release	✓ Raised efficacy	✓ Attacks tumor cells along with angiogenesis and immune evasion like supportive processes
	✓ Can build theranostic platforms		
	✓ Personalized and tailored medicine		
	✓ Increase stability and solubility of drug substance		

was found to be 34 days for novel liposomes in comparison to 21 days in the free treatment group.[54] Ying and coworkers formulated PEGylated DOX-loaded liposomes with surface functionalization by a modified DA7R ligand with myristic acid (an effective ligand for neuropilin-1) and evaluated it in U87-MG-induced mice. IV administration of these modified liposomes gave an extended median survival time of 29 days in comparison to a low median survival time, *i.e.*, 22 days, with free DOX.[55] Similarly, Zhang and coworkers formulated surface-modified CB5005-PEGylated DOX liposomes. The *in vivo* efficacy of the liposomes was compared with free liposomes in U87-MG-bearing mice. The mean survival time with the liposomes was found to be 33.5 days in comparison to 27.5 days for the free drug.[56] Lundy and coworkers formulated a lipoDox (liposomal doxorubicin) surface coated with VEGF (vascular endothelial growth factor). They studied lipoDox, VEGF-decorated lipoDox, and multi-VEGF-decorated lipoDox rates of survival in tumor-bearing mice with results of 60, 67 and 79 days.[57] Fig. 2 shows a schematic illustration of nanotechnology-based carriers and their role in delivering therapeutics to cancerous tissues.

3.1.2 Polymeric nanoparticles. In recent years, polymeric nanoparticles (PNPs) have received a lot of attention because of characteristics related to their small size. Various types of polymer are used in the formulation of PNPs, such as polyethylene glycol (PEG) or polylactide-*co*-glycolide (PLGA) and they can be loaded with a range of bioactive compounds with applications in drug delivery. Wang and coworkers formulated TMZ-encapsulated albumin nanoparticles, and surface decoration was done with sinapic acid (a BBB-guiding moiety). These NPs demonstrated enhanced survival time of 35 days in BALB mice induced with C6 tumor cells when administered *via* IV in comparison to 25 days survival time in the free drug.[58] Similarly, Kumari and coworkers prepared lactoferrin-decorated TMZ-albumin NPs. After IV administration of these NPs into cancer-induced mice, >1.5 times survival time was observed in comparison to the free drug.[59] In another study, Zhang and coworkers formulated cisplatin NPs in polyaspartic acid with surface modification by PEG. PEGylated NPs, when administered using convection-enhanced delivery (CED), displayed a survival rate of more than 100 days in comparison to non-PEGylated NPs (40 days) and free drug (12 days).[56] Zhao and coworkers formulated cilengitide-encapsulated gelatin NPs coated with heparin-Poloxamer 188 grafted polymer. These NPs demonstrated >2.5 fold survival time in comparison to free drug in C6-induced Sprague–Dawley (SD) rats.[60] Tylawsky and coworkers formulated fucoidan-based nanoparticles targeting endothelial P-selectin to induce caveolin-1-dependent transcytosis. Therefore, the nanoparticle system reaches into the brain tumor microenvironment in a selective and active manner, the efficiency of which is increased by radiation treatment.[61]

3.1.3 Metallic nanoparticles. MNPs (metallic nanoparticles) have uses in the field of cancer immunotherapy. The higher density of MNPs enables them to enter cancerous cells very easily, which is a good strength for cancer vaccines, when

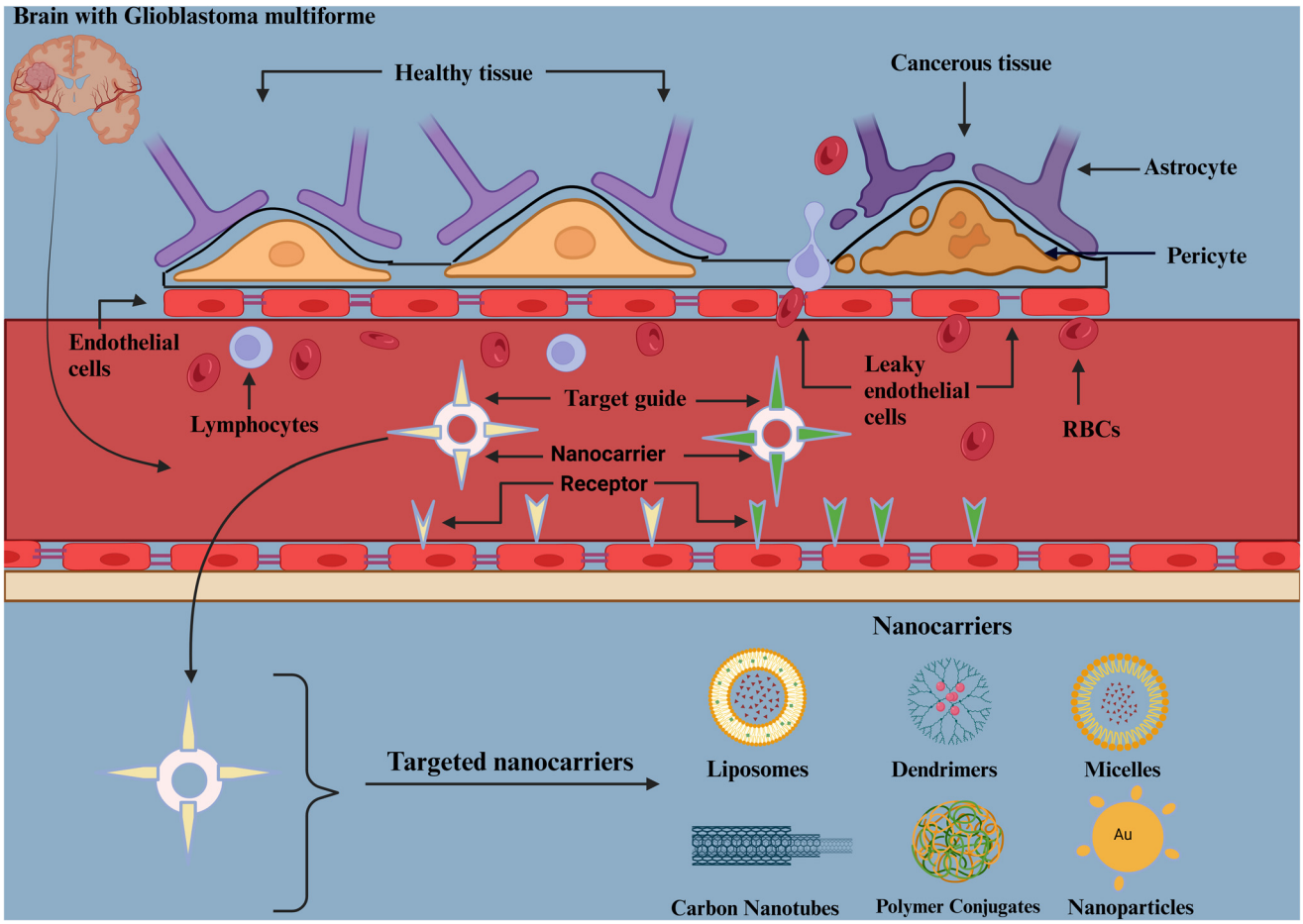

Fig. 2 Schematic illustration of nanotechnology-based carrier drug delivery as a potential therapeutic strategy for GBM. The endothelial cells, tight junctions, and basement membrane limit drug delivery to the tumor niche. Therefore, a nanocarrier conjugated with target guide molecules and loaded with chemotherapeutic agents can efficiently cross the BBB and deliver the therapeutics to the cancerous tissues. The composites of the nanocarrier can be liposomes, micelles, dendrimers, polymer conjugates, carbon nanotubes, metal, or polymeric nanoparticles.

compared to different NPs of same sizes.[62] In the latest research, dectin-1 and TACA (tumor-associated carbohydrate antigen) were delivered by use of gold-coated nanoparticles.[63] It is evident that the production of both priming of antigen recognising T cells and high titer antibodies by gold nanoparticles provide high anti-tumor immunity against dectin-1. MNPs also help in the stimulation of immunity by acting as adjuvant therapeutics. Although inhibition of tumor proliferation and anti-tumor qualities are exhibited by some bare MNPs, these MNPs are employed in immunotherapy in association with heat-based and optical-based therapeutic strategies due to their unique optical features. Thus, MNPs could be an excellent candidate in multi-therapy for GBM.[64] Iron oxide nanoparticles are among the growing therapeutic approaches used for management of GBM. Their specific advantages, such as good water solubility, biocompatibility, decreased toxicity, excellent catalytic behaviour and superparamagnetic properties, lead to them being a desirable option for applications in the field of biomedicals. Additionally, the interaction of the inherent promoting features and interaction of iron oxide nanoparticles with the immune system raise the capability of these nanoparticles for the treatment of GBM. For instance, Norouzi and coworkers formulated polyethylenimine (PEI)-polyethylene glycol (PEG)-iron oxide nanoparticles (IONPs) loaded with salinomycin for GBM chemotherapy. These IONPs demonstrated reduced cancer cell proliferation and viability in U251 GBM cell lines.[65] However, the real process of immune stimulation against the tumor is still not clear, but phagocytosis by nanoparticles and activation of proinflammatory cells to destroy tumor cells has been confirmed by the latest available proofs. For example, Korangth and coworkers demonstrated that T-cell entry into a tumor occurs through the administration of iron oxide nanoparticles. Additionally, Han and coworkers formulated nimotuzumab nanocapsules encapsulated inside methacrylamide decorated with choline. These demonstrated an enhanced survival rate of 1.2-fold in comparison to free MAb.[62,66] Peng and coworkers prepared gold nanoparticles conjugated with aptamer U2 (U2-AuNP)-targeting GBM therapy. U2-AuNP suppresses the growth of and attack by cancerous cells in U87-MG EGFRvIII cell lines *in vitro* and

enhances the survival time in a GBM-bearing mouse model. U2-AuNP can block the EGFR-related mechanism and prevent repair to DNA damage in GBM cells. These results highlight the encouraging potential of U2-AuNPs as a drug candidate for targeted therapy in GBM.[67]

3.2. Micelles

Amphiphilic molecules which are formed from a joint structure of hydrophilic and hydrophobic molecules are known as micelles. The structural moiety of the micelles is maintained by the interaction of the hydrophilic and hydrophobic molecules.[68] In 1980, Ringsdorf and his associated coworkers found the first polymeric micelles used for the treatment of cancer. Mostly the micelles are spherical, with a size of around 10–100 nm.[69] The most common merits of micelles include features such as preventing the modification of a drug during drug delivery and increased shelf life. The nominal diameter of polymeric micelles permits the drug release at the cancerous tumor location. Two methods are used for the preparation of micelles. Copolymers, which are soluble in water are produced by direct dissolution or film casting. However, if the copolymer employed is not readily soluble in water, two other strategies are the dialysis method or the oil-in-water method.[70] Polymeric micelles have wide applications in delivering therapeutics, such as proteins, siRNA, DNA, and chemotherapeutic medicines, to several malignancies. The flexible nature and excellent biocompatibility of micelles enable the incorporation of a variety of drug compounds and targeting approaches.[71] Die and coworkers formulated a redox-sensitive micellar system (HCA-A2) for improving glioblastoma treatment outcomes. The HCA-A2 system was aimed at co-delivering temozolomide (TMZ) and β-lapachone (β-Lapa) to target angiopep-2 (A2). Hyaluronic acid (HA) and arachidonic acid (CA) were used as the hydrophilic and hydrophobic agents in the HCA-A2 system. Non-targeting (HCA) and non-redox-sensitive (HDA-A2) versions were used as controls. HCA-TMZ-Lapa micelles released all their contents in 24 h *in vitro* and HCA-A2 micelles demonstrated better BBB permeation and enhanced cytotoxicity when consumed *via* clathrin-mediated endocytosis. *In vivo*, a dramatic decrease in tumor progression indicates the potential for treating GBM.[72] Zhang and coworkers incorporated anti-PD-L1 antibodies (aPD-L1) into redox-responsive micelles to increase the checkpoint blockade (ICB) effectiveness with paclitaxel (PTX)-induced immunogenic cell death (ICD). These micelles cross the BBTB by staying in the tumor microenvironment and maintain aPD-L1 bioactivity. The combination of aPD-L1 and PTX boosts ICB efficacy and suppresses primary and recurrent GBM. *In vivo* accumulation of cytotoxic T cells, and induction of long-lasting immune recognition was observed in a GBM-bearing mouse model. This type of approach suggests that chemo-immunotherapy can reprogram local immunity to enhance GBM treatment.[73]

3.3. Dendrimers

Dendrimers are nanosized, branched, symmetric, homogeneous and well-defined monodispersing structures with a diameter of around 2–10 nm. The word "dendrimer" is derived from the two Greek words "dendron" meaning "tree or branch" and "meros" meaning "part". There are three main elements of dendrimers: branch systems, classes of terminals and the central nucleus. If the number of repeating units of branches is increased, then they are proven to be effective in the progression of the globular system. The increased amount of control over their architecture leads them to be most promising candidates for drug delivery. Various types of dendrimer have been proposed since the 1980s, but polyamidoamine (PAMAM) dendrimers are the most commonly used. These have the advantages of being biocompatible, hydrophilic and non-immunogenic delivery systems. The core moiety of PAMAM is ethylene diamine, but several other hydrophilic molecules, such as diaminobutane, diaminododecane or diaminoexane, are more readily employed.[74,75]

The polypropylene imine (PPI) dendrimer delivery system was first discovered in 1938 by Buhleier and colleagues. PPI dendrimers depend on the diaminobutane moiety in the core, which can be generated by a double Michael addition reaction from the core of molecules like EDTA (ethylene diamine). The oligonucleotide can be compacted using peptide-based poly-L-lysine (PLL) dendrimers, which are used primarily as gene carriers. A biodegradable nature, water solubility, mobility, and high biocompatibility are some of their salient features. The amino acid lysine is responsible for the branching units and the centre of the structure of the peptide bond. Variation in the dendrimers is a remedy to the problem of fast immune system clearance of dendrimers. Zhu and coworkers suggested a method of combining α-tocopherol succinate (α-TOS) with the dendrimer, which could help in the elimination of tumor cells. They formulated dendrimer-entrapped gold nanoparticles (Au DENPs) Au-TOS-RGD DENPs or Au-TOS-FA DENPs, which are widely used for the computed tomography imaging of cancerous cells and targeted chemotherapy. Free α-TOS have an IC_{50} of 33.8 μmol L^{-1}, much higher than that for α-TOS in Au-TOS-RGD DENPs with a value of 18.2 μmol L^{-1} for U87-MG cell treatment. The significant difference in the IC_{50} value between Au-TOS-FA DENPs and Au-TOS-RGD DENPs may be due to particular target modifications. The tumor inhibition effect in *in vivo* antitumor efficacy tests of the Au-TOS-FA DENPs-tried group (5.23 ± 0.72 times tumor growth) exhibited greater inhibition power than for Au-TOS DENP (6.65 ± 1.00 times tumor growth), and it is somewhat higher than in free α-TOS (7.37 ± 0.65 times tumor growth) in the same α-TOS that shows the result of targeting effects.[76]

3.4. Carbon nanotubes

The most widely and frequently employed system of drug delivery from nanotechnology is carbon nanotubes. There are two types of CNTs: muti-walled (MWCNTs) and single-walled (SWCNTs). The strong optical absorption of CNTs in the near-infrared region provides an excellent medium for thermal imaging. It is very normal for CNTs to ingest nanoparticles with sizes ranging from 50 to 100 nm. SWCNTs in PEGylated form are located in a specific compartment of the cells and

MWCNTs have the capability of crossing through various barriers of the cellular compartment. CNTs are being studied as possible nanocarriers for protein distribution, genes and medication. Most investigations into CNTs are focused on their anti-cancer potential of drug delivery. Furthermore, this interest might be because of their adaptable needle-like shapes, which allow them to bind and absorb a variety of medicinal compounds into malignant cells. Ren and coworkers developed PEGylated oxidized multi-walled carbon nanotubes (O-MWNTs) modified with angiopep-2 (O-MWNTs-PEG-ANG) as a dual-targeting drug delivery system for GBM treatment. These O-MWNTs offers a large surface area for loading doxorubicin (DOX) and dispersing the drug efficiently in the brain. Generally, LRP is overexpressed on the BBB and glioma cells and is considered a target of angiopep-2. Compared to DOX alone, DOX-loaded O-MWNTs-PEG-ANG showed better antiglioma effects. When biological safety assessments were compared to DOX, they revealed minimal toxicity, reduced cardiac toxicity, and excellent biocompatibility. Overall, O-MWNTs-PEG-ANG is a promising delivery system for DOX in the treatment of glioblastoma.[77] Eldrich and coworkers undertook carbon-nanotube-mediated thermal therapy (CNMTT), which offers a novel approach, using near-infrared lasers to heat CNTs localized in tumors for thermal ablation. Phospholipid-poly(ethylene glycol)-coated MWCNTs enhance brain diffusion and maintain ablative temperature capabilities without inducing a heat shock response (HSR) in GBM cells, as HSR activation causes a reduction in CNMTT efficacy. Coated MWCNTs enable rapid, uniform tumor heating with near-infrared (NIR) exposure, achieving higher peak temperatures while minimizing damage to surrounding tissues.[78] Wang and coworkers proposed magnetic carbon nanotubes (mCNTs) for treating chemoresistant GBM through a mechanical approach using precision control over a magnetic field. GBM cells internalize mCNTs, and their mobilization *via* rotating magnetic fields induces cell death. Functionalizing mCNTs with anti-CD44 antibodies enhances tumor targeting, retention, and therapeutic efficacy. In mouse models with TMZ-resistant GBM, mCNT treatment effectively suppressed tumor growth without significant toxicity to major organs. This research highlights mCNT-based mechanical nanosurgery as a promising therapy for chemoresistant GBM.[79]

3.5. Quantum dots

These types of nanoparticles (NPs) are semiconductive in nature and made from the period II–VI and III–V group in the modern periodic table. Quantum dots (QDs) have variable diameters ranging from 2 to 10 nm, which is almost equivalent to Bohr's radius. As a result, the freedom of charged particles (holes and electrons) inside nanoscale dimensions is restricted, and this quantum restriction effect furnishes QDs with particular electrical and optical properties. In comparison to regular organic dyes, quantum dots offer some benefits in terms of fluorescence properties. Biological applications of QDs can be summarised as: (1) QDs offers a range of light excitation with symmetrical emission and narrow spectra. Unique colours with the same light of excitation are exhibited by multiple QDs; therefore, differently coloured QD specimens might be utilised to concurrently photograph and track different chemical targets. (2) The coefficients of molar extinction of QDs were in the scale of 0.5–5.0, equal to 10^6 M^{-1} cm^{-1}, which was around 10–50% greater than those of organic dyes. Therefore, QDs can absorbs 10 to 50 times more photons than organic colours at the same stimulation index leading to a rapid increase in the brightness of the sample; individually, QDs are 10–20 times lighter than organic colours. (3) The peak emission wavelength in QDs can be controlled by altering the composition and particle size or by altering the surface coating. Optical carriers and nanosamples are biological applications that use the distinctive features of QDs. QD nanocarriers allow the dispersion, absorption, adsorption, and incorporation of drug products within them. Chemical and physical qualities (such as particle surface hydrophobicity, dissolution rate, hydrophilicity, saturation solubility and crystal form), physical reactions and biological aspects can be changed by the involvement of carriers and thereby the absorption, metabolism, rate of excretion and distribution of a drug can be varied. Finally, the drug therapeutic index is raised, side effects are reduced, and the efficacy of a drug is increased by these nanocarriers for GBM treatment. Additionally, drug nanocarriers can effectively increase the absorption of small-molecule drugs. Accordingly, investigative reports on the transportation of macromolecular drugs have confirmed these promising results.[80,81]

Dash and coworkers were successful in developing graphene oxide QDs conjugated with photosensitizing agent IR-820 for the photodynamic treatment (PDT) of GBM. The simultaneous incorporation of an *in situ* hypoxia-relieving agent (MnO_2) and a heat shock protein inhibitor (HSP70) leads to increased efficacy of localized PDT and controls the drawbacks of this therapy *in vitro*.[82] Seabra and her coworkers targeted tumor cells using CdTe QDs which are conjugated to anti-glial fibrillary acidic protein (anti-GFAP) *in vivo*. The optimized QDs were used for the imaging of GBM cells in mouse cell parenchyma using eosin and hematoxylin staining dyes.[83] In another study, Perini and coworkers formulated graphene QDs that are carboxylated to enhance drug membrane permeability and to increase the effect of chemotherapy by decreasing tumor proliferation and viability.[84]

3.6. Polymer conjugates

To improve the effectiveness of the drug, TMZ was combined with lipid–polymer hybrid nanoparticles along with siRNA (small interfering RNA) to oppose the action of tumor growth factor-β (TNF-β) to check the synergistic effects of GBM. Angiopep-2-induced nanoparticles were utilised for the purpose of drug targeting. The lipid–polymer hybrid carrier increased the survival rate to a significant time of 36 days in an intracranial GBM-bearing mouse model compared to that of TMZ + siTMZ-β arms or TMZ. Poly[aniline-*co*-*N*-(1-one-butyric acid)] aniline coated magnetic nanoparticles were loaded with carmustine and administered in C6-bearing

Sprague–Dawley rats at different dose levels. Carmustine-containing magnetic nanoparticles enhance life expectancy compared to the free drug. Monoclonal antibodies against EGFR, which is elevated in GBM, serve as crucial components for brain tumor targeting in nanomedicines. This is especially significant for nanomedicines bypassing the blood–brain barrier, using alternative delivery systems like CED or magnetic targeting.[85] In early investigations, mice implanted with highly tumorigenic GBM (U87-MG EGFRvIII) received CED of 5 μg of cetuximab encapsulated in iron oxide nanoparticles. For the median survival time for CED of cetuximab-decorated iron oxide nanoparticles (IONPs) compared to free cetuximab, a small increase of 19 days was observed. This work set the stage for a subsequent study that showed the enhanced therapeutic efficacy of cetuximab-loaded IONPs *via* CED in three separate orthotopic mouse experimental models of human GBM (two models used U87-MG wildtype-EGFR and LN229-wildtype-EGFR produced from human GBM cell lines, and one model produced from patient-derived GSC-containing neurospheres).[86,87] In all three models, the athymic nude mice orthotopically transplanted with GBM xenografts had a significantly higher median survival rate (164 against 147 days, 42 *versus* 33 days, and 72 *versus* 30 days, respectively) using cetuximab-loaded nanoparticles compared to free cetuximab.[87] Albumin nanoparticles enriched with mannose (Man) and peptide-12 (T12) were developed for co-administration of a disulfiram/copper combination and regorafenib.[88] Sun and coworkers proposed a focused ultrasound (FUS)-assisted delivery of flexible conjugates of HA loaded with camptothecin (CPT) and DOX for the treatment of GBM. *In vitro* assay evaluation of CPT-DOX-HA conjugates demonstrated synergistic activity in a proportion-dependent manner. FUS was utilized to increase the brain permeation of CPT-DOX-HA polymer conjugates in a mouse model *in vivo.* The CPT-DOX-HA polymer conjugates produced superior efficacy with the greatest mobility when the treatment was given to mice with GBM *in vivo.*[89] Researchers aim to improve anti-glioma efficacy by crossing the blood–brain barrier and the blood–brain tumor barrier incorporating the TfR-binding D-T7 peptide. Mice with orthotopic C6 gliomas were given intraperitoneal (i.v.) doses of paclitaxel (1.7 mg kg^{-1}) and cediranib (3.6 mg kg^{-1}) to evaluate this nanosystem. Animals treated with targeted nanoparticles showed a considerably longer median survival (53 days) compared to mice administered with free drugs at the same dose (19 days).[90] These outcomes underscore the vital role of nanocarriers in enhancing the efficacy of pharmaceuticals for treating GBM. While bevacizumab is one of the few FDA-approved treatments for recurrent GBM, there is still much work to be done in developing its encapsulation into nanocarriers for *in vivo* testing in orthotopic animal models of the disease. Sousa and coworkers were successful encapsulating bevacizumab into PLGA-coated nanoparticles; however, information on median survival span was absent from their groundbreaking *in vivo* study conducted in orthotopic U87-MG-bearing mice. Rather, they assessed the levels of VEGF tissue.[91] Ferber and coworkers developed a conjugated nanocarrier system where the PTX and TMZ were conjugated to dendritic polyglycerol sulfate (dPGS) for co-targeting the tumor endothelium and P-selectin-expressing GBM cells, leading to a significant therapeutic outcome. This combination demonstrated significant synergistic anticancer activity on intracranial human and murine GBM through the induction of Fas and Fas-L, with no side effects compared to free PTX or TMZ.[92]

4. Surface-modified nanocarriers for drug targeting to GBM

The surface modification or functionalization of nanocarriers aids in targeted drug delivery to GBM by maintaining a therapeutic concentration at intended locations and tumor-specific targeting. Surface functionalization can be carried out using certain targeting ligands, such as monoclonal antibodies, peptides (*e.g.*, arginine-glycine-aspartic (RGD) peptide) or small molecules that bind to receptors upregulated on GBM cells. Surface modification helps in the enhanced biodistribution and pharmacokinetics of drugs loaded in nanocarriers.

4.1. Monoclonal antibodies (MAbs)

MAbs are immunoglobulins that specifically target the surfaces of tumor cells and recognize cell surface proteins and/or receptors as antigens. MAbs are categorised into radioimmunoconjugates (to radioisotopes), unconjugated and conjugated (to cytotoxic agents or protein toxins). Other types of MAbs can also be obtained from murine regions, human regions, and chimeric (a hybrid made up of human and murine) regions. Panitumumab and nimotuzumab are examples of humanised MAbs, while MAb 806 and cetuximab are anti-EGFR chimeric MAbs. Cetuximab, an unconjugated chimeric murine–human IgG1 MAb, binds to the extracellular domain of EGFR and blocks EGF from binding to its receptor. It binds to EGFR (including EGFRvIII) more strongly than TGF-α or EGF. It also produces apoptosis, inhibits metastasis and cell growth, induces cell-mediated cytotoxicity in the presence of antibodies, and reduces VEGF synthesis. When administered alone, cetuximab demonstrated a PFS-6 in 9.2% of patients with recurrent high-grade glioma with an average time to progression (TTP) of 2 months, and a median OS of 5 months.[93] Despite stratifying patients based on EGFR amplification, no association between response and EGFR amplification was discovered. A PFS-6 of 30%, an average OS of 7.2 months and a radiological recovery of 34% were observed in patients with recurrent GBM with a combined dose of irinotecan, cetuximab and bevacizumab. The kind of EGFR mutation (EGFRvIV or EGFRvIII) and EGFR amplification may influence the prognosis of GBM patients administered with cetuximab. Patients with expression of EGFvIII (p = 0.08) have poorer OS than patients with no EGFRvIII expression or EGFR amplification. No studies to date have shown cetuximab as a cure in newly found high-grade gliomas. MAb 806, which can suppress the development of U87-MG, appears to improve the effectiveness of ionising radiation in glioma xenografts with the EGFRvIII

mutation. A humanised MAb nimotuzumab that selectively binds to high-EGFR-density tissues (such as cancers) while protecting normal tissue, was evaluated in children with recurrent and high-grade GBM. An average survival rate of 31.06 months and desired safety appeared with the combined treatment of radiotherapy and nimotuzumab compared to the 21.07 months of the control group. Clinical stage II studies for the combination of TMZ/RT and nimotuzumab held in China showed better tolerability and safety without increasing the survival rate in comparison to the normal treatment. Human MAbs panitumumab (ABX-ECF) in combination with irinotecan selected for HER-1 was used for the treatment for GBM, but data have still not been obtained.[94]

4.2. Folic acid

There are different types of small molecules with various properties and structures, which are cheap to manufacture. One of the most abundant small molecules used for drug delivery is folic acid or folate. Folic acid is a B6 vitamin that is soluble in water, specifically during the growth of an embryo. This vitamin is also important for cell division and cell growth, and differentiation in men. Riboflavin plays a major role as an important vitamin in the metabolism of cells. In metabolically active cells, riboflavin carrier protein (RCP) is significantly increased. The role of two small molecules, endogenous RCP ligand and FMN (flavin mononucleotide), is ligand targeting in endothelial cells or metabolically active cancer.[95] Glioblastoma therapies are limited by rapid metabolism, low bioavailability, and poor BBB penetration. Ramalho and coworkers developed folic acid (FA)-modified poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles (NPs) for improved gallic acid (GA) delivery to GBM. The optimized NPs enabled drug internalization in BBB and GBM cells. Evaluation of *in vitro* release showed slow and sustained release for 40 days. Targeted accumulation and increased GA antigrowth performance through the generation of reactive oxygen species (ROS) were shown in *in vitro* studies using U215 GBM cell lines.[96] Minaei and coworkers formulated FA-functionalized magnetite NPs coated with three polymers (poly(ethylene glycol)–poly(butylene adipate)–poly(ethylene glycol)) loaded with TMZ (TMZ-PEG-PBA-PEG-FA NPs) for targeted chemotherapy for GBM. A decrease in GBM cell proliferation was observed in TMZ-P xenograft EG-PBA-PEG-FA NPs in C6 cancer lines *via* FA-receptor regulated endocytosis for 24 hours and 48 hours of treatment.[97]

4.3. Functional peptides

Functional peptides are appealing targeting compounds due to their minimal immunogenicity, small size and low cost of manufacturing. Functional protein targeting receptors could be identified using a variety of approaches. They are usually derived from the binding areas of the desired peptide. A cyclic peptide with integrin-binding specificity is in clinical stage II for the treatment of NSCLC (non-small cell lung cancer) and pancreatic cancer.[98]

A peptide sequence with the ability to target activities is called angiopep-2, which is the complementary ligand to the LRP (lipoprotein receptor-related protein) of low-density lipoproteins. Pituitary tumors or GBM are typically incurable, as both are upregulated with LRP. When angiopep-2 and LRP are employed together, they will cross the BBB when used in an optimal concentration for the treatment of glioma. Xin and coworkers were instrumental in integrating poly(ethylene glycol)-*co*-poly(-caprolactone) (PEG-PCL) nanoparticles with angiopep-2, which are thought to be engaged in the simultaneous suppression of gliomas. The efficacy of *in vivo* targeting was evaluated by comparing the enhanced cellular absorption of ang-target U87-MG cells to blank controls. Mice with an intracranial U87-MG model received fluorescent nanoparticles (both blank and combined with angiopep-2) *via* the tail vein. This change in concentration suggests that angiopep-2-incorporated PEG PCL nanoparticles can penetrate through the BBB by active targeting and concentrate in gliomas.[44]

The BBB acts as a major obstacle in the delivery of bioactives/drugs to the CNS. Ligand-directed delivery is as an excellent solution to this obstacle due to specific receptor–ligand interactions. Various developments have been made in targeting different receptors and proteins expressed at the BBB, such as low-density lipoproteins (LDLs), insulin, connexins and apolipoprotein E (APOE) receptors. APOE is a widely used apolipoprotein as it interacts with LDL receptors in the LDL receptor family, which are known for their highest expression at the BBB. Nanocarriers should be designed to mimic or bind APOE, which could facilitate receptor-mediated transcytosis (RMT) across the BBB.[99] Jiang and coworkers reported chimeric polymersomes conjugated with APOE (APOE-CP) for binding to the LDL receptor as a targeted protein therapy for GBM. APOE-CP demonstrated efficient BBB crossing as well as accumulation and permeation in an *in vivo* mouse model.[100] In another study, Wei and coworkers developed APOE-functionalized polymersomes encapsulating granzyme B (GrB), which could penetrate BBB-mimicking endothelial cell monolayer *in vitro*. APOE-functionalized polymersomes were further taken up by LCPN cells of a murine model, causing strong immunogenic cell death (ICD). The APOE-functionalized systemic nanocarrier based delivery of GrB and immunoadjuvants like CpG oligonucleotide (CpG) acts as a potent immunotherapy for malignant glioma.[101] Re and coworkers investigated the cellular uptake of nanoliposomes covalently coupled with a monomer or tandem dimer of APOE-derived peptides (residues 141–150), at different densities. The penetration of a tritiated curcumin derivative was enhanced after its entrapment into APOE-nanoliposomes, specifically compared to those conjugated with the dimer. Therefore, these NLs were found suitable for implementing further approaches for drug brain targeting.[102]

4.4. Lectins

Lectins, which are highly specialised proteins found in many plants, animals, and microbes that bind to carbohydrates.

Plant lectins are known to fight off possible infections, whereas animal lectins are known to help in cell connection. Although all lectins have variable degrees of interaction with the immune system and control both regular and harmful physiological activities. A number of approaches can be used to introduce a gene-expressing lectin into cancerous cells. A viral vector that carries the gene coding for a particular lectin is the technique most often employed in laboratories. A non-viral method known as transfection and another called gel blot hybridization are utilized to administer lectin plasmids into cells to facilitate lectin synthesis. Apoptosis may be induced by lectins in a variety of ways, but some are more successful than others in certain cell lines. Caspases or other molecular cascade proteins can be synthesised by stimulating their synthesis. Certain genes associated with apoptotic suppression or induction may be downregulated or upregulated because of these mechanisms. A number of miRNAs inhibit ribosomal inactivating proteins (RIPs) and are downregulated in response to lectin activity, which permits RIPs to function properly while preventing the proliferation of tumors. Table 3 shows some lectins along with their mechanism of action with a role in GBM treatment.[103,104] Song and coworkers isolated extracellular vesicles from human glioma cells and functionalized them with annexins A2 (AnxA2) for cellular uptake through heparan sulfate (HS). The study depicts that AnxA2 and HS interactions increases the angiogenesis controlled by extracellular vesicles. These interactions are helpful in increasing the prediction of GBM in patients.[105] Schotterl and coworkers evaluated the synergistic anticancer activity of VE ISCADOR Qu, recombinant mistletoe lectin 1 (ML-1) (Aviscumine), and native ML-1 in combination with a temozolomide-(TMZ)-based radio-chemotherapy. This combination induced cancer cell death and prolonged the survival of mice with GBM *in vivo.*[106] Sina and coworkers tested cytotoxicity, inflammation, and apoptotic effects of different doses of concanavalin A (Con A) on C6 glioma cell lines. Con A stimulates catalytic independent activation of cyclooxygenase (COX-2) by promoting membrane type 1 matrix metalloproteinases 1 (MT1-MMP) *via* IκB Kinase gamma (IKKγ)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) dependent pathway and is essential for therapy resistant phenotype of tumor cells.[107]

4.5. Transferrin

Transferrin (Tf) is a glycoprotein which has a specific function in the metabolism of iron and is important in the delivery of ferric ions (Fe^{3+}). A ferric ion binds to the Tf receptor and produces Fe^{2+}, which is a ferrous ion. Toxic iron present in the blood and brain is also removed by Tf. Tf belongs to the transferrin family, which involves ovo-, melano-, and serum-Tf. Transferrin receptors are regulated by several sites, such as various types of cancerous cells, brain endothelial cells and red blood cells (RBCs). Overexpression of Tf receptors occurs on tumor cells and endothelial cells of brain capillaries, which makes this receptor system provides an excellent source for targeted therapy. The nucleotide ligands are attached to the more selective targets; thus the moieties can bind to one- and three-dimensional conformations, and are known as aptamers.[112,113] Ramalho and coworkers prepared Tf-functionalized PLGA NPs loaded with asiatic acid using a single emulsion technique. The NPs demonstrated sustained release of asiatic acid for 20 days and exhibited excellent entrapment efficiency. *In vitro* evaluation showed that surface functionalization of NPs with Tf was successful in increasing cellular uptake in cancer cells and reducing their toxicity in normal cells.[114] Gabold and his coworkers developed chitosan-coated NPs coated with Tf for nose-to-brain delivery of proteins. These NPs were employed to assess the transport of a model protein *via* the nasal epithelium barrier. The benefits of a specific targeting ligand were observed by increased cellular uptake and rapid passage through epithelial layer in U87-MG cell lines *in vitro.*[115]

Table 3 Lectins with their mechanism of action showing potential in GBM treatment

Lectins	Mechanism of action	Example
Annexins	p53 apoptotic pathway, Ras-Raf-MAPK pathway, NF-κB signal transduction pathway	Combining AnxA2 on glioma cells with HS on endothelial cells may effectively improve the prognosis evaluation of GBM patients[105]
Mistletoe lectin	Interleukin mRNA activation, Wnt signaling, NK-mediated cell lysis, miR-135a & b cell lysis	Mistletoe in synergy with radio-chemotherapy demonstrated improved survival rate *in vitro* and *in vivo* in GBM-bearing mice[106]
Concanavalin A/ConA (lectin)	Caspase activation, mitochondrial apoptotic process	ConA or direct overexpression of a recombinant MT1-MMP resulted in the induction of COX-2 expression leading to direct cell death induction in brain cancer[107]
Polygonatum odoratum lectin (POL)	Fas-mediating apoptotic pathway, Akt-mTOR pathway, tumor necrosis factor (NFα) enhancement	POL showed potent anti-cancer properties *in vivo*[108]
Sialic acid attached to *Haliotis discus* lectin (HddSBL)	Negative regulation of Bcl-2 enzyme	HddSBL reduced adverse effects of oncolytic vaccinia virus glioblastoma mouse model *in vivo*[109]
C-type lectins	TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), Le glycan recognition, perforin granzyme pathway and FAS ligand binding	C-type lectin domain family 5, member A (CLEC5A, MDL-1) stimulates brain glioblastoma tumorigenesis by controlling PI3K/Akt signalling *in vivo*[110]
Galectins	Ca^{2+}-calpaincaspase-1 pathway, specific integrin binding and T-cell binding	Glycosylation of PAMAM dendrimers enhanced tumor macrophage targeting and specificity in GBM[111]

4.6. Glutamic acid

L-Glutamine synthetase converts L-glutamic acid to L-glutamine. By supplying 3- and 9-nitrogen groups of purine bases, the 2-amino group of guanine, the 3-nitrogen group, and amino group of cytosine, L-glutamine biosynthesized purines and pyrimidines, which are the bases of DNA and RNA. Glutamic acid is employed for conjugation because it improves the efficiency of anticancer drugs while lowering their toxicity to healthy and normal cells. Polyglutamic acid is biodegradable, palatable, and harmless to humans.[116] In the case of IDH (isocitrate dehydrogenase)-mutant GBM, there are metabolic changes in glutamate and αKG, which play a role in lipid and glioma energy production. Therefore, a sound knowledge of these pathways helps in the development of good drug candidates.[117]

4.7. Growth factors

Alternative targets in GBM include abnormal transduction pathways that regulate angiogenesis, differentiation, cell proliferation, and apoptosis. Receptor tyrosine kinases (RTK) play a vital role in the majority of the signalling mechanism disrupted in GBM.

4.7.1 Inhibitors of EGFR (epidermal growth factor receptor). EGFR belongs to a class of the RTK family, which regulates the process of the tumor growth factor pathway. Different preclinical studies are being conducted to unravel EGFR inhibitors. Monoclonal antibodies and EGFR tyrosine kinase inhibitors are used as anti-EGFR agents. The catalytic performance of EGFR is selectively inhibited by small-molecule EGFR RTK inhibitors. This category includes the drugs Afatinib, gefitinib, and erlotinib. However, the survival of GBM patients has not greatly increased with any of these medications. While many small-molecule RTK inhibitors inhibit a wider range of kinases, they often have a greater antagonistic effect on a specific kind of kinase. Lapatinib and vandetanib are multitargeting tyrosine kinase antagonists that have a strong EGFR inhibitory impact. However, combining lapatinib with TMZ and employing vandetanib as monotherapy in the case of recurrent GBM produced only 6.3 and 5.9 months of overall survival, respectively. Vandetanib added to standard chemoradiotherapy did not significantly increase prognosis compared to the Stupp regimen (14.6 months) in stage II research involving newly diagnosed GBM patients.[118,119] Liu and coworkers studied the anti-tumor ability of AZD9291, a third-generation irreversible EGFR inhibitor, in a preclinical GBM model. AZD9291 exhibited dose-dependent growth inhibition against six GBM cell lines and was over 10 times more effective than first-generation EGFR inhibitors in reducing GBM cell proliferation. It induced cell cycle arrest, inhibited colony formation, and reduced the migration and invasion of GBM cells. In an orthotopic GBM model, AZD9291 significantly inhibited tumor growth and extended survival. Unlike erlotinib, AZD9291 consistently and effectively inhibited EGFR/ERK signaling. AZD9291 demonstrated strong preclinical efficacy in GBM both *in vitro* and *in vivo*.[120]

4.7.2. VEGFR inhibitors. Tumor angiogenesis relies primarily on the VEGFR pathway. Tumor cells release VEGF, which attaches to VEGF receptors to stimulate cell invasion, migration, and division. VEGFR inhibitors halt metastasis by blocking both angiogenesis and lymph angiogenesis, resulting in tumor regression. Monoclonal antibodies directed against VEGFR and small-molecule VEGF RTK inhibitors, such as sorafenib, vatalanib, cediranib, and regorafenib, are examples of anti-VEGFR medicines. In clinical trials, no small-molecule VEGF RTK inhibitor has demonstrated encouraging results comparable to EGFR antagonists. In a stage III clinical trial for recurrent GBM, comparing cediranib alone, cediranib with lomustine, and lomustine alone, the median OS were 8, 9.4, and 9.8 months, respectively. Adverse effects like nephrotic syndrome, arterial thromboembolic events, and hypertension raised concerns. Bevacizumab, an VEGFR monoclonal antibody, is FDA-approved for recurrent GBM. Debate surrounds the significance of side effects in newly diagnosed GBM, such as nephrotic syndrome hypertension, and arterial thromboembolic events.[121]

To improve GBM treatment, researchers are exploring the incorporation of VEGFR inhibitors into drug delivery systems. Albumin nanoparticles, modified with peptide-12 (T12) and mannose (Man), were developed to co-deliver a disulfiram/copper combination and regorafenib.[122] Peptide-12 facilitates blood–brain barrier penetration and uptake by glioma cells by binding to the transferrin receptor (TfR), while the Man ligand targets the Man receptor on tumor-associated macrophages. To assess the *in vivo* anti-glioma effectiveness of a disulfiram/copper combination and regorafenib, 1.5 mg kg^{-1} of each drug was given to a U87-MG-bearing nude mouse model. Compared to mice receiving free drugs at equivalent doses (survival time unspecified) or those given nanoparticles functionalized solely with Man or T12 (with survival times of 32 and 28 days, respectively), the group treated with drug-containing nanoparticles functionalized with both T12 and Man exhibited the longest survival time (42 days). A study investigated the effectiveness of cediranib and paclitaxel-loaded D-T7 peptide-modified PEGylated bilirubin nanoparticles in the treatment of gliomas. By incorporating the TfR-binding D-T7 peptide, researchers aimed to enhance anti-glioma effectiveness by crossing the BBB/BBTB. In mice with orthotopic C6 gliomas, this nanosystem was assessed intraperitoneally at dosages of 1.7 mg kg^{-1} paclitaxel and 3.6 mg kg^{-1} cediranib. Compared to mice treated with free drug at the same dose (19 days), animals treated with targeted nanoparticles had a much longer median survival period (53 days). These findings demonstrate once more how crucial nanocarriers are to enhancing the efficacy of a drug substance in the management of GBM.[122] Although bevacizumab, an FDA-approved drug for recurrent GBM, is being slowly incorporated into nanocarriers for *in vivo* testing in orthotopic animal models, Sousa and coworkers loaded it into PLGA nanoparticles. However, information on median survival lengths was absent from their latest *in vivo* evaluation in U87-MG-bearing mice. VEGF measurement and tissue histology investigations were carried out instead.[121,123]

5. Immunotherapy interventions as newer paradigms in GBM treatment

Immunotherapy uses the body's immune system to fight cancerous cells. Conventional treatment options for GBM, such as radiation, chemotherapy and surgery, find it difficult to evade the present challenges in drug delivery to cancerous cells, and issues like chance of recurrence, rapid progression, *etc*. can also be addressed with immunotherapy. Various immunotherapeutic approaches, such as CAR T and NK therapy, dendritic cell vaccines, oncolytic virotherapy and immune checkpoint inhibitors, have evolved as GBM treatments in the last decade. All these approaches act by promoting, increasing or blocking the immune function to target or eradicate cancerous cells. Ongoing immunotherapy-based clinical trials could be a potential treatment option for GBM in future, but it also faces substantial challenges. Table 4 shows recent ongoing and completed clinical trials for different types of immunotherapeutic intervention.

5.1. Dendritic cell vaccines

Dendritic cells (DC) capture antigens in tissues, migrate to lymph nodes, and present these antigens to T cells, activating cytotoxic T lymphocytes (CTLs) and helper T cells (TH). Their mode of action is shown in Fig. 3(A). DC vaccination (DCV) involves injecting tumor-associated antigen (TAA)-loaded DCs into patients to induce a T-cell response against tumors, aiming for tumor cell destruction and prevention of recurrence through immunological memory.[124] Dhodapkar and coworkers demonstrated the efficacy of mature dendritic cells (DCs) as adjuvants in humans, expanding CD4+ helper, CD8+ effector, and memory T-cell immunity. Rapid responses within a week, lasting over 90 days, were observed after a single DC injection, contrasting with subcutaneous antigen injection without DCs. Notably, endotoxin-depleted antigens alone failed to elicit T-cell responses, highlighting the role of DCs in priming and boosting CD4+ T-cell immunity. This finding underscores the safety and tolerance of DC injections in humans, crucial for protective immu-

Table 4 Recent ongoing, and completed clinical trials for different types of immunotherapeutic interventions

NCT ID	Treatment (alone/combination)	Clinical phase/status	Sponsor/company	Target	Indication
Dendritic cells vaccine					
NCT04201873	Autologous tumor lysate pulsed dendritic cells (ATL-DCs)	Phase 1/ ongoing	Jonsson Comprehensive Cancer Center	Autologous tumor antigens	Recurrent GBM
Oncolytic viral therapies					
NCT04479241	Lerapolturev (PVSRIPO) + pembrolizumab	Phase 2/ ongoing	Istari Oncology	Poliovirus targeting tumor cells	Recurrent GBM
NCT03973879	Lerapolturev (PVSRIPO)	Phase 2/ ongoing	Istari Oncology	Poliovirus targeting tumor cells	Recurrent GBM
NCT03576612	AdV tk + nivolumab + RT + TMZ (MGMT unmethylated *vs.* MGMT methylated)	Phase 1/2/ ongoing	Sidney Kimmel Comprehensive Cancer Center	Adenovirus delivering HSV-TK	Newly diagnosed GBM
NCT04006119	Ad-RTS-hIL12 + cemiplimab	Phase 2/ ongoing	Alaunos Therapeutics	Adenovirus targeting tumor cells	Recurrent or progressive GBM
Adoptive T cell therapies					
NCT04943913	Tumor infiltrating lymphocyte (TIL)	Early phase 1/ ongoing	Shanghai Juncell Therapeutics	Tumor cell	Malignant glioma
NCT04003649	IL-13Rα2-CAR T cells + nivolumab + ipilimumab (I), IL-13Rα2-CAR T cells + nivolumab (II), IL-13Rα2-CAR T cells (III)	Phase 1/ ongoing	City of Hope Medical Center	IL-13Rα2	Recurrent GBM
Immune checkpoint inhibitors					
NCT04396860	RT + TMZ *vs.* RT + nivolumab + ipilimumab	Phase 2/3/ ongoing	National Cancer Institute	PD-1, CTLA-4	Newly diagnosed GBM, MGMT unmethylated
NCT02658981	BMS-986016 (A1), urelumab (A2), BMS-986016 + nivolumab (B1), urelumab + nivolumab (B2)	Phase 1/ completed (2023)	Sidney Kimmel Comprehensive Cancer Center	LAG-3, CD137, PD-1	Recurrent GBM
NCT04656535	AB154 + AB122 (safety A), AB154 (B1), AB122 (B2), AB154 + AB122 (B3), placebo (B4)	Early phase 1/ ongoing	Yale University	TIGIT, PD-1	Recurrent GBM
NCT03493932	Nivolumab + BMS-986016	Phase 1/ completed (2023)	National Institute of Neurological Disorders and Stroke (NINDS)	PD-1, LAG-3	Recurrent GBM
NCT04047706	MS 986205 + nivolumab + RT + TMZ *vs.* BMS-986205 + nivolumab + RT	Phase 1/ ongoing	Northwestern University	IDO1, PD-1	Newly diagnosed GBM
NCT02052648	Indoximod + TMZ (I), indoximod + TMZ + bevacizumab (II), indoximod + TMZ + RT (III)	Phase 1/2/ completed (2020)	NewLink Genetics Corporation/Lumos Pharma	IDO1	Recurrent GBM

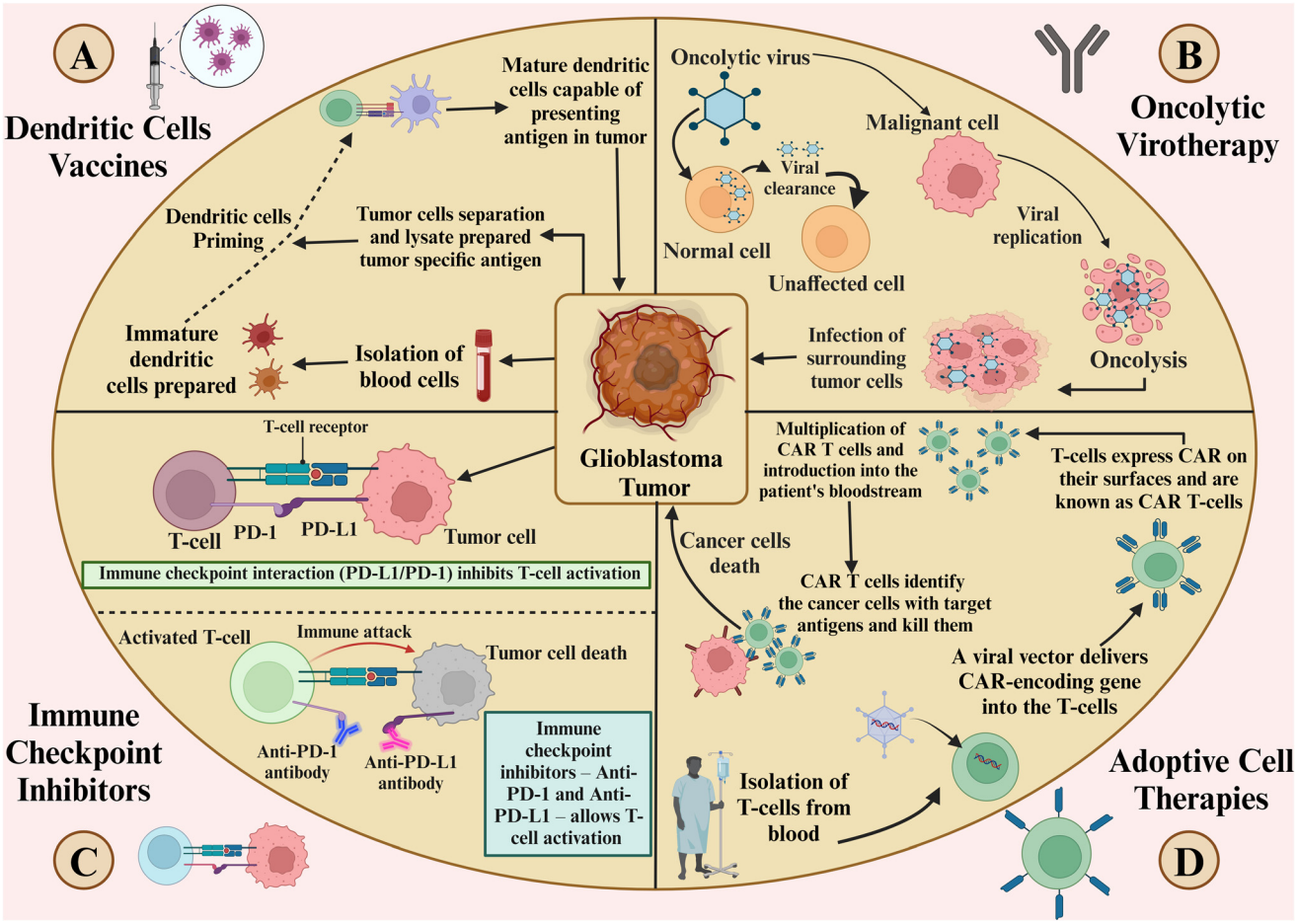

Fig. 3 A mechanistic illustration of immunotherapeutic approaches for GBM treatment: (A) dendritic cell vaccines; (B) oncolytic virotherapy; (C) immune checkpoint inhibitors; (D) adoptive cell therapies.

nity against viruses and tumors. Unlike previous methods requiring multiple injections, DCs enable immediate, robust T-cell responses without prolonged culture or stimulation.[125] In a clinical study, Zhou and his colleagues delivered DCV in combination with other immunotherapeutic agents in a patient with GBM. The combination with DCV includes aPDL-1, cyclophosphamide as a chemotherapeutic agent and chemoradiation therapy. The patient remained free from disease for almost 49 months, which showed that DCV is safe in combination immunotherapy and feasible for long-term treatment.[126] Yajima and coworkers developed "personalized peptide vaccines" to treat GBM by active immunization and conducted a phase 1 study to assess the safety and efficacy of the vaccines. *In vivo*, vaccination protocols were well tolerated, with most patients experiencing mild redness and swelling at injection sites. More than six vaccinations were done among 21 patients; 14 showed cellular and 11 humoral responses to at least one peptide. Significant peptide-specific IgG levels were found in the tumor cavity or spinal fluid of patients with favourable outcomes.[127] Sampson and coworkers developed an EGFRvIII-targeted vaccine for EGFRvIII-positive GBM. There were no autoimmune reactions observed after vaccination. The 6-month PFS rate post-vaccination was 67%, and post-diagnosis was 94% (n = 18) and mOS was 26 months. Vaccinated patients had significantly better OS than matched controls (HR 5.3; P = 0.0013; n = 17). EGFRvIII-specific antibody (P = 0.025) or delayed-type hypersensitivity responses (P = 0.03) significantly improved OS.[128]

5.2. Oncolytic virotherapy

Clinical trials primarily deliver viruses locally to ensure effective tumor targeting. Various viruses, including herpesvirus, adenovirus, and measles virus are being tested for safety and efficacy, some engineered to express immune-stimulating proteins to counter the suppressive tumor microenvironment. These proteins not only disrupt immunosuppression but also recruit and activate pro-inflammatory immune cells. Engineered viruses delivering therapeutic proteins locally aim to optimize efficacy while minimizing systemic toxicity, representing a promising strategy in glioma treatment.[129] Oncolytic viruses (OVs) target tumors through a variety of methods. A schematic illustration of oncolytic virotherapy is demonstrated in Fig. 3(B). They reproduce only within tumor cells because of common biological changes that mimic viral infections. Viral particles are released during direct cell lysis during viral replication, which increases the therapeutic

effect by infecting nearby cells. By generating a pro-inflammatory tumor microenvironment, OVs boost anticancer immune responses and make the immune system of "cold" tumors visible. It is possible to modify them to express immune modulators such as PD-L1 and GM-CSF, which will increase tumor immunogenicity and decrease treatment resistance. To prevent tumor vascularization, OVs also target stromal cells linked to tumors, such as endothelial cells. These diverse functions highlight the promise of OVs for cancer treatment.[130] Zhou and coworkers evaluated the oncolytic virotherapy of zika virus against glioma stem cells and demonstrated that mice with GBM survived more and longer when the tumor was inoculated with a mouse-adapted strain of ZIKV.[131] Hardcastle and coworkers combined measles virus strains with anti-PD-1 antibody as immunovirotherapy and showed significantly improved survival results in a syngeneic GBM model both *in vitro* and *in vivo*.[132]

5.3. Immune checkpoint inhibitors

Zeng and coworkers demonstrated that in animal models, single-session focused radiation treatment (RT) and PD-1 inhibition were highly effective against cerebral gliomas. This method had long-lasting effects with no discernible side effects, indicating a potential supplement to immunotherapy treatment for glioblastoma multiforme (GBM). A mechanistic diagram for immune checkpoint inhibitors is shown in Fig. 3(C). Anti-PD-1 therapy demonstrated positive responses, in contrast to earlier research on anti-CTLA-4 therapy, which had significant rates of adverse events. The survival benefit was decreased by the depletion of cytotoxic T cells, highlighting their contribution to the therapeutic impact. A measure of the receptiveness of glioma cells to immune therapy, the CD8 to Treg cell ratio, increased as a result of the treatment's enhancement of the pro-inflammatory profile of these cells. This unique method has the potential to change GBM treatment strategies and should be evaluated in clinical trials.[133,134] In a clinical study, patients who were randomized to receive neoadjuvant pembrolizumab with continued adjuvant therapy following surgery had significantly increased OS compared to patients who were randomized to receive adjuvant, post-surgical programmed cell death protein 1 (PD-1) blockade alone. These results imply that the neoadjuvant administration of PD-1 inhibition improves antitumor immune activity both locally and systemically and could be a more effective therapeutic strategy for this consistently deadly brain tumour.[135] Dangoor and coworkers combined CCL2 inhibition with immunomodulators targeting either PD-1/PD-L1 or P-selectin/P-Selectin Ligand 1 axes in human 3-dimensional tumoroid models and *in vivo* presented more desirable results than each monotherapy. *In vitro* and *in vivo* models depicted that CCL2 has a key role in brain metastasis, and adhesion molecule P-selectin is also a chief target of currently approved immunotherapies.[136]

5.4. Adoptive cell therapies: CAR T and NK therapy

Cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells have strong cytotoxic effects on malignant tumors. Numerous NK receptors, such as activating and inhibitory killer inhibitory receptors (KIRs), are expressed by NK cells. NK cells can be rendered inactive by interactions between KIRs and MHC-class I molecules on tumor cells, underscoring the compensating function that NK cells play in tumor immunity alongside CTLs. In addition, NK cells engage in interactions with DCs, which are essential for MHC-class I-restricted immune responses. The process of development for adoptive cell therapies is depicted schematically in Fig. 3(D). Malignant tumors may benefit from adoptive immunotherapy, which uses pre-activated NK cells, CTLs, or LAK cells. Although direct autologous CTL injections produce excellent response rates in patients with brain tumors, their extensive use is restricted by their intricate protocols. Simplifying these treatments is essential for wider application in the management of cancer. Treatment for hematologic malignancies has been transformed by CAR T immunotherapy, but solid tumors—glioblastoma in particular—have not yet fully benefited from this cutting-edge approach. Anecdotal evidence of CAR T efficacy and excellent safety profiles, such as objective radiographic responses, antigen elimination, and long-term survivability, have been reported in early glioblastoma trials. However, glioblastoma presents distinct difficulties: a great deal of tumor heterogeneity makes antigen targeting more difficult, immunosuppression reduces the effectiveness of CAR T responses, and assessment is hampered by modeling issues. Current approaches tackle these issues by looking for new antigens, improving T-cell effectiveness, and using adjuvant immunotherapies such checkpoint inhibition and lymphodepletion to get past resistance. To fully realize the potential of CAR T immunotherapy against glioblastoma, it appears promising to integrate these advances from preclinical to clinical settings.[137,138] Kitahara and coworkers have undertaken passive immunotherapy for GBM by generating autologous brain-tumor-specific cytotoxic T lymphocytes from patient peripheral blood lymphocytes *via* mixed lymphocyte–tumor culture and maintained them with IL-2 for over two months after which the T cell lines were safely administered into the tumor bed to treat malignant glioma, showing >50% tumor regression in 2 out of 5 cases. One patient remained alive and fully active 104 weeks post-immunotherapy without complications or toxicity.[139]

6. Recent advances in dual/multi-drug and combined therapy for GBM treatment

Dual/multi-drug and combined therapy approaches have been a promising drug delivery tool against GBM in the last few decades. Due to the complex and spontaneous spreading nature of GBM, researchers are looking into a number of different treatment approaches. Several clinical trials are underway to explore the potential of different drugs combination, which are shown in Table 5. Combination therapy

Table 5 Different recent clinical studies of drug combinations for GBM treatment

NCT ID	Drugs	Clinical phase/status	Sponsor/company	Mechanism	Indication
NCT00777153	Lomustine; cediranib	Phase III/ completed (2016)	AstraZeneca	Alkylating agent; tyrosine kinase	Recurrent GBM
NCT00921167	Irinotecan; bevacizumab	Phase II/ completed (2013)	Clinical Research Center for Solid Tumor, Korea	Topoisomerase I inhibitor; anti-VEGF antibody	Recurrent gliomas
NCT00615927	Imatinib; hydroxyurea	Phase II/ completed (2012)	Novartis Pharmaceuticals	Tyrosine kinase inhibitor; ribonucleoside diphosphate reductase inhibitor	Recurrent/progressive grade II low-grade glioma
NCT01110876	Erlotinib; vorinostat; temozolomide	Phase II/ terminated (2014)	Merck Sharp & Dohme	Tyrosine kinase inhibitor; histone deacetylase inhibitor	Recurrent GBM
NCT00329719	Sorafenib; temsirolimus	Phase I/II/ completed (2013)	National Cancer Institute (NCI)	Tyrosine kinase inhibitor; mTOR inhibitor	Recurrent GBM
NCT00672243	Sirolimus; erlotinib	Phase II/ completed (2009)	Genentech/OSI Pharmaceuticals	mTOR inhibitor; tyrosine kinase inhibitor	Recurrent GBM
NCT00621686	Sorafenib; bevacizumab	Phase II/ completed (2009)	National Cancer Institute (NCI)	Tyrosine protein kinases; anti-VEGF antibody	Recurrent GBM
NCT02669173	Bevacizumab; capecitabine	Phase I/ recruiting	Cleveland Clinic Taussig Cancer Institute	Anti-VEGF antibody; target myeloid-derived suppressor cells	Recurrent GBM
NCT00641706	Vorinostat; bortezomib	Phase II/ completed (2010)	National Cancer Institute (NCI)	Deacetylase inhibitor; proteasome inhibitor	Recurrent GBM
NCT03466450 (EudraCT Number 2017-002410-31)	Glasdegib; temozolomide	Phase IB/II/ recruiting	Grupo Español de Investigación en Neurooncología	Inhibits SHH pathway interfering with cancer stem cells and endothelial migration; alkylating agent	Newly diagnosed GBM
NCT02340156	Temozolomide; SGT-53	Phase II/ recruiting	SynerGene Therapeutics	Alkylating agent; liposome-p53 DNA	Recurrent GBM
NCT03643549	Bortezomib; temozolomide	Phase IB/II/ recruiting	Haukeland University Hospital	Deplete the MGMT enzyme; alkylating agent	Recurrent GBM with unmethylated MGMT promoter
NCT00671970	Bevacizumab; erlotinib	Phase II/ completed (2010)	Genentech	Anti-VEGF antibody; tyrosine kinase inhibitor	Recurrent GBM

involves additional challenges that need to be addressed compared to single therapy. The most important point to be considered in selecting the right treatment plan involves deciding which techniques and substances to mix and making sure they work in synergy, while another significant factor is delivery of these combination therapies. For a combined treatment to be effective, these devices need to be able to load several agents and properly deliver them to the targeted areas. The combination of chemotherapies for GBM treatment has been widely used to improve the results in patients. A single chemotherapy agent frequently causes the tumor to become resistant to the drug over time. As the "combination of chemotherapies" refers to the use of several chemotherapy agents in one treatment for GBM, the aim of this strategy is to improve therapeutic efficacy and overcome resistance that may arise with single-agent therapies. For GBM, the effectiveness of a tumor-necrosis factor related apoptosis-inducing ligand (TRAIL) is limited by resistance. DOX enhances TRAIL-induced apoptosis, suggesting a combined treatment. Guo and coworkers developed DOX and TRAIL liposomes (DOX-LP and TRAIL-LP), showing improved safety and efficacy in sensitizing GBM cells, demonstrating a promising therapeutic strategy for GBM.[140] Graham-Gurysh and his coworkers formulated a synergistic drug combination made of a biodegradable polymer implant. This aims to deliver interstitial therapy of paclitaxel, which works in combination with the standard care of chemotherapy, TMZ and everolimus, a mammalian target of the rapamycin (mTOR) inhibitor. In *in vitro* and *in vivo* evaluation of the formulation, it was demonstrated that there was a strong synergism between paclitaxel, TMZ and everolimus at nanomolar quantities, leading to the death of GBM cells in a significant ratio, as shown in Fig. 4.[141]

Brain gliomas pose a serious health risk. To enhance treatment efficacy and reduce side effects, Chen and coworkers developed a dual-ligand delivery system by conjugating TAT (cell-penetrating peptide) and transferrin (a particular targeting ligand) onto liposomes (TF/TAT-LP) combining DOX and PTX. This approach improved drug penetration and targeting, significantly reducing tumor growth. *In vivo* studies confirmed superior brain penetration and anti-glioma activity, showing

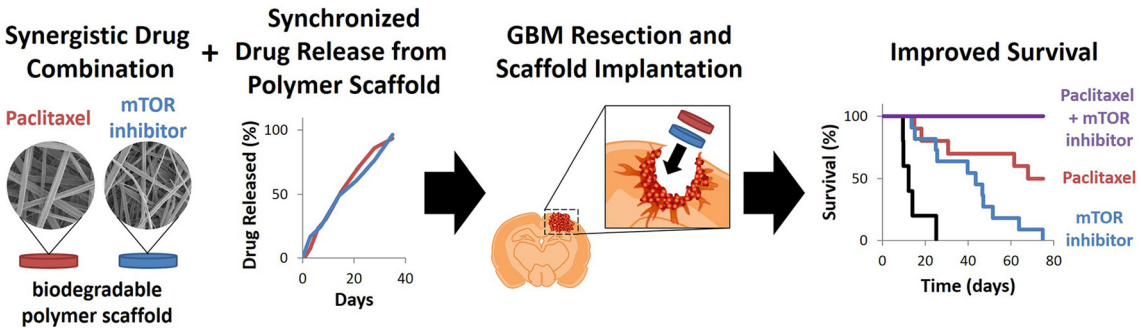

Fig. 4 A summary of synergistic drug combination as interstitial therapy of paclitaxel with TMZ and everolimus, an mTOR inhibitor in a murine GBM model. Interstitial therapy was achieved *via* a biodegradable polymer implant that aided in the delivery of chemotherapy to cancerous tissues. This combination strategy resulted in improved overall survival and overcame the BBB and broadened the range of medications used in therapy. Reproduced from ref. 141 with permission from Elsevier, copyright 2020.

great potential for clinical use. *In vivo* experiments showed that dual-targeted liposomes demonstrated notably stronger brain penetration, glioma targeting, and also increased the chemotherapeutic effects of the two drugs in comparison to other formulations.[142] A strategy of combining chemotherapy with radiotherapy was also used for GBM. Adjuvant radiation therapy doubles GBM survival rates. Villa and coworkers found postoperative external beam radiation to be effective, especially with TMZ. Targeted high-dose radiation, using modern imaging, should be 1.8–2.0 Gy fractions with a total dose of about 60 Gy. Hypofractionation benefits older patients, but radiosensitizers and dose-intensification show no improvement. Currently, TMZ plus concurrent and adjuvant radiation therapy is the accepted course of treatment for individuals with GBM.[143] Some approaches include combining chemotherapy with a phototherapy combination approach for GBM. Combining chemotherapy with phototherapy effectively treats brain cancer due to its targeted, minimally invasive approach. Photothermal therapy uses near-infrared (NIR) light to target tumors without harming healthy cells. This combination enhances efficacy by increasing drug cytotoxicity and improving delivery into cancer cells through higher temperatures.[144,145] Kwon and coworkers demonstrated that Fe_3O_4 magnetic nanoparticles (MNPs) loaded with TMZ and indocyanine green (ICG) enhance antitumor effects on U-87 MG glioblastoma cells *via* chemo-photothermal therapy. Near-infrared (NIR) light irradiation induced apoptosis by generating reactive oxygen species and modulating apoptotic genes, significantly increasing anticancer efficacy. Both internal and extrinsic apoptotic genes, including as Bcl-2, cytochrome c, caspase-3, caspase-8, Fas-associated *via* death domain, and Bcl-2-associated X protein, were modulated to achieve this improvement.[146] When immunotherapeutic approaches were combined with chemotherapy, significant amelioration was observed in GBM patients in several cases. Immunotherapy, known for stimulating specific immune responses against cancer, offers the potential to reduce metastasis and recurrence. Techniques include cancer vaccines, monoclonal antibodies, oncolytic viruses, T-cell engineering, and immunomodulation. Challenges in glioblastoma treatment include low tumor immunogenicity and immunosuppressive environments. Chemotherapy along with an immunotherapy combination approach for glioblastoma multiforme is a promising approach to enhance efficacy.[147,148] A list of a few instances for some drug combinations with their design and formulation aspects along with *in vitro* and *in vivo* model outcomes are listed in Table 6.

7. Treatment affordability for GBM and addressing pediatric GBM

7.1 Treatment affordability for GBM

GBM is one of the most threatening and aggressive cancers to treat, which puts financial burdens on the patient for the management of this cancer. To improve accessibility and equitable care, it is essential to comprehend the financial effects of treating GBM. The main sources of direct expense in GBM treatment are radiotherapy, surgery and chemotherapy. Treatment costs are further increased by sophisticated surgical methods like fluorescence-guided surgery and imaging modalities like MRI or PET scans. Furthermore, radiation therapy costs can reach tens of thousands of dollars, when used in combination with drugs like temozolomide. Advanced treatments like TTF therapy which increased the survival rate of patients to a significant extent, also add a substantial cost of around $20 000 per month to the expenses of patient treatment.[135] All costs which arise directly from the therapies cause direct financial burdens on the patient. Additionally, there are various indirect costs involved for the patients and their families, including travel expenses, caregiving responsibilities, nutritional demands, rent, supporting staff salaries, and loss of income. Patients with GBM generally experience fast cognitive loss, which makes full-time caregiving and sometimes early end-of-life planning necessary. This all adds to the financial burden.[155]

Newer treatments such as immune checkpoint inhibitors, nanotechnology-based therapies and CAR T cell treatments show significant potential, but high clinical translational costs

Table 6 A list of different drugs used in combination with formulation design and their *in vitro*/*in vivo* outcomes

Drugs used in combination	Formulation design	*In vitro* and *in vivo* results	Ref.
siRNA, CXCL10, MIT	Metallic organic framework loaded with siRNA embedded in hydrogel system containing MIT and CYCL10	siRNA: linear release 100% at 15 days MIT: linear release 100% at 18 days, CXCL10: linear release 100% at 12 days; orthotopic, C57BL6 mouse model, survival *i.e.* no resection occurred	149
BCNU, CIS, CA-4 irinotecan	Irinotecan and, BCNU CIS electrospun into polymer fiber layer, followed by layer of CA-4 within polymer fibers	Orthotopic model, wistar rat, no resection (survival)	150
PTX, plasmid DNA for RNAi of MMP2	DNA-laden polymer nanoparticles electrospun with polymer-fiber scaffolding and loaded with plasmids	PTX: ~10% release over 42 days, plasmid DNA: ~15% release over 42 days; orthotopic, nude mouse model, no tumor excision	151
ALA, AUR	Combination of both ALA and AUR was used	Inhibition of migration and metastasis of GBM U87-MG cancer cells	152
TMZ, PTX	TMZ-containing photopolymerizable hydrogel with PTX incorporated polymeric microparticles	Orthotopic nude mouse model, tumor resection (survival)	153
Simulated microgravity plus oncolytic virotherapy	Cisplatin using clinostat-based 3D model as simulated microgravity with rat parvovirus H1 employed for oncolytic virotherapy	Induced GBM cell growth inhibition in D54MG cell lines	154

make them extremely expensive. For instance, CAR T therapy for one patient can costs up to $373 000, which makes affordability a matter of great concern, specifically the unavailability of enough resources.[156] In developed countries, cutting-edge technology-based therapies may be available but not accessible to underinsured or uninsured patients. However, in underdeveloped or developing nations, basic care such as radiotherapy or diagnostic facilities may not be accessible because of fiscal deficits and poor health infrastructure. If these inequities are addressed at global level, we can delimit the challenges in the treatment affordability for GBM patients. Healthcare organizations and policymaking authorities should focus on cost reduction and affordability improvement for the patients. Innovative strategies such as telemedicine consultations, the development of biosimilars, value-based pricing and similar efforts could be a gamechanging step in encouraging affordable treatment available to all.[157] A multi-stakeholder strategy is required to ensure that life-extending therapies are accessible to all patients, irrespective of socioeconomic status.

7.2 Addressing pediatric GBM

The specific problems of pediatric GBM originate from its accelerated progression, unusual molecular profile, and effect on young children. In comparison to adult GBM, pediatric GBM lacks IDH mutations and exhibits differences in molecular patterns, such as H3K27M alterations in diffuse midline gliomas. These variations highlight the significance of treating pediatric GBM as a distinct entity in GBM research and treatment evolution and urges customized therapeutic methods.[158] Currently, conventional pediatric GBM management involves radiotherapy, TMZ-based chemotherapy and maximal surgical removal of the tumor. Radiotherapy is used but it is considered unsafe for children because it has a potential threat to developing brains. Several efforts are being made to improve and standardise radiation protocols for pediatric patients, such as proton beam therapy, to preserve efficacy and reduce side effects.[159] Different emerging therapies, such as targeted therapies, precision medicine, oncolytic virotherapy, and immunotherapy are being developed; however, there are challenges in circumventing the immunosuppressive tumor microenvironment. Viruses designed to specifically infiltrate and destroy tumour cells are a new treatment option for pediatric GBM that is undergoing clinical investigation. With advances in genomic analysis, customised treatment regimens based on individual tumour mutations are offering new hope for better results. In certain subtypes of paediatric GBM, medications that target BRAF V600E mutations or ALK inhibitors have shown significant potential.[160–162]

Due to the rarity of pediatric GBM compared to adult, extensive data collection and large-scale clinical trials become challenging. Successful drug delivery becomes more difficult because of the BBB, therefore there is a need for novel delivery techniques like convection-enhanced delivery or nanotechnology-based drug delivery. Furthermore, therapeutic procedures must incorporate psychosocial assistance due to the emotional and psychological trauma that young patients and their families suffer. Various challenges faced by long-term survivors of pediatric GBM include physical limitations, learning deficits, and secondary malignancies brought on by rigorous treatment plans. In summary, it can be concluded that managing pediatric GBM needs a multimodal strategy that incorporates cutting-edge treatments, continuous research, and supportive care. Scientists, medical professionals, and policymakers should work together to create safe, efficient, and affordable remedies for this severe illness. An emphasis on improving survival rates and clinical results will also be helpful in resolving the specific challenges of pediatric GBM.[163,164]

8. Conclusion and future perspectives

Although a large number of clinical investigations have been carried out and many are under post-market surveillance,

GBM therapies have not achieved a significant milestone. Since GBM proliferation and progression of GBM are not easily detectable and the present treatment strategies offer little to enhance overall survival without growth. In the current scenario, nanotechnology has become a leading approach for research on GBM therapy. Due to the slight increase in survival rates from current therapeutic methods, research on nanocarriers and their surface modification along with multi-drug or combination therapy must be conducted in a standardized manner. The clinical use of nanocarriers requires some improvements, including reduced exposure and decreased dosage without affecting the deposition of nanoparticles in the tumor region. There is also a need to evaluate the alarming variety of versatile and flexible materials, such as porous materials and hitchhiking nanocarriers. The delivery of immunotherapy drugs can be achieved with such materials because of their ability to surmount numerous biological barriers and they hold great potential for application in GBM therapy. Research on immunotherapeutic approaches has proven fruitful in the last decade with respect to aspects of safety and efficacious drug delivery for GBM. However, the clinical translation of nanocarriers from the lab to lead candidates and other factors, such as biocompatibility, patient access, toxicity, scale-up, and repeatability, still require a lot of research.

To understand the clear and concise future aspects of nanomedicine for GBM treatment, mainly with respect to modern materials, new models for *in vivo* and *in vitro* investigation must be established. An integrated approach is needed to combine biological, physical, and chemical intervention to treat GBM and overcome resistance to individual therapies and innate heterogeneity. Future findings must involve issues related to biocompatibility, toxicity, safety, and accessibility, among others. Treatment affordability must also be addressed, as multi-drug or combination therapy will cost more than individual treatments or single drugs. Effective therapies must be tested in a variety of *in vivo* models to obtain a better and more precise statistical setup for clinical development. Moreover, detailed studies on the timing of treatment must be undertaken. For instance, the efficacy of immunotherapy is influenced by the time of chemotherapy. Therefore, there is a need to enhance the research focus on the intricate tumor microenvironment. Additionally, different evidence predicts that personalized treatment of GBM with targeted drugs could be beneficial. However, elaborate research is required to determine the safety and effectiveness of new medicines in specific GBM populations with unique molecular targets. In conclusion, the development of multi-drug or combination therapy, surface-modified nanocarriers, and immunotherapeutics should be followed by biological research on GBM malignancy and its CNS progression.

Abbreviations

ALA	Alpha-lipoic acid
Anti-GFAP	Anti-glial fibrillary acidic protein
Anti-PD-1	Anti-programmed death 1
AnxA2	Annexins A2
APOE	Apolipoprotein E
AUR	Auraptene
BBB	Blood–brain barrier
BCNU	Carmustine
BSA	Bovine serum albumin
CA-4	Combretastatin
CBTRUS	Central Brain Tumor Registry of the United States
CED	Convection-enhanced delivery
CIS	Cisplatin
CNS	Central nervous system
CNTs	Carbon Nanotubes
CXCL10	C-X-C Motif Chemokine Ligand 10
DENPs	Dendrimer entrapped nanoparticles
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
EDTA	Ethylene diamine
EGFR	Epidermal growth factor receptor
FA	Folic acid
GBM	Glioblastoma multiforme
GICC	Glioma international Case-Control (Study)
HSP-70	Heat shock protein 70
HSR	Heat shock response
ICB	Immunity checkpoint blockade
ICD	immunogenic cell death
IMRT	Intensity-modulated radiation therapy
IN	Intranasal
IONP	Iron oxide nanoparticle
IV	Intravenous
KPS	Karnofsky Performance Score
LDL	Low density lipoprotein
LipoDox	Liposomal doxorubicin
LRR	Lipoprotein related protein
MGMT	*O*-6 methyl guanine DNA methyl transferase
MMR	Mismatch repair (system)
MNP	Metallic nanoparticle
mOS	Median overall survival
mPFS	Median progression free survival
MWCNTs	Multi walled carbon nanotubes
NCCN	National Comprehensive Cancer Network
NSAIDs	Non-steroidal anti-inflammatory drugs
ORR	Objective response rate
PAMAM	Polyamidoamine
PDT	Photodynamic treatment
PFS	Progression free survival
PPI	Polypropylene imine
PPL	Poly-L-lysine
PTX	Paclitaxel
QDs	Quantum dots
RIP	Ribosomal inactivating protein
RMT	Receptor-mediated transcytosis
ROS	Reactive oxygen species
RT	Radiotherapy
RTKs	Receptor tyrosine kinases
siRNA	small interfering RNA

SRS	Stereotactic radiosurgery
SWCNTs	Small walled carbon tubes
TACA	Tumor-associated carbohydrate antigen
Tf	Transferrin
TfR	Transferrin receptor
TMZ	Temzolomide
TTF	Tumor treating field
U87-MG	Uppsala 87 malignant glioma
VEGF	Vascular endothelium growth factor
vs.	*versus*

Author contributions

Ashish Dhiman: conceptualization, literature survey, writing original draft, review & editing; Yagni Shah: conceptualization, writing, review & editing; Dhwani Rana: conceptualization, review, editing, and investigation; Kalpna Garkhal: conceptualization, editing, supervision, validation and investigation.

Notes

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

The authors confirm that the content of the manuscript has not been published or submitted for publication elsewhere.

Data availability

No primary research results, software or code has been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no competing interests.

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