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REVIEW

# Role of Polymeric Local Drug Delivery in Multimodal Treatment of Malignant Glioma: A Review



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**Abstract:** Malignant gliomas (MGs) are the most common and devastating primary brain tumor. At present, surgical interventions, radiotherapy, and chemotherapy are only marginally effective in prolonging the life expectancy of patients with MGs. Inherent heterogeneity, aggressive invasion and infiltration, intact physical barriers, and the numerous mechanisms underlying chemotherapy and radiotherapy resistance contribute to the poor prognosis for patients with MGs. Various studies have investigated methods to overcome these obstacles in MG treatment. In this review, we address difficulties in MG treatment and focus on promising polymeric local drug delivery systems. In contrast to most local delivery systems, which are directly implanted into the residual cavity after intratumoral injection or the surgical removal of a tumor, some rapidly developing and promising nanotechnological methods—including surface-decorated nanoparticles, magnetic nanoparticles, and focused ultrasound assist transport—are administered through (systemic) intravascular injection. We also discuss further synergistic and multimodal strategies for heightening therapeutic efficacy. Finally, we outline the challenges and therapeutic potential of these polymeric drug delivery systems.

**Keywords:** malignant glioma, chemoresistance, local delivery, nanofiber, nanoparticle, focused ultrasound, magnetic nanoparticles

## Introduction

Malignant gliomas (MGs) come in the form of glioblastomas, anaplastic oligodendrogliomas, anaplastic astrocytomas, and anaplastic oligoastrocytomas; among these, glioblastoma multiformes (GBMs) have the highest mortality.[1] MGs are highly proliferative and extensively invade the brain parenchyma, resulting in devastating tumor recurrence and poor prognosis with a median survival of approximately 12–15 months.[2,3] Although the standard treatment primarily involves surgical debulking followed by radiation therapy and possible chemotherapy,[4–6] a multidisciplinary approach may be required for MGs to be managed efficiently. In the previous decades, multimodal studies and therapeutic trials have been conducted, but the advances have only extended the median survival rate of patients with MG by a few months.[5,7,8]

MGs present major therapeutic challenges because they are poorly circumscribed (Figure 1). MGs originate in glial cells (>90% of which are brain cells), which make neurons chemically and physically sustainable. Glioma cells aggressively invade and infiltrate healthy brain tissues through the extensive diffusion among and intermingling with surrounding brain parenchyma, making total surgical removal difficult or impossible.[9,10] Furthermore, >98% of drugs, including the most advanced

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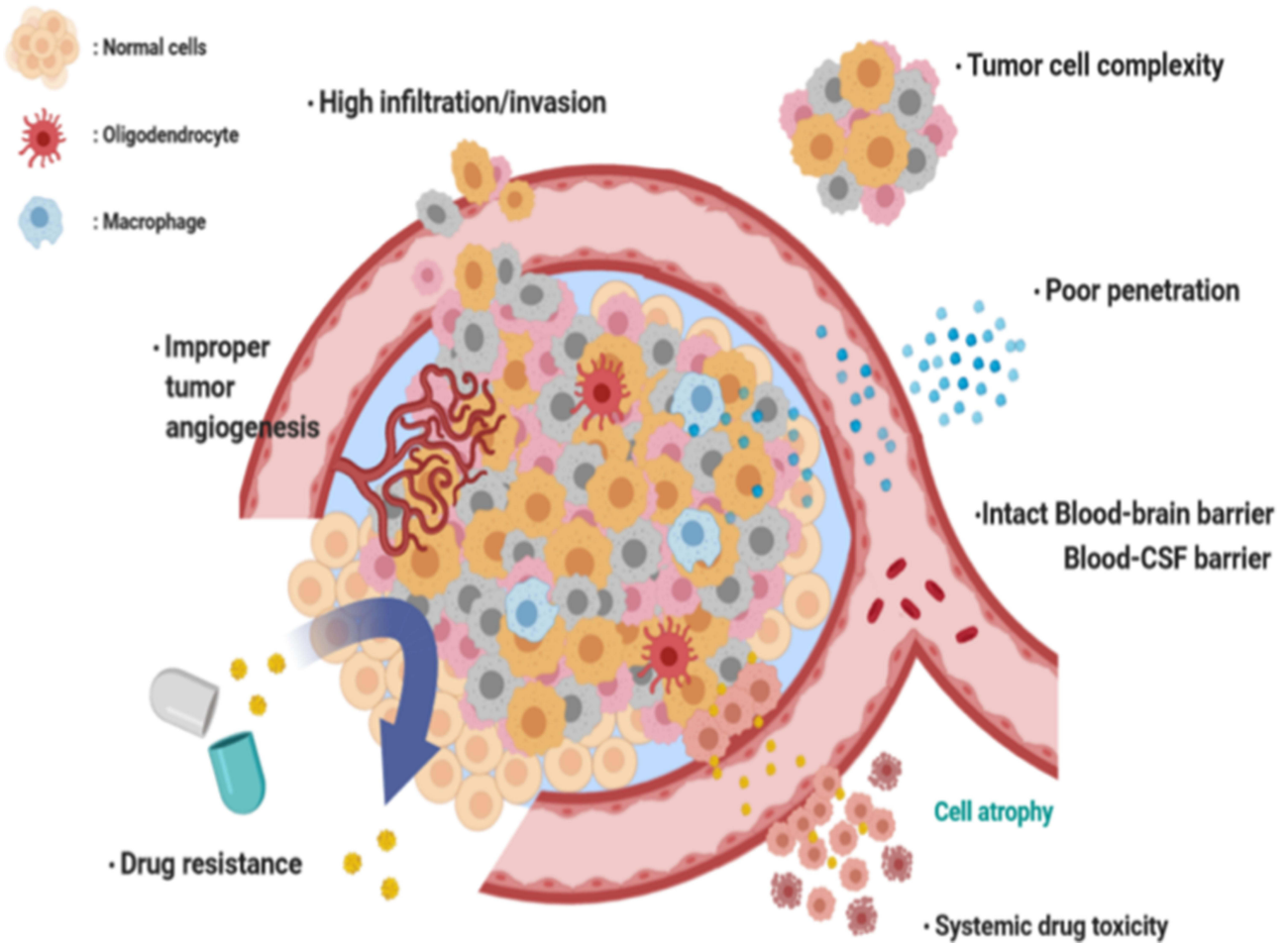


**Figure 1** Illustrations of challenges in treating malignant glioma.

chemotherapy agents, cannot penetrate the blood–brain barrier (BBB).[11–13] The BBB is a distinct coordination barrier that shields the brain from direct exposure to systemic blood. The BBB impedes the access of most therapeutic and diagnostic agents to the brain tissue even when the systemic concentration reaches a toxic level.[12,14,15] Nanoscale vectors with unique characteristics have been designed to interact with cells forming the BBB at a molecular level; these vectors enable biotherapeutic molecules (such as chemotherapy agents, nucleic acids, peptides, or imaging agents) to penetrate the BBB without interrupting normal brain functions.[15–17] Although the BBB may hinder the intracerebral transport of chemotherapy drugs, the major limitation of MG treatment lies in its high resistance to chemotherapy. For example, the commonly used chemotherapy drug temozolomide (TMZ) is ineffective in approximately 60–75% of patients with MG because MG tumors are unresponsive or resistant.[18,19]

Polifeprosan 20 with bis-chloroethylnitrosourea (BCNU, also called carmustine) is currently the only clinically used implant for the local delivery of BCNU to high-grade gliomas after tumor resection. Gliadel wafers (Guilford Pharmaceuticals, Baltimore, MD) distribute BCNU throughout the brain parenchyma over a mere 5 days. When in continuous contact with cerebrospinal fluid (CSF), the wafers biodegrade entirely within 6–8 weeks.[20,21] Furthermore, a series of postimplantation complications have been reported, specifically perioperative surgical site infection, CSF leakage, meningitis, poor incisional wound healing, symptomatic malignant edema, susceptibility to seizures for at least 3 months, deep-vein thrombosis, and pulmonary embolism.[22,23] In primary MG treatment, BCNU-incorporated wafers lead to improved survival without an increased incidence of adverse events, when compared with placebo wafers. However, in patients with newly diagnosed GBM[24] and recurrent GBM,[25] the median survival period increased

by only approximately 2.3 months and 8 weeks, respectively, after they received therapy with Gliadel wafers. Furthermore, a study reported that Gliadel wafers confer no additional benefits in patients with recurrent MG.[26] Low local concentration, inadequate diffusion distance, a short therapeutic period, and high resistance to BCNU are the major causes of the negligible effectiveness of Gliadel wafers.[25,27,28] Therefore, various innovative treatments and management modalities have been formulated in an attempt to surmount such resistance to chemotherapy. As a contribution to our understanding of the problem, this article is a review of studies on the role of polymeric vehicles for local drug delivery in the multimodal treatment of malignant glioma.

## Polymeric Vehicles for Local Drug Deliveries

### Polymeric Vehicles

Polymeric vehicles, especially nanoscale carriers, have gained increasing attention in recent years because of their advantages, such as high drug-loading capacity, excellent biocompatibility, and low volume requirement; these advantages, specified as follows, mean that such vehicles do not induce the mass effect when administered in the central nervous system (CNS).

1. High drug-loading capacity: Drug-loaded polymers can be fabricated as fibers, particles, micelles, or wafers (discs) that possess high porosity, open 3D porous structures, and a large surface-to-volume ratio. These properties offer numerous chemically active sites for biomolecule conjugation,[29,30] which increase the drug-loading capacity of polymeric carriers.
2. Low volume requirement: Due to their high drug-loading capacity, manufactured polymeric carriers can have a low volume, and they do not induce the mass effect when introduced into the CNS. This is crucial in the treatment of CNS diseases.[27,31]
3. Excellent biocompatibility: Polymeric materials possess good biocompatibility and are thus ideal for use in drug or molecule carriers. When present in the body, these materials degrade through hydrolysis to become monomers, which, under normal physiological conditions, are byproducts of various metabolic pathways in the body. When applied to the CNS for the delivery of multiple chemotherapy agents or other bioactive agents, these highly biocompatible polymers cause no gross tissue reaction and no obvious accumulation of transudate and exudate fluids (Figure 2A and B). However, microscopic pathological examinations have indicated temporal inflammation and leucocyte accumulation from the use of such materials, with the leucocytes dissipating eventually through polymer degradation (Figure 2C and D).[32–34]
4. Biodegradability: One of the exceptional properties of polymeric materials for drug delivery to the CNS is its biodegradability. Polylactic-co-glycolic acid (PLGA) is one of the most investigated synthetic degradable polymeric materials for controlled and targeted drug delivery. It biodegrades through the hydrolysis of ester linkages in the presence of water. The duration required for PLGA degradation is determined by the ratio of the composed monomers: the greater the percentage of lactic monomers, the longer the time required for degradation relative to that for principally glycolic monomers. A special case of such regulation involves copolymers with a 50:50 monomer ratio, which degrade rapidly. This versatility in degradation has made PLGA a good candidate for use in implants as part of treatment with a tailored period and order (Figure 2C). Liu et al.[35,36] exploited bistructured anticancer drug-loaded nanofibers that comprised core-sheath-structured $O^6$-BG on 50:50 PLGA nanofibers and alkylating agents (TMZ and BCNU) on 75:25 PLGA nanofibers. Hybrid-structured nanofibrous membranes (HSNMs) can sequentially deliver a high concentration of $O^6$-BG prior to the delivery of BCNU and TMZ. Resistance to alkylating agents is oriented by the DNA repair protein $O^6$-methylguanine-DNA methyltransferase (MGMT). $O^6$-BG can necessarily inactivate MGMT through contending with $O^6$-methylguanine, thus promoting the treatment efficacy of alkylating agents.[36–38]
5. Good conformity: In contrast to Gliadel wafers, most newly-developed polymeric carriers have been designed as membranes, particles, pastes, and hydrogels, and they can conform satisfactorily to the wall of the cerebral cavity after brain tumor removal and cover the brain parenchyma, thus achieving effective local drug transport.[35,39]
6. Easy codelivery of multi chemotherapy agents: Currently, the chemotherapy cocktail for GBM is procarbazine, lomustine (CCNU), and vincristine (PCV); in the PCV regimen, CCNU (110 mg/m$^2$) is intravenously infused on day 1, procarbazine (60 mg/m$^2$) is intravenously infused daily for 14 days beginning

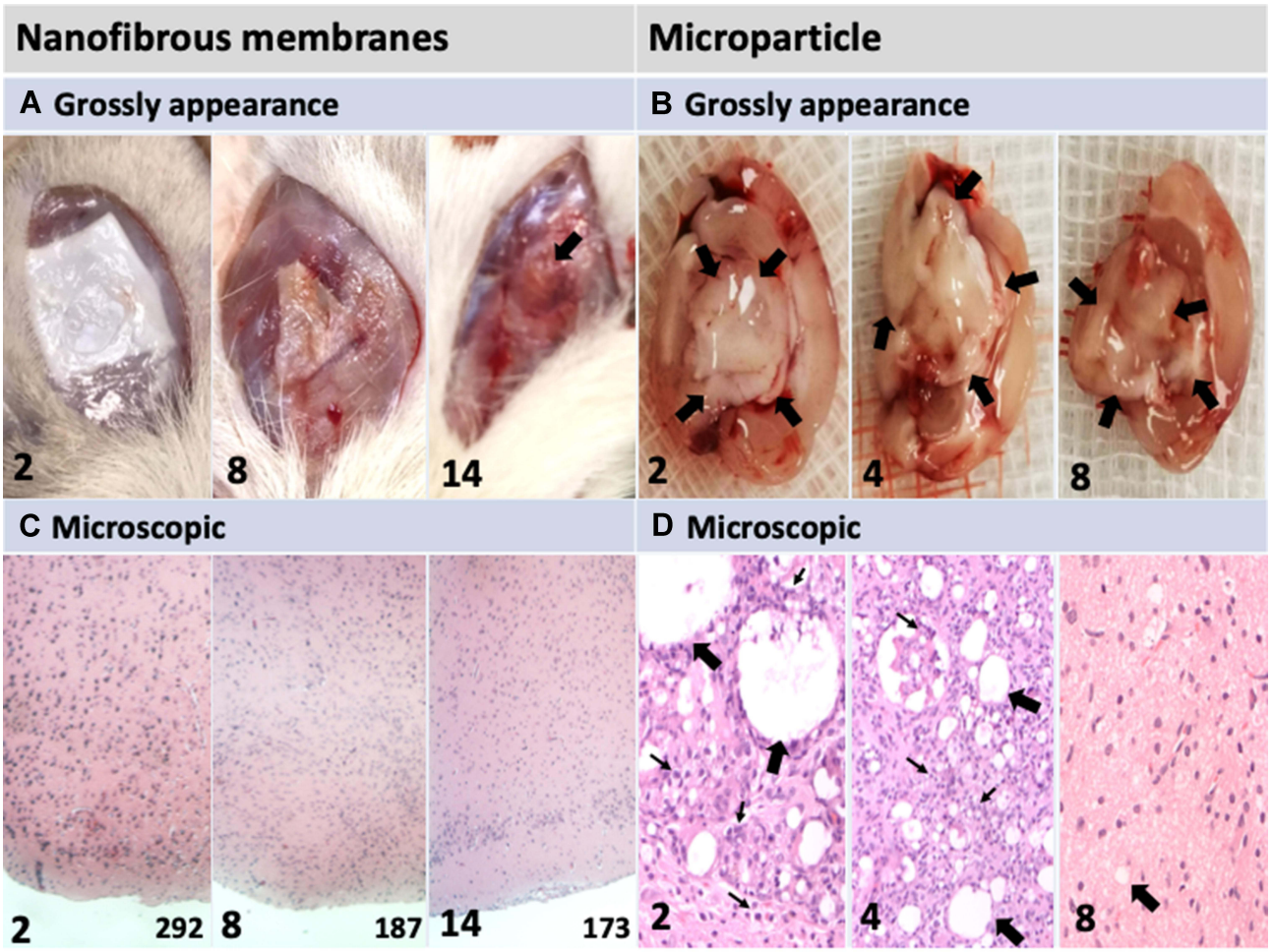


**Figure 2** Gross appearances and microscopic images of postimplantation parenchyma. The number in the lower left corner of each image indicates the number of weeks following the implantation of nanofibrous membranes (NMs) or microparticles. (**A**) Implanted PLGA NMs degraded without causing the accumulation of transudate and exudate fluids. (**B**) Injected microparticles were initially dense and large (indicated by black arrows); few dense areas were observed at the end of the study. (**C**) Pathological examination (H&E stain) indicated no leukocyte accumulation after implantation with NMs. The number in the lower-right corner of each image indicates cell numbers ($mm^2$). Progressively decreased cellularity was noted after chemotherapy agent loaded NMs implantation. (**D**) Injected microparticles (indicated by black arrows) degraded progressively and the presence of temporal inflammation reaction (accumulation of numerous inflamed leukocytes, indicated by small arrows). Magnification: 100×.

on day 8, and vincristine (1.4 $mg/m^2$) is intravenously infused on days 8 and 29 of each 6-week cycle.[40,41] The PCV regimen demands an intricate course of therapy, whereas biodegradable multiagent polymeric vehicles can contemporaneously transport different chemotherapy agents[42–45] or biopharmaceutic agents[35,46–48] into the CNS in one step.

## Local Drug Deliveries

Although multimodal treatments are currently available, relapses of MGs are common, with >90% of MGs recurring within 2 cm of the original resection cavity.[49–51] Researchers have developed local and controlled drug delivery systems, such as the facilitated infusion of biotherapeutic molecules through convection-enhanced delivery, intracranially implanted catheters, or polymer-based drug delivery systems (Figure 3A).[27,52] These polymer-based drug carriers exhibit promise in the treatment of brain tumors. Local delivery systems can bypass the BBB and reduce systemic toxicity, significantly increasing the therapeutic concentration at the targeted site. Chemoresistance has been primarily attributed to the increased efflux of tumoricidal agents, which results in a reduced intracellular drug reservoir.[53,54] Resistance due to extraordinarily high drug efflux rates, which reduce drug concentration at the targeted site, is intrinsic or acquired if it existed before or developed after drug administration, respectively.[53] Clinicians can improve therapeutic efficacy and prevent chemoresistance by increasing the anticancer drug concentration at the target tissue.

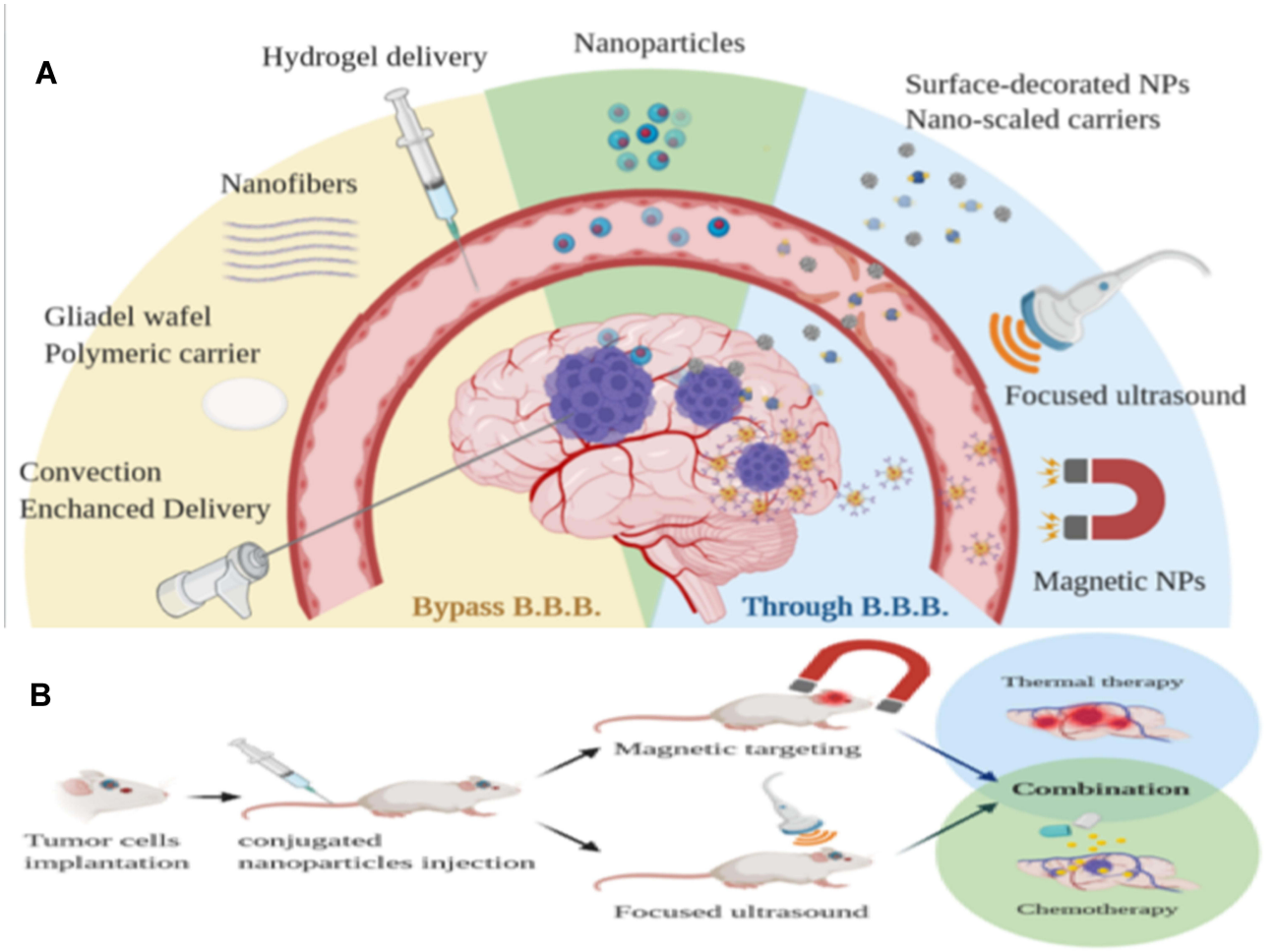


**Figure 3** (**A**) Local delivery system that bypasses the blood–brain barrier (BBB) to reach the brain tumor. (**B**) NPs crossing the BBB with the aid of FUS and an external magnetic field.

Various polymers, including natural polymers, synthetic polymers, and copolymers, have been used as drug vehicles to achieve a sustained release of therapeutic molecules to targeted areas. Drug release characteristics are highly dependent on the physicochemical features of employed polymers and on their interaction with therapeutic compounds.[55] To enhance therapeutic responses and prevent drug toxicity, chemotherapy may be locally administered.[56] To treat malignant brain tumors, clinicians have implemented interstitial chemotherapy, in which chemotherapy agents are directly administered into tumors; it offers enhanced and extended drug concentration in the brain tissue, thus bypassing the BBB and minimizing systemic toxicity. Clinicians must remember the four following key points when implanting polymer-based drug delivery systems into the CNS. First, an implant with a small volume should be chosen to prevent the occurrence of the mass effect when it is introduced into the brain parenchyma or spinal cord. Second, the drug-loaded implant with the lowest toxicity should be chosen to avoid damage to functional nerve cells. Third, the implant should be implanted in a manner that induces the least inflammatory reaction, which could result in cerebral edema and poor wound healing. Fourth, care must be taken to avoid complications, such as infection and seizure, during implantation.[22,23,27,30] The theoretical benefits of polymer-based drug delivery systems have spurred the development of interstitial chemotherapy for patients with MG.[27,57] Various technologies have been adopted in the development of drug-loaded polymeric implants for treating MG, including electrospinning,[36,42,58,59] electrospraying[33] emulsification-solvent evaporation,[60] the emulsion-evaporation method,[61] and the use of self-assembly.[32] Table 1 lists the polymer-based local delivery systems that have been effective in treating MG in vitro and in vivo.

**Table 1** Summary of Polymeric Vehicles for Local Delivery with Therapeutic Potential in MG Treatment

| **Single Agent** | | | | | |
|---|---|---|---|---|---|
| **Therapeutical Agent** | **Type of Polymer** | **Structure of Polymeric Vehicle** | **In vivo/in vitro Model** | **Treatment Outcome** | **Ref.** |
| SN-38 | PLGA | MP | Orthotopic glioma rats (F98) | Significant therapeutic efficacy | [33] |
| SN-38 | NK-012 | Micelle | Orthotopic GS rats and GBM mice (9L, U87) | Excellent efficacy | [68] |
| SN-38 | PLEC | Depot | Orthotopic GBM mice (U87) | Better antitumor efficacy and reduced toxicity | [69] |
| SN-38 | PCL/GT | Nanofiber | In vitro U251/ U87 cell | Good anti-tumor function in vitro | [70] |
| BCNU | Poly-CPP-SA | Disc | Orthotopic GS rats (9L) | Effective antitumor efficacy and prolong survival rate | [64] |
| BCNU | PEG-PLA | Ultrafine fiber | In vitro, C6 glioma cell, | Not affect the growth of C6 glioma cell | [58] |
| BCNU | PLGA | Wafer | 9L GS, subcutaneous | Delayed tumor growth | [62] |
| BCNU | PLGA | Wafer | In vitro, XF-498 cell | Increase antitumor activity | [63] |
| BCNU | PLGA | Nanofiber | In vivo, concentration | Sustained release high concentration > 8 week | [39] |
| BCNU | Shell: panH<br>Core: $Fe_3O$ | Core-shell magnetic NP | In vivo, concentration | Increase the concentration and retention | [119,137] |
| Rapamycin | Caprolactone-glycolide (35:65) | Beads | Orthotopic GS rats (9L) | Significant increase in survival | [65] |
| Doxorubicin | Polysorbate | Polysorbate-coating NP | Orthotopic glioma rats (101/8) | Considerable antitumor effect | [138] |
| Doxorubicin | PLGA | NP | Orthotopic glioma rats (101/8) | Considerable anti-tumor effect | [139] |
| 5-FU | PLGA | Wafer | Orthotopic glioma rats (C6) | Drug diffusion is limited to the implantation site. | [140] |
| 5-FU | PLGA | Microspheres | Orthotopic glioma rats (C6) | Decrease mortality | [141] |
| Bucladesine | PLGA | Pellets | Clinical GBM patient | Delay of recurrence | [142] |
| n-butyliden-ephthalide | Polyanhydride | Wafer | In Vitro GBM cell line | Increased the survival rate and inhibited tumor invasion. | [28] |
| *TMZ* | MPC | Nanostructures from the block | Orthotopic GBM mice (U87 and T98) | 2- to 19-retention times longer than that of free TMZ. | [143] |
| Idarubicin | PLGA, PGACL | Wafer | In vitro (U87MG cell line). | High inhibition of proliferation | [144] |

(*Continued*)

**Table 1** (Continued).

| | | | | | | |
|---|---|---|---|---|---|---|
| Paclitaxel | PLGA, PEG | NP | Orthotopic GS rats (9L) | Delayed tumor growth and enhance drug distribution | | [145] |
| Camptothecin | EVAc | Particles | Orthotopic GS rats (9L) | Significantly extended survival | | [66] |
| Doxorubicine | PLA, BEP | Patch | Orthotopic U87-MG canine | Suppressed tumor volume and enhanced survival rate | | [146] |
| **Multiple Agents** | | | | | | |
| **Concurrent Different Chemotherapy Agents** | | | | | | |
| **Therapeutical Agent** | **Type of Polymer** | **Structure of Polymeric Vehicle** | **In vivo/in vitro Model** | **Treatment Outcome** | | **Ref.** |
| BCNU, Cisplatin, Irinotecan | PLGA | Nanofiber | Orthotopic glioma rats (C6) | Prolong survival and reduced the malignancy | | [42,43] |
| Emozolomide, Etoposide | PLGA/PEG | MP/ paste | Orthotopic GS rats (9L) | Significant overall survival benefit | | [44] |
| **Combined Other Biotherapeutic Agent** | | | | | | |
| **Therapeutic Agent** | **Biotherapeutic Agent** | **Type of Polymer** | **Structure of Polymeric Vehicle** | **In vivo/in vitro Model** | **Treatment Outcome** | **Ref.** |
| BCNU, Cisplatin, Irinotecan | Antiangiogenic (Combretastatin) | PLGA | Bi-layered NM | Orthotopic GS, glioma rats (9L, F98) | Prolong survival and reduced tumor progression and malignancy | [46,86] |
| BCNU, TMZ | $O^6$-BG | PLGA | Hybride -structured NM | Orthotopic glioma rats (9L, F98) | Prolong survival and reduced tumor progress and malignancy | [35,36] |
| Irinotecan | Metformin | PLGA | NP | In vitro GBM cell (U-87) and Orthotopic GBM mice (U87) | Significantly reduced the volume of extracted cancer | [90] |
| None | T-lymphocyte-associated antigen 4 (a-CTLA-4) and programmed cell death-1 (a-PD-1) | Poly(β-L-malic acid) | NP | Orthotopic GBM mice (GL261) | Effective GBM treatment via activating immune response. | [47] |
| None | Several anti-GBM genes (Robo1, YAP1, NKCC1, EGFR, and survivin) | PBAE | NP | Orthotopic mice model of human GBM cell | Leads to high GBM cell death, reduces GBM migration | [48] |
| None | siRNA, linear DNA, and circular DNAs | PBAE | NP | In vitro, GBM 319 cells | Increase delivery of both DNA and siRNA | [147] |

(*Continued*)

**Table 1** (Continued).

| | | | | | | |
|---|---|---|---|---|---|---|
| None | Binimetinib | Poly(butadiene-b-ethylene oxide) | Polymersomes | In vitro BBB model | Cross the in vitro BBB model | [148] |
| None | siRNA | Chitosan | NP | Orthotopic mice model (GL261) | Targeting Gal-1 gene, effective treatment of GBM | [149,150] |
| None | Curcumin | PLGA Chitosan | NP | RG2 rat glioma model | Tumor size decreased significantly | [91] |
| Paclitaxel | Curcumin | PLGA | MNP | Orthotopic mice model (U87) | Prolong survival and reduced tumor size | [121] |

**Abbreviations:** GBM, glioblastoma multiforme; GS, gliosarcoma; PLGA, poly(L-lactide-co-glycolide); PGACL, poly(glycolide-co-ε-caprolactone); PBAE, poly(beta-amino ester); PEG-PLA, poly(ethylene glycol)-poly(L-lactic acid); MPC, 2-methacryloyloxyethyl phosphorylcholine; EVAc, ethylene-vinyl acetate co-polymer; MP, microparticle; NM, nanofibrous membrane; NP, nanoparticle; BEP, biodegradable electronic patch.

## Monotherapies

BCNU is considered to be the most effective systemic chemotherapy for MG and has been widely used for local chemotherapy. Studies have incorporated BCNU into both PLGA[39,62,63] and copolymers, such as poly-CPP-SA[64] and poly(ethylene glycol)–poly(L-lactic acid) (PEG-PLA)[58] fibers, for the controlled release of anticancer agents. In a previous study, the antitumor activity of BCNU-loaded fibers was consistently high throughout the experimental process whereas that of pristine BCNU diminished within 48 h. These results suggest that BCNU/PEG-PLLA fibers provide the sustained release of BCNU and are suitable for chemotherapy after the surgical removal of brain tumors.[58]

Some chemotherapy agents that cannot effectively pass through the BBB have been incorporated into polymers for interstitial MG chemotherapy. These chemotherapy agents, such as doxorubicin, rapamycin, and bucladesine, have been used to effectively treat cancers other than MG. Rapamycin was loaded into biodegradable caprolactone–glycolide (35:65) polymer beads at 0.3%, 3%, and 30% loading doses and implanted intracranially. Dose-escalating rapamycin bead treatment had a significant increase in survival relative to orthotopic glioma controls in rats.[65] Camptothecin was loaded into a controlled-release polymer (ethylene-vinyl acetate copolymer), and its efficacy was tested in 9L gliosarcoma orthotopic rats. Survival was significantly extended only when camptothecin was delivered locally through a polymer; camptothecin that was injected directly into the tumor through systemic administration did not extend survival.[66]

Irinotecan, a topoisomerase I inhibitor, is effective in treating many malignancies, including fluorouracil-resistant colorectal cancer. The potent chemotherapy agent 7-ethyl-10-hydroxycamptothecin (SN-38) is the active metabolite of irinotecan and is approximately 100–1000-fold more potent than irinotecan.[33,67] However, inherently poor aqueous solubility and inherent instability at pH > 6 hamper the direct utility of SN-38; consequently, several pro-drug, polymer-conjugated micelles, fibers, particles, and implants were investigated to improve SN-38's biopharmaceutic properties.[67] SN-38 has been loaded into various polymers, including PLGA,[33] NK-012,[68] PLEC,[69] and PCL/GT,[70] for local delivery. These drug-loaded polymers exhibited superior antitumor properties in vitro[70] and in an orthotopic animal model.[33,68,69] Furthermore, SN-38 was embedded into 50:50 biodegradable PLGA microparticles through the electrospraying technique and stereotactically injected into the tumors of F98 orthotopic glioma rats. The study outcomes demonstrated the significant treatment benefits of SN-38-incorporated PLGA microparticles with respect to extended survival, decelerated tumor growth, and attenuated malignancy.[33]

## Multiagent Treatments

Due to the heterogeneity of cancer, treatment with a single agent is usually insufficient for suppressing cancer growth and metastasis. In a previous study, single-agent chemotherapy was only marginally effective in treating rare human malignancies.[71] To reduce chemoresistance, studies have investigated several chemotherapy

agents with different tumor-inhibiting mechanisms.[8,71,72] Special groups of biopharmaceutical agents that comprise, for example, chemotherapy agents, antiangiogenic agents, cytotoxin, and peptides, have been concurrently administered for immune and gene therapy. Studies have demonstrated that the concurrent delivery of various biotherapeutic molecules with different physiochemical properties to tumor sites reduces the required dosage of chemotherapy agents and achieves synergistic therapeutic effects in treating cancers,[73,74] thus minimizing dose-related side effects and preventing or delaying drug resistance.[75,76] Further studies and clinical trials in patients with glioblastoma are required to determine the optimal combination therapies that overcome drug resistance.[76]

The regimen of administering a chemotherapy agent at a relatively low, minimally toxic dosage for prolonged periods with no extended drug-free interval is called periodic chemotherapy.[77] Using a human melanoma xenograft model, Wedge et al demonstrated that the prolonged administration of $O^6$-benzylguanine ($O^6$-BG) in combination with TMZ can increase the therapeutic index of TMZ.[35,78,79] However, high drug toxicities and the associated side effects are caused by strategies such as combining different biopharmaceutical agents, increasing the targeted area concentration, and prolonging the treatment.

Because cancer is complex, combination chemotherapy is required to treat brain tumors. Formulated to treat MGs (particularly GBM, gliomas, and astrocytomas), the PCV regimen necessitates a complex treatment procedure, comes with a high drug toxicity, and yields only marginal therapeutic benefits.[41,42] To address this problem, Tseng et al adopted biodegradable nanofibrous membranes (NMs) to concurrently distribute three chemotherapy agents with different therapeutic mechanisms in one procedure to treat surgically resected gliomas;[42] this method was more effective than the PCV regimen for treating MG. Smith et al.[44] used a blend of PLGA and PEG paste and combined TMZ and etoposide to treat high-grade glioma following surgical removal. The experimental results suggested a significant overall improvement in survival among postoperative 9L gliosarcoma–bearing rats treated with intracavity-delivered PLGA/PEG/TMZ/etoposide and adjuvant radiotherapy. The PLGA/PEG paste may also serve as an outstanding platform for the combinatorial delivery of molecular-targeted compounds.

## Combined Treatments with Nonchemotherapy Bioactive Agents

### Antiangiogenetic Agent

MG characteristically exhibits vigorous but improper neovascularization (angiogenesis); it has thus received extensive attention as part of the development of anti-angiogenic therapeutic strategies for MG. The suppression of angiogenesis—that is, the gemmation of new capillaries from pre-existing vasculature, which is crucial in mature gliomas larger than a few cubic millimeters—is a highly promising treatment strategy that interferes with the growth of gliomas.[46,80–82] Furthermore, to curb drug resistance, clinicians may need to adopt antiangiogenic strategies that induce apoptosis or the death of neovasculates.[83,84] Tseng et al.[85,86] concurrently impregnated three chemotherapy agents (BCNU, irinotecan, and cisplatin) into 50:50 PLGA nanofibers and an antiangiogenic agent (combretastatin) into 75:25 PLGA nanofibers. Compared with C6 glioma–bearing rats treated without antiangiogenic agents, C6 orthotopic glioma rats treated with antiangiogenic agent-incorporated NMs exhibited retarded tumor growth and attenuated malignancy.

### Immunotherapy

Immunotherapy for brain gliomas is largely unsuccessful because inhibitor antibodies cannot cross the BBB. Galstyan et al.[47] used poly(β-L-malic acid), a natural polymer, to deliver covalently conjugated cytotoxic T-lymphocyte-associated antigen-4 and programmed cell death-1 antibodies to brain cancer cells, which led to local immune system activation and extended survival among intracranial GL261 GBM orthotopic mice. Moreover, their study demonstrated that the trans-BBB delivery of tumor-targeted polymer-conjugated checkpoint inhibitors is a valuable method for MG therapy that acts through the activation of the systemic and local privileged brain tumor immune response.[47]

### Gene Therapy

Gene therapy implicates the delivery of genes that treat cancer cells. Kozielski et al.[48] designed poly(beta-amino ester), a synthetic, biodegradable polymer, that simultaneously incorporates and transports hundreds of siRNA molecules to several anti-GBM genes (Robo1, YAP1, NKCC1, EGFR, and survivin). Their results demonstrated high GBM cell apoptosis, reduced GBM migration in vitro, and decreased tumor burden over time after

intratumoral injection.[48] The resistance of brain tumor cells to alkylating agents is managed by the DNA repair protein MGMT. $O^6$-BG irrevocably deactivates MGMT through contestation with $O^6$-methylguanine, thus elevating the therapeutic sensitivity and activity of alkylating agents.[35,37] Liu et al.[35,36] developed HSNMs that enable the transporting of $O^6$-BG prior two alkylators (BCNU and TMZ) and provide the sustained release of drugs for >8 weeks. The HSNMs were inculcated into the tumor cavity of F98 glioma–bearing rats through surgery. The HSNM-treated group exhibited a decelerated glioma growth rate and extended mean survival time compared with the rats treated with an intraperitoneal injection of $O^6$-BG in combination with surgical transplantation of carmustine wafer and oral TMZ.

### Other Nonchemotherapy Agents

Metformin, 1,1-dimethylbiguanide hydrochloride is used as first-line medication for type II diabetes mellitus. A recent investigation reported that the drug possesses anticancer properties against many types of tumors, including those associated with colon, breast, prostate, and pancreatic cancers; leukemia; melanoma; lung and endometrial carcinoma; and gliomas.[55] Metformin treatment has been demonstrated to reduce the proliferation rate of tumor-initiating cell-enriched cultures, which were isolated from four human GBMs.[55,87] The administration of a high dose of metformin combined with TMZ inhibited fatty acid synthase expression in an orthotopic model. The inhibition of fatty acid synthase might be a potential therapeutic target of GBM.[88] The radiosensitizing effects of metformin on glioblastoma cells treated with irradiation and TMZ in vitro was consistent in terms of G2/M arrest and changes in pAMPK levels.[89] Nevertheless, the systemic administration of high-dose metformin results in severe hypoglycemia. The local delivery of metformin using a polymer is an alternative treatment strategy. Taghizadehghalehjoughi et al developed irinotecan- and metformin-loaded PLGA nanoparticles (NPs) and tested them on U-87 MG glioblastoma cells and on an animal model to evaluate their efficacy in GBM treatment. Their results demonstrated that metformin- and irinotecan-loaded PLGA NPs significantly decrease the volume of extracted cancer.[90] Curcumin (CCM) has shown promise for the treatment of GBM in experimental models. CCM-loaded chitosan-PLGA NPs modified with sialic acid were reported to efficiently traverse the BBB and subsequently inhibit the proliferation of glioblastoma cells.[91]

## Thermal Therapy

The prognosis of glioma is still poor despite advances in radiotherapy techniques.[92] Glioma resistance to chemoradiation therapy may partly result from the hypoxic area within the tumor.[92,93] Hypoxic cells have great potential because they can infiltrate into the brain tissue and locally extend the tumor. Hyperthermia therapy (HT) is a recognized treatment modality that can sensitize tumors to the effects of radiotherapy (RT) and chemotherapy by heating tumor cells to 40 to 45°C.[93–97] Specifically, intralesional temperature is monitored throughout HT using MRI thermometry, which offers visual indications of temperature over a definite period; the high temperature induces cell death, usually at 43°C for 10 min.[98,99] Magnetic resonance imaging–guided laser interstitial thermal therapy was demonstrated to be safe and effective in selected patients with GBMs and may add an average of 2 months to the patient's life expectancy relative to the current standard of care.[100] Li et al.[101] reported a nanotherapeutic vehicle established on bis-diketopyrrolopyrrole conjugated polymer (PBDPP) NPs with remarkable near-infrared (NIR) absorption at 808 nm and high photothermal energy conversion efficiency up to 60%. Their results revealed that the precise glioblastoma-specific capability and killing ability of glioblastoma cells can be effectively realized in vitro by dealing with only PBDPP NPs to incur cell apoptosis or by interacting with PBDPP NPs under NIR laser irradiation to trigger cell necrosis.[101] Antiglioma efficacy can be enhanced by coupling HT with chemotherapy[102] and radiotherapy.[103] Although the literature is limited by small sample sizes and the dominance of retrospective studies, HT is considered a safe and effective treatment for brain lesions when applied in the correct patient population.[95,104,105]

# Strategies for Enhancing Efficacy at the Target Site

Nanoscale drug delivery systems have demonstrated outstanding potential in delivering drugs through the BBB with minimal side effects. Nanoparticles and nanofibers, especially those measuring approximately 100 nm, are likely to be advantageous because they are absorbed by cells at rates 15–250 times faster than those of microparticles and microfibers.[106–109] Furthermore, the nanocarrier surface can be functionalized with molecules, such as therapeutic agents, peptides, antibodies, and RNA aptamers, and macromolecules can be bound to receptors

appearing at the endothelial cell surface of the BBB. This ensures that the nanocarriers can penetrate the BBB and subsequently deliver biomacromolecules to the brain for the treatment or imaging of neurological disorders. During the imaging and treatment of brain tumors, nanocarriers can serve theranostic purposes as both an MRI-based contrast agent and a radiosensitizer.[110–112]

In our previous study, we developed biodegradable PLGA NMs to incorporate BCNU; the in vivo drug concentration results revealed that BCNU-loaded NMs consistently released high levels of BCNU into the cerebral cavity of rats over a 6-week period (Figure 4A).[39] Moreover, we concurrently embedded three chemotherapy agents (namely BCNU, irinotecan, and cisplatin) with different mechanisms into PLGA NMs, and the results revealed that anticancer drug-eluting PLGA nanofibers can promote the sustained and concurrent transport of various chemotherapy agents into the brain parenchyma, thus strengthening the efficacy of MG therapy and avoiding the influence of toxicity from a systemic regimen of chemotherapy agents.[42,43] Furthermore, we concurrently embedded three chemotherapy drugs (namely BCNU, irinotecan, and cisplatin) into 50:50 PLGA nanofibers and added an antiangiogenic agent (combretastatin) to 75:25 PLGA nanofibers to fabricate double-layer NMs. The chemotherapy agents were swiftly eluted from the 50:50 PLGA nanofibers after surgical implantation, and combretastatin was eluted from the 75:25 PLGA nanofibers approximately 2 weeks later. All drug levels were higher in the brain tissues than in the blood for >8 weeks (Figure 4B).[86] The double-layered NM was surgically implanted into C6 glioma–bearing rats. The efficacy of the double-layer NMs was empirically indicated by, for example, attenuated malignancy, retarded tumor growth, and prolonged survival in glioma-bearing rats (Figure 4D).[46] Furthermore, we used 50:50 PLGA to embed $O^6$-BG and developed nanofibers with a core–sheath and used 75:25 PLGA to load BCNU and TMZ; we also exploited single-strain nanofibers. The two types of nanofibers were merged to form HSNMs. The biodegradable HSNMs sequentially and sustainably transported high levels of $O^6$-BG, BCNU, and TMZ over 14 weeks (Figure 4C). HSNM treatment yielded therapeutic advantages with regard to retarded and restricted tumor growth, prolonged survival time, and attenuated malignancy in rats with orthotopic glioma (Figure 4D).[35,36] Biodegradable

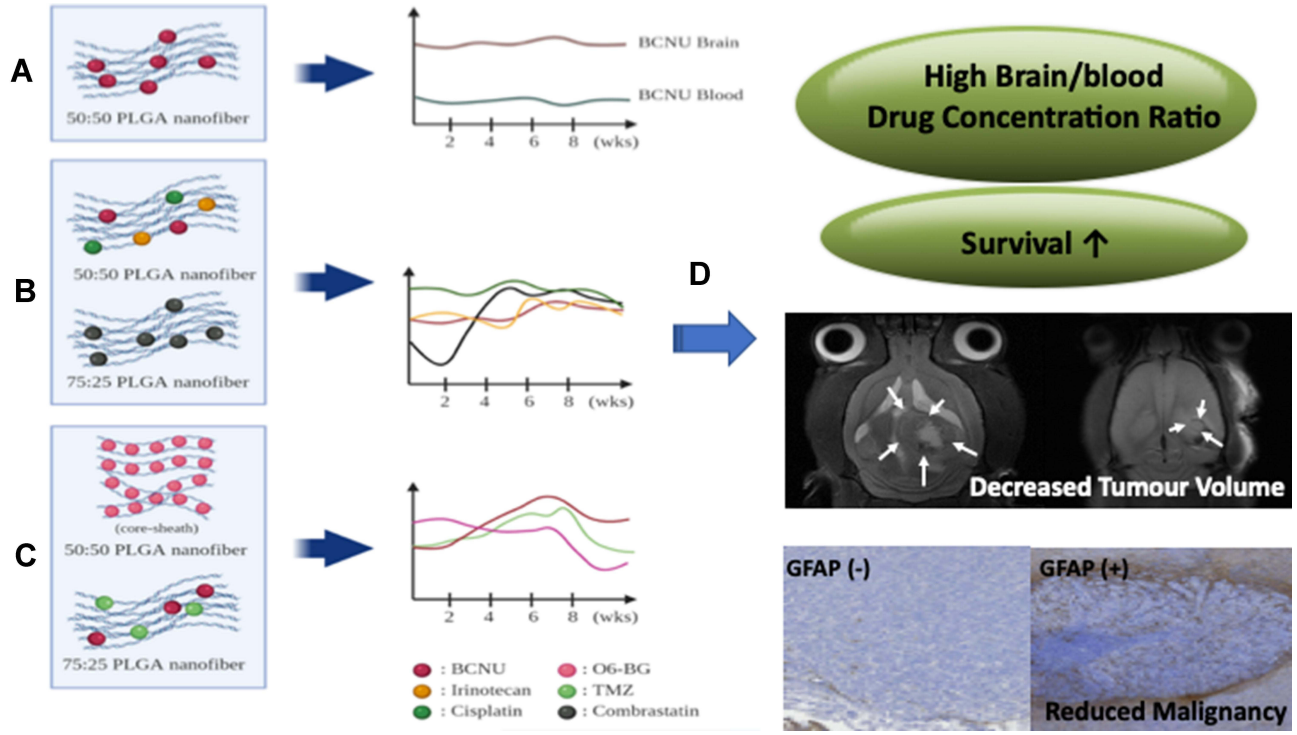


**Figure 4** (**A**) Sustained release of a single chemotherapy agent (BCNU) from 50:50 PLGA nanofibrous membranes (NMs). (**B**) Sequential release of three chemotherapy agents (BCNU, irinotecan, and cisplatin) from 50:50 PLGA NMs followed by release of an antiangiogenetic agent (combrastatin) 75:25 PLGA NMs. (**C**) Sequential release of $O^6$-BG from 50:50 PLGA NMs followed by release of two alkylating agents (BCNU and TMZ) from 75:25 PLGA NMs. (**D**) Contribution of NMs of different designs to antiglioma efficacy in an orthotopic animal model.

anticancer-drug-loaded nanofibers can enhance therapeutic efficacy and minimize systemically toxic effects. These drug-loaded NMs require only short-term hospitalization, incur low costs from hospitalization and drugs, and improve the patient's quality of life.

## Strategies to Promote Drug Delivery Across the BBB

Many novel strategies have been developed for effective drug delivery. Intravascular (generally intravenous) infusion is a common route for NP administration into the CNS. Injected NPs are rapidly cleared from the circulation, leading to a short retention time and consequently reduced BBB permeability. Studies have estimated that, at best, <5% of initially administered NPs reach the CNS.[113–115] The augmentation of NP surfaces with a variety of ligands can increase BBB penetration through transport- and receptor-mediated transcytosis or through increased particle retention in circulation.[114] Targeting NPs through an externally applied magnetic field enhances NP retention in the CNS. Focused ultrasound (FUS) is a potential means for the targeted delivery of diagnostic or therapeutic particles to the brain without damaging surrounding normal tissues (Figure 3B). Table 2 presents the mechanism, advantages, and limitations of advanced local delivery and systemic delivery (with magnetic and FUS-assisted techniques).

### Surface-Decorated NPs

Transferrin-containing gold NPs can reach the brain parenchyma through systemic administration in mice via a receptor-mediated transcytosis pathway.[116] Studies have conjugated Angiopep-2 (ANG), a cell penetrating peptide, to NPs of iron and gold; the ability of the ANG-Fe-Au NP conjugate in restricting glioma growth through magnetic field–induced hyperthermia has then been assessed.[99,114] Increasing NP retention in the circulation may facilitate brain uptake through ligands such as PEG, thus reducing NP opsonization and sequestering the reticuloendothelial system.[117] Recently, zwitterionic materials were developed as alternatives to PEG to prolong the circulation of NPs without triggering an immune response.[117] Chen et al.[118] reported that PEG-coated PLGA nanoparticles had

**Table 2** Comparison of Advanced Local Delivery with Systemic Delivery Methods for Treating MG

| | **Advanced Local Delivery** | **Nanoparticle** | **Surface-Decorated Nanoparticle** | **Magnetic Assisted Nanoparticle** | **Focused Ultrasound** |
|---|---|---|---|---|---|
| Mechanism | Bypassing BBB | Open BBB | Open BBB<br>Increase retention | Increase retention of MNPs | Increase permeability of BBB |
| Transport | Direct release of agents into tumor site | Through BBB | Open BBB | Tumor vascularity change → allow NP cross BBB | Transient disruption of BBB |
| Administration route | After tumor resection<br>Intratumoral injection* | Intravascular<br>CED* | Intravascular<br>CED* | Intravascular<br>CED* | Intravascular<br>CED* |
| Systemic toxicity/ side effect | Less | As systemic administration | As systemic administration | As systemic administration | As systemic administration |
| Efficacy | 100 | 0.5–4.3% | 0.8–21.2% (1.91–4.93 fold higher than NP) | 3.6–12 fold higher than NP | 2–10 fold retention than NP |
| Limitation | Short diffuse distance | Small size (15–20 nm) is preferred | Small size (15–20 nm) is preferred | Large nanoparticles (>100 nm) may be difficult to target MGs | Need image guided Small size (15–20 nm) is preferred |

**Note:** *Need minimal operation- burr hole.
**Abbreviations:** MNP, magnetic nanoparticles; CED, convection-enhanced delivery.

a penetration of 8.2%–21.2%, which was better than that of PLGA nanoparticles (4.3%).

## Magnetic Assistance–Based Techniques

The magnetic characteristics of magnetic nanoparticles (MNPs) distinguish them from typical NPs. A synergetic drug transport strategy was formulated in previous studies, and it offered an approximately 3.4-fold enhancement of the drug's half-life (from 18 to 62 h) and significantly extended the median survival rate of animals that received a low dose of BCNU relative to animals that received a high dose of free BCNU (63 days for those that received 4.5 mg/kg BCNU delivered through the nanocarrier vs 50 days for those that received 13.5 mg of free BCNU). This strategy enhances the potential of magnetic targeting treatment in clinical implementations of cancer therapies.[119,120] A transferrin receptor–binding peptide T7–modified PLGA MNP system was prepared through the co-encapsulation of combination of two drugs (paclitaxel and curcumin) in hydrophobic MNPs. This dual-targeting, codelivery-MNP system provides synergistic effects in the inhibition of tumor growth and serves as a potential strategy for both delivering drugs to the brain and improving antiglioma efficacy.[121] Moreover, the distinct magnetic characteristics of MNPs can be leveraged to induce local hyperthermia through safely employing magnetic fields in thermotherapy and magnetically targeting malignant brain cancers.[99,122,123] Imaging findings have indicated that MNPs contribute to a 3.6–12-fold increase in MNP accumulation in brain tumors.[121,124–126]

## FUS-Assisted Techniques

The application of FUS sonication where microbubbles appear can temporarily disrupt the BBB and increase its permeability. FUS sonication is an early-stage, noninvasive therapy with the potential to reduce the cost of treatment and improve quality of life for patients with brain tumors. The oscillation and destruction of microbubbles and microstreaming and the characteristics of radioactive forces are the most crucial parameters for transiently rupturing vascular barriers to increase the tumor's vascular permeability.[127] This noninvasive technique enables the extent of drug delivery to be adjusted through repeated treatment and through controlling the length of sonications and intervals between them.[128] Furthermore, repeated pulsed high-intensity focused ultrasound (HIFU) can be used to selectively transport high doses of atherosclerotic plaque-specific peptide-1 (AP-1)-conjugated liposomes to brain tumors. Moreover, the integration of repeated pulsed HIFU with both AP-1 liposomal doxorubicin and untargeted liposomal doxorubicin has exhibited similar antitumor effects.[128–130] Previous studies have demonstrated that transcranial FUS exposure significantly increases permeation into the BBB by 2–10 times.[131–133] Compared with 3- and 120-nm NPs, medium-sized (15 to 20 nm) NPs had the highest delivery efficacy.[133,134]

FUS and magnetic targeting have been synergistically employed to increase BBB permeability and the retention of chemotherapeutic or other biotherapeutic agents. Liu et al used epirubicin-embedded MNPs to treat tumor-bearing animals. Epirubicin transport through the BBB and accumulation in brain tumors were significantly strengthened by combining FUS-assisted and magnetic assistance–based therapies to target epirubicin MNPs.[135] Li et al developed polysorbate 80–modified paclitaxel-loaded PLGA NPs and enhanced local delivery into the brain for glioma treatment using FUS, resulting in significantly stronger antiglioma efficacy and increased survival time in tumor-bearing mice.[136]

# Conclusion

Biodegradable drug delivery carriers, especially nanoscale variants, can allow drugs to bypass the BBB, thus increasing the local concentrations of drugs at targeted sites of action to effective levels and reducing systemic adverse effects. Many immunotherapies and gene therapies have also been formulated for multimodal MG treatment. However, macromolecules (eg, antigens and antibodies, genes, peptides, and nucleic acid) in these therapies cannot directly penetrate the BBB and are sensitive to physical (temperature) and chemical (eg, solvent and pH) factors, making the choice of the delivery vector vital. By using multiple chemotherapy agents in combination with different tumoricidal mechanisms or by adopting gene therapy and immunotherapy in the form of monotherapy or combinatorial therapy through concurrently loaded biopharmaceutical agents onto polymeric carriers, we may be able to overcome chemoresistance and offer more effective treatments.

NPs possess tremendous potential as drug delivery systems. Surface decoration of NPs can increase retention time in circulation and promote their uptake, the application of an external magnetic field can increase MNP accumulation in the targeted site (the brain), and FUS helps NPs to cross the BBB. All these treatment strategies help drugs permeate the BBB, and they are particularly valuable for patients who are unable to withstand a major

operation or whose lesions are deep-seated and challenging to remove safely. Moreover, the treatment of malignant brain tumors through local hyperthermia is possible through the use of MNPs with the aid of pulsed HIFU or an external magnetic field. These technologies can be used in monotherapy or combined therapy for more effective treatment. MNPs not only serve to enhance tumor contrast in MRI but also offer targeted drug delivery, controlled release, and the induction of hyperthermia.

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## Disclosure

The authors declare no conflicts of interest.

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