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Review

Glioblastoma multiforme: a glance at advanced therapies based on nanotechnology

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ABSTRACT

Glioblastoma multiforme (GBM, grade IV) is the most common malignant and invasive central nervous system tumor with poor survival outcome. Various pathogenesis signatures such as genetic mutation, hypoxia, necrosis and neo-angiogenesis are involved in GBM. Standard treatment includes surgical resection along with radiation therapy and temozolomide (TMZ) chemotherapy that do not improve the overall survival of patients. In this review, we focused on the diagnosis, risk factors and novel therapies, using advanced therapies such as nanotechnology in drug delivery, gene therapy and hyperthermia that have promising roles in the treatment of aggressive brain tumors.

Keywords: Brain tumor; neuro-oncology; glioblastoma; nanotechnology

1. Introduction

Benign, malignant and metastatic brain lesions are different types of brain tumor with various effects on the patients' quality of life.[1] According to the World Health Organization's (WHO) classification, brain tumors are divided into primary and secondary.[2–4] Every year, in the United States approximately 51000 patients are diagnosed with primary brain tumors.[5] Glioma tumors arise from the glial cells, namely the astrocytes, oligodendrocytes and ependymal cells that account for 30% of all primary brain tumors.[6] In adults, common primary tumors are astrocytoma, meningioma, and oligodendroglioma, while secondary brain tumors are metastatic ones that originate from the lung, breast, kidney, skin cancers, etc.[2–4] GBM is the most malignant and aggressive primary brain tumor with poor survival outcome (~15 months), representing 40–65% of the glioma tumors.[1,7–9] Annually, 3.19 per 100,000 individuals are diagnosed with GBM tumor around the globe with higher incidence rate among the males and non-Hispanic whites.[10–12] GBM is known by high cell growth, necrosis, angiogenesis, high cell density, atypia, low survival, high rates of recurrence, and resistance to chemo-radio therapy.[4,6,9]

As to the diagnosis, the neurologic tests such as vision, hearing, alertness reflexes, magnetic resonance imaging (MRI), computed tomography (CT) scan, angiogram, spinal tap, and biopsy were carried out.[13] Today, treatment modalities for GBM are a combination of surgery, radiation therapy, and chemotherapy; however, the mortality rate is approximately 90%.[8,9]

2. Risk factors

Genetic and environmental factors affect GBM, such as ionizing radiation, a well-known risk factor, and some genetic diseases can also lead to GBM, namely neurofibromatosis type 1 and 2, tuberous sclerosis, Li-Fraumeni syndrome, turcot syndrome type 1 and 2, Von Hippel-Lindau disease, and retinoblastoma.[14–16] It has demonstrated that environmental exposure including vinyl chloride, pesticides, smoking, petroleum byproducts, synthetic rubber manufacturing, infection with simian virus 40, and electromagnetic radiation are the other risk factors of GBM.[4,17,18]

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3. Standard therapy

The main reason why GBM is chemoresistance is rooted in its cancer stem cells (CSCs), or in particular glioblastoma stem cells (GSCs). These cells have stem cell-like properties and originate from the embryonic stem cells or downstream progenitors. GSCs are recognized via markers, including CD133, CD90, CD44, CD15, integrin-α6, L1 cell adhesion molecule (L1CAM), A2B5, sal-like protein 4 (SALL4), octamer-binding transcription factor 4 (OCT-4), SRY-Box 2 (SOX2), signal transducers, and activators of transcription (STAT3), NANOG, c-Myc, krüppel-like factor 4 (KLF4), nestin and glial fibrillary acidic protein (GFAP).[6,19]

Another cause of resistance to treatment is hypoxia (low O_2 partial pressure), which creates autophagy around the tumor. Hypoxia impression on cancer cells was revealed by vascular endothelial growth factor (VEGF) secretion from the hypoxic cells and angiogenesis; in addition, VEGF is upregulated with CD133+.[20,21] Autophagy occurs as a result of defect in nutrients or oxidative stress condition that kills the cells.[20]

Currently, surgical resection with or without radiation therapy and chemotherapy is considered as a standard treatment. Radiation therapy increases the survival time to approximately 12.1 months, and chemotherapy with TMZ improved it to 15.6 months. Tumor-treating fields (TTFields) deliver device is a technology, approved by Food and Drug Administration (FDA), for delivering low intensity and intermediate-frequency alternating electrical fields with TMZ chemotherapy into the GBM tumor, with overall survival reaching 20.5 months.[17] Furthermore, there are 3 years of survival time for 3-5% of GBM patients.[22,23] Systemic injection of drugs such as doxorubicin (DOX), paclitaxel (PTX) and cisplatin has not penetrated well to the central nervous system (CNS).[14]

The optimal treatment for GBM is surgical resection followed by radiation therapy along with adjuvant chemotherapy of TMZ. Regrettably, even with advanced surgical treatments, patients can survive up to 15 months.[5,17,24]

It should be mentioned that in addition to understanding the mechanism of GBM tumor formation, advanced technologies in medical therapy are necessary. We reviewed different aspects of cancer therapy through nanotechnology in drug delivery, gene therapy, and hyperthermia therapy (HT), as an advanced science:

4. Advanced therapies based on nanotechnology

A new approach which is of interest in recent years is the use of novel technologies for the treatment of diseases, which we will discuss as advanced therapies. To overcome the low effectiveness of standard therapies, the use of modern technologies in the context of medicine such as nanotherapies can be promising.

Nanoparticles (NPs)/nanomaterials, with submicron sized, have a wide range of applications and each have different properties.[25,26] They are capable of delivering anticancer drugs or genes into the tumor zone as a local or systemic rout.[27] Moreover, NPs are suitable for targeting the tumor cells as a carrier of therapeutic agents and tend to agglomerate within the tumor tissue for achieving more effectiveness of conventional therapies.[25,26] However, disadvantages including cytotoxicity, neurotoxicity, efficient delivery, short half-life and non-biodegradability have reduced the use of NPs in the clinic.[27] The graphical abstract of nanotechnologyapplications in GBM treatment showed in Figure 1.

4.1. Drug delivery

The blood-brain barrier (BBB) is a dominant obstacle against efficient chemotherapy that reduces the effective penetration of drugs into the brain and spinal cord. The BBB is created by the cerebral endothelial cells (CECs), pericytes, astrocytes, microglial cells, smooth muscle cells, and perivascular macrophages.[14,28] Blood-brain tumor barrier (BBTB) in brain tumors is displaced with CECs-originated BBB. To reach the brain tumor site, three paths exist: intracranial injection, intranasal administration, and intravenous administration.[6,14,28]

Nanoscience and nanotechnology are potent in curing illnesses and disorders. The use of nanotechnology has led to eradication of some of medical problems, namely insufficient drugs penetration into the brain, untargeted drugs in the tumor environment, and high dose of anticancer drugs. Accordingly, there are many NPs and nanocarriers that can be used to treat CNS disorders.[6] Nanostructures are employed in two ways: active targeting (ligand/receptor) and passive targeting (enhanced permeation and retention (EPR)).[14,28] Pores cutoff size of the healthy tissue vessels and tumor vessels are 4–25nm and 380–780nm, respectively.[14] Nanostructures in the size of <10 nm are cleared by the kidneys and 10–100nm reduced hepatic filtration in systemic rout administration.[14] We defined some nanomaterials as NPs or nanocarriers, as shown in Table 1, that are being used in research on GBM.

4.1.1. Polymeric nanoparticles

The biocompatible, biodegradable, natural and synthetic polymers are used as solid carriers. Poly-(butyl cyanoacrylate) (PBCA) nanocarriers have a small size, are simple to synthesize, can easily penetrate, and have *in vitro* stability and rapid

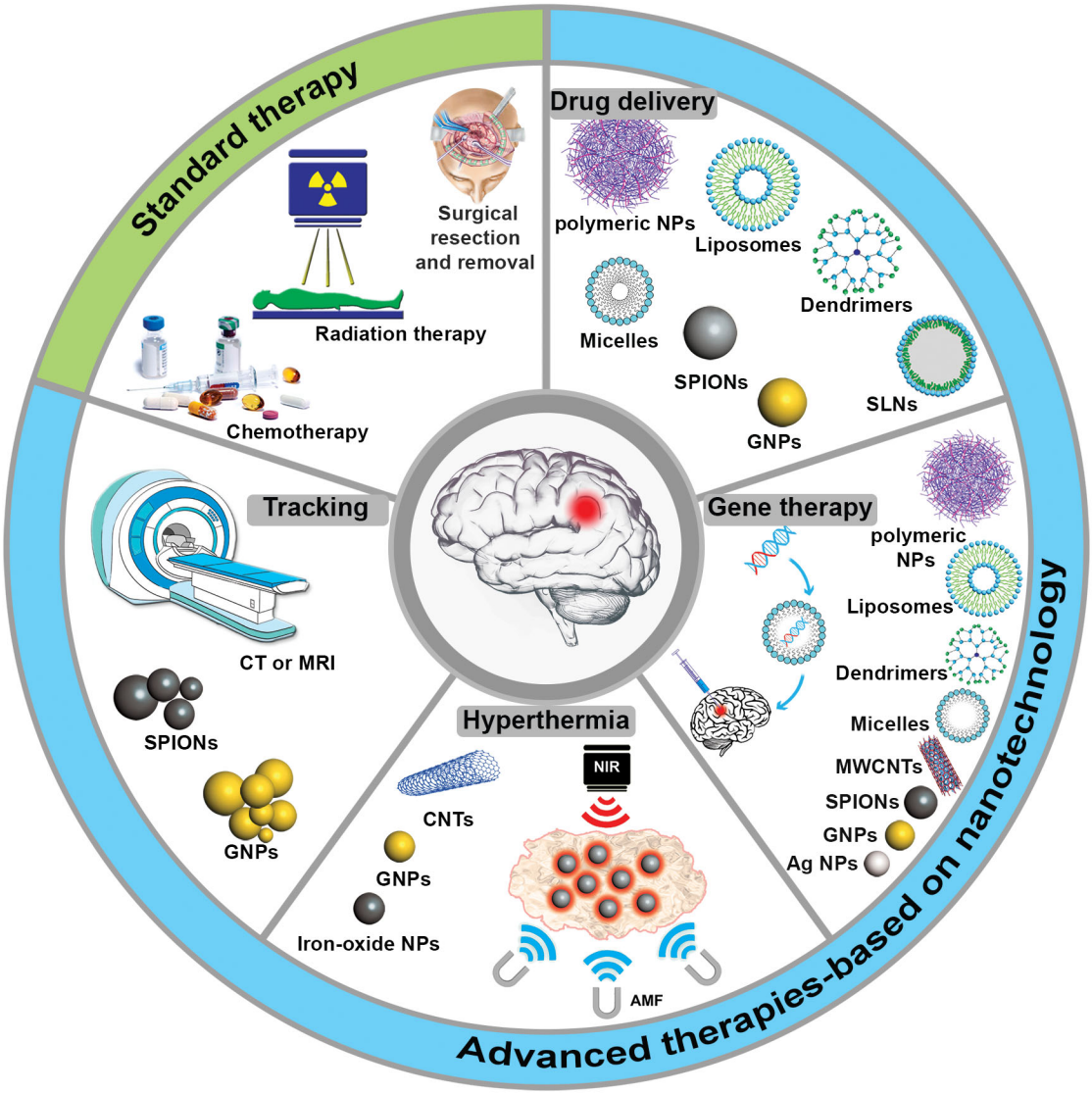

Figure 1. Graphical abstract.

clearance. To enhance the permeability from BBB, this particle is coated with polysorbate 80 and conjugated with apolipoprotein E.[32,49] Poly-(lactic-co-glycolic acid) (PLGA) is a biodegradable and biocompatible polymer, approved by FDA applied in drug delivery.[49] Molecular envelope technology (MET) polymers are engineered by N-palmitoyl-Nmonomethyl-N, N-dimethyl-N,N,N-trimethyl-6-O-glycol chitosan, and have amphiphilic properties in which drugs can load into these structures.[37] Some studies have been carried out using polymeric NPs, as shown in Table 1.[22,24,29,32–34,37,41,45,47,48]

4.1.2. Micelles

Micelles have the structure of amphiphilic copolymer with a hydrophobic core and hydrophilic surface. To improve passing from BBB, some ligands such as methoxy poly (ethylene glycol)-poly-(ε-caprolactone), poly-(ethylene glycol)-block-poly-(L-glutamic acid), poly-(ethylene glycol)-block-poly-(D, L-lactide acid), cholesterol conjugated polyoxyethylene sorbitol oleate (CPSO), and cyclic Arg-Gly-Asp (cRGD) have been conjugated to the micelles.[40,49]

4.1.3. Dendrimers

Dendrimers are branched and three-dimensional shapes.[49,50] Polyamidoamine (PAMAM) is an ethylene diamine core and have a repeated amido-amine branch structure. PEGylation (poly-ethylene glycol) of PAMAM causes prolonged circulation time and decreased toxicity. Nanoparticles with large size (>200 nm) are absorbed by Reticuloendothelial System (RES); hence, the small size of PEGylated PAMAM (<15 nm) are good particles to escape from RES.[51] These particles are able to deliver the drugs and genes, and brain tumors imaging. Due to their small size, retention of this structure in the brain

Table 1. Nano-based drugs used in GBM therapy; in vitro and in vivo.

Study	Drug(s)/chemical agent(s)	Nanoparticle/nanocarrier	Size	In vivo/in vitro	Outcome	Reference
Qian L et al. 2013	BCNU and O^6-BG	Chitosan Surface modified PLGA	177 nm	In vivo (F98 glioma-bearing rats) & in vitro	Inhibit growth GBM cells; increase survival time; suppress tumor MGMT level; decreased size of tumor Survival time was 23 days	29
Lim WM et al. 2014	ITZ	NLCs with polysorbate 80	313.7 ± 15.3 nm	In vivo (mice) & in vitro	Sustained release and increased the concentration of ITZ in the brain (target delivery)	30
Setua S et al. 2014	Cisplatin	Gold nanosphere (capping GNPs with human serume albumin and PEI)	51 nm in Average size	In vitro	Ablation of tumor cells	31
Ebrahimi Shahmabadi et al. 2014	Cisplatin	PBCA with polysorbate 80	489 nm	In vivo (rats) & in vitro	Increased bleeding; reduced side effect and toxicity Survival time was 19.6 days than 17.5 days for free drug	32
Nance et al. 2014	PTX	PEG-PLGA	70 nm	In vivo (rats) & in vitro	Inhibit growth GBM cells	33
Wang et al. 2015	PTX	PEG-PLGA conjugated with Pep-1 (a penetrating peptide)	95.78 ± 2.37 nm	In vivo (intracranial C6 glioma-bearing nude mice) & in vitro	Inhibit growth GBM cells; increased PTX delivery through IL-13Rα2 receptors Survival time was 32 days	34
Wu et al. 2015	VCR and TMZ	SLNs and NLCs	SLN ∼ 180 nm and NLC ∼ 120 nm	In vivo (BALB/c nude mice) & in vitro	VT-NLCs higher inhibition tumor growth efficacy than the VT-SLNs	35
Kuo et al. 2016	DOX	SLNs conjugated with aprotinin and melanotransferrin antibody	140–177 nm	In vitro	Enhanced crossing from BBB and inhibit growth GBM cells with sustained release	36
Fisusi et al. 2016	CCNU	MET polymeric NPs	336 ± 0.44 nm	In vivo (mice) & in vitro	Reduced liver deposition; decreased size of tumor Survival time was 33.2 days	37
Mu et al. 2016	PTX	Magnetic iron oxide NP conjugated with CD and CTX, loaded with fluorescein, and coated with PEG	Approximately 44 nm	In vitro	Killed tumor cells; cell apoptosis	38
Tseng et al. 2016	BCNU, irinotecan, and cisplatin	PLGA nanofibers	375 to 1200 nm	In vivo (rats)	Reduced Risk of mortality; reduced malignancy of C6 glioma Survival time was 60 ± 44.43 days	24
Shaw et al. 2017	DTX	Liposomes	45.9 ± 12.3 nm	In vivo (rats) & in vitro	Sustained release	39
Gao et al. 2017	DOX and HK	MPEG-PCL micelles	34 nm	In vivo (zebrafish & mice) & in vitro	Suppress proliferation of GBM; cell apoptosis; inhibit from angiogenesis	40
Maleki et al. 2017	MTX	PLGA NP	150-200 nm with 170 nm average	In vitro	pH sensitive (MTX release was increased in acidity	41

(*Continued*)

Table 1. (*Continued*).

Study	Drug(s)/chemical agent(s)	Nanoparticle/nanocarrier	Size	In vivo/in vitro	Outcome	Reference
					environment);cytotoxicity for GBM cells;sustained release	
Battaglia et al. 2017	MTX	SLNs conjugated with ApoE	350 nm	In vivo (Wistar and Fischer rats) & in vitro	Decreased of tumor volume growth; apoptosis	42
Wang et al. 2017	Curcumin and quinacrine	Liposomes modified by *p*-aminophenyl-α-d-mannopyranoside (MAN)	119.7 ± 0.17 nm	In vivo (imprinting control region mice) & in vitro	Inhibit growth of glioma cells and glioma stem cells; inhibit expression of Bcl-2 and activated p53, caspase-9, and caspase-3; apoptosis Survival time was 15–48 days	43
Ramachandran et al. 2017	TMZ	PLGA-PLA-PCL nanofiber (as an implant)	200-1400 nm	In vivo (orthotopic rats) & in vitro	Sustained release; apoptosis; inhibit growth and recurrence of tumor Survival time was >4 months	22
Irani et al. 2017	TMZ	Gold-coated by PCL-Diol-b-PU/Au composite nanofiber	18-23 nm by TEM 20-26 nm by DLS	In vitro	Sustained release of TMZ and high cytotoxicity against GBM cells	44
Hua et al. 2018	DTX	RVG29 peptide (specific ligand) conjugated to PEG-PLGA	116.5 ± 3.4 nm	In vivo (rats) & in vitro	The RVG29 is appropriate ligand for glioma targeting; apoptosis tumor cells Survival time was 42 days	45
Coluccia et al. 2018	Cisplatin	Spherical GNPs coated with PAA	7 nm	In vivo (NOD SCID Gamma mice) & in vitro	Inhibit growth GBM cells; DNA damages by γH2AX phosphorylation; and enhance permeation to BBB with magnetic resonance-guided focused ultrasound (MRgFUS)	46
Madala et al. 2018	DSF	PEG-PLGA nanoparticles	70-80 nm	In vivo (mice) & in vitro	Activation the MAP-kinase pathway leading to apoptosis; induced reactive oxygen species (ROS); Enhanced Permeability Retention (EPR)	47
Shirvalilou et al. 2018	IUdR	NGO/SPION/PLGA	71.8 nm	In vivo (Wistar rats) & in vitro	Increase effect of IUdR radiosensitizer; significant reduction tumor volume at present of magnetic field; Median survival time was 38 days	48

Abbreviation: BCNU-O^6-BG: Carmustine and O^6-Benzylguanine; PLGA: Poly (lactic-co-glycolic acid); GBM: Glioblastoma multiforme; MGMT: O-6-methylguanine-DNA methyltransferase: ITZ: Itraconazole; NLCs: Nanostructured lipid carriers; GNPs: Gold Nanoparticles; PEI: Polyethylenimine; PBCA: polybutylcyanoacrylate; PTX: Paclitaxel; PEG: Poly (ethylene glycol); VCR: Vincristine; TMZ: Temozolomide; SLNs: Solid lipid nanoparticles; VTNLC: Vincristine + temozolomide loaded to NLC; VTSLN: Vincristine + temozolomide loaded to SLN; DOX: Doxorubicin; BBB: Blood-brain barrier; CCNU: Lomustine; MET: Molecular envelope technology; CD: Cyclodextrin; CTX: Chlorotoxin; BCNU: Carmustine; DTX: Docetaxel; HK: Honokiol; MPEG: Methoxy poly (ethylene glycol); PCL: Poly (ε-caprolactone); MTX: Methotrexate; ApoE: Apolipoprotein E; PLA: Poly (lactic acid); PU: Polyurethane; TEM: Transition electron microscopy; DLS: Dynamic light scattering; RVG29: Rabies virus glycoprotein; PAA: Polyacrylic acid; DSF: Disulfiram; IUdR: 5-iodo-2-deoxyuridine; NGO: Nano-graphene oxide.

Table 2. Gene therapy-based nanocarriers used in GBM therapy.

Nanocarrier origins	Modified nanocarrier	Anticancer agents	Results	References
Micelles	R7L10 micelle	HSV-tk + TMZ	Apoptosis and dullness tumor growth	66
	PLA + PEG micelle	DTX + RGDyK	Dullness tumor growth	67
	Deoxycholic acid + PEI micelle	Curcumin + miR-21 antisense oligonucleotide	Tumor growth suppression	68
	ch-K*n*(s-s)R8-An micelle	Angiopep2 + Dbait	Apoptosis and radiosensitizer improvement	69
Liposomes	Cationic liposome (pilot study)	IFN-β	Decrement of tumor size, pyknotic, necrotic and apoptotic change	70
	Cationic liposome	hTRAIL + PTX + angiopep2	Apoptosis and survival improvement	71
	Paramagnetic cationic liposome	TNF-α + stress inducible promoter *gadd153*	Dullness tumor growth and decrement of tumor size	72
	LipoTrust	siRNA + TMZ	Dullness tumor growth and improvement of TMZ sensitizer by downregulation of MGMT expression	73
	SNALP	CTX + anti-miR-21 + sunitinib	Dullness tumor growth, decrement of tumor size, apoptosis and survival improvement	74
	Liposome (phase I/II clinical study)	HSV-tk + ganciclovir	Decrement of tumor size up to more 50%	62
PAMAM	PAMAM + Arginine	IFN-β	Apoptosis	75
	PAMAM + Tat peptide + BMNs	siRNA anti-EGFR	Dullness tumor growth and EGFR expression	76
	PAMAM + phenylalanine + histidine + arginine	Apoptin	Apoptosis	77
	PAMAM + Folate	ASODN	Tumor growth suppression, EGFR knock down and survival improvement	78
	PAMAM + PEG + transferrin	TRAIL	Apoptosis and survival improvement	79
Metallic NPs	Iron NP@PEI	dsRNA (ATN-RNA)	Decrement of tumor cells migration and cell death	80
	ION@PEG-PEI-chitosan	GFP + CTX	Targeted gene delivery and improvement of tumor cell uptake	81
	SPION@PEG-PEI	DOX + siRNA + PinX1	Decrement of tumor cell viability and suppression tumor growth	82

Abbreviation: HSV-tk: Herpes Simplex Virus-1 Thymidine Kinase; TMZ: Temozolomide; PLA: Poly (lactic acid); PEG: Poly (ethylene glycol); DTX: Docetaxel; RGDyK: arginine-glycine-aspartic acid-tyrosine-lysine; PEI: Polyethylenimine; Dbait: DNA double-strand breaks repair inhibitors; IFN-β: interferon beta; hTRAIL: human tumor necrosis factor-related apoptosis inducing ligand; PTX: Paclitaxel; TNF-α: tumor necrosis factor alpha; siRNA: Small interfering RNA; MGMT: O-6-methylguanine-DNA methyltransferase; SNALP: stable nucleic acid lipid particle; CTX: chlorotoxin; PAMAM: Polyamidoamine; BMNs: bacterial magnetic nanoparticles; EGFR: Epidermal growth factor receptor; ASODN: antisense oligonucleotides; IONs: iron oxide nanoparticles; GFP: Green fluorescent protein; SPION: Super paramagnetic iron oxide nanoparticle; DOX: Doxorubicin; PinX1: PIN2-interacting protein 1.

is weak.[50] The conjugation of drug-dendrimer showed fast drug release profile in low acidic pH and stable in the physiological environment. To improve the crossing from BBB, angiopep-2 is conjugated with dendrimer, and to enhance retention in tumors, CREKA (cysteine-arginine-glutamic acid-lysine-alanine) is conjugated with PEGylated PAMAM; also, to overcome BBTB, dendrimers were modified with interleukin 13 receptor α2 (IL-13Rα2) mediated endocytosis; also, glioma homing peptides (Pep-1) conjugated with PEGylated PAMAM were reported.[49–51]

4.1.4. Liposomes

Liposomes are phospholipid bilayers with an aqueous core, applied in drug delivery. They are able to pass from the blood vessel (6–9 µm in diameter) into the targeted tissues.[49] They can carry on both hydrophilic and hydrophobic therapeutics to GBM cells with good biocompatibility. To reduce rapid opsonization and low transportation of the therapeutics rate of liposomes, they are coated with poly (ethylene glycol) (PEGylation) and conjugated with targeting ligands.[49] Two kinds of treatment strategies are mentioned in Table 1.[39,43]

4.1.5. Solid lipid nanoparticles (SLNs)

Solid Lipid Nanoparticles, aqueous colloidal surface with the hydrophobic core, are appropriate for delivering therapeutic agents to the GBM cells.[36,49] Biocompatible polymers such as stearic acid (SA), stearylamine, triglycerides were used to make SLNs.[49,52] These particles can overcome solubility, permeability and toxicity problems.[52] SLNs are a suitable alternative to liposomes.[53] Advantages of

SLNs included good biocompatibility, degradability and large surface for functionalized to brain targeting, and its disadvantages were hydrophobicity and fast clearance by RES.[49] Moreover, several results of studies on SLNs are shown in Table 1.[35,36,42]

4.1.6. Nanostructured lipid carriers (NLCs)

NLCs are the second generation SLNs.[30] NLC is fabricated via blending lipids with solid and liquid states.[35] NLCs have overcome the problems of instability and low loading capacity of therapeutic agent, belonging to SLNs.[30] The study results have revealed the persistent therapeutic effect of NLCs as well as the capability of tumor cell growth inhibition in comparison with SLNs.[35]

4.1.7. Gold nanoparticles (GNPs)

To reduce the side effects of radiation therapy, sensitized tumor tissues by reducing its effects on normal tissues, high atomic number elements such as gold (Au) and platinum have been proposed as a sensitizer to radiation.[54] Gold nanoparticles were discovered more than a century ago with unique properties such biocompatibility, very low toxicity, high atomic number, and high X-ray absorption coefficient, proving its feasibility in theranostic applications.[55]

Multifunctional nanoparticles (NPs) such as GNPs have a high capacity for photoelectric interactions at lower energy levels. They can increase the effect of radiation therapy by increasing the absorption of energy in the tumor tissue.[54] Application of GNPs in combination with ionizing and non-ionizing radiation significantly improved the effects of radiation therapy. Due to surface plasmon resonance, they have been able to convert non-ionizing radiation into heat, which plays a significant role in HT treatments. Also, they can be chemically modified to selectively target the tumors, which renders them suitable for advanced cancer therapies.[56] In comparison with the use of gadolinium (Gd) alone, GNPs have the ability to remain in the tumor mass for hours and even days after a single injection.[57] There are three studies that have used GNPs, as shown in Table 1.[31,44,46]

4.1.8. Superparamagnetic iron-oxide nanoparticles (SPIONs)

SPIONs are able to be identified in a specific tissue in the body using an external magnetic field.[58] Due to lower toxicity, magnetic manipulation and high magnetic sensitivity SPIONs are suitable candidates for theranostic interventions.[59] Based on surface modification by biomolecules and drugs, SPIONs are highly applied in cancer research.[60] In addition, the HT feature has made SPIONs a promising option in treating tumors like brain tumors.[61] Some treatment strategies with SPIONs are shown in Table 1.[38,48]

4.2. Gene therapy

Today, due to the complexity and hereditary cancer, gene therapy has been widely considered.[62] Providing genetic material such as a cancer suppressor gene, small interfering RNA (siRNA), micro-RNA (miRNA) into the tumor restores or silences the defective genes.[25–27] GBMs' patients have more than two mutated genes in their genome.[63] Some molecules are expressed in GBM, which consists of transferrin, folate, $\alpha\nu\beta3$ integrin, vascular endothelial growth factor (VCAM-1), VEGF and matrix metalloproteinases (MMP).[14,23] Studies revealed the involvement of genetic factors in GBM, namely alteration in chromosome 7, 9, 10, 13 and 19; mutation and amplification of epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor A (PDGFRA); mutation and deletion of neurofibromatosis type 1 (NF1) and phosphatase and tensin homolog (PTEN); isocitrate dehydrogenase 1/2 (IDH1/2) mutation; mouse double minute 2/4 (MDM2/4) amplification; and cyclin-dependent kinase Inhibitor 2 A/B (CDKN2A/B) deletion.[14,15,64] Receptor tyrosine kinases (RTKs) with the highest percentage of alteration in GBM patients lead to angiogenesis, invasiveness and anti-apoptosis, which can be targeted for treatment.[15,64] Generally, RTKs cell surface receptors are good targets as a treatment strategy, which are receptors for the growth factor, hormones, cytokines, neurotrophic factors, and the other molecules.[4,23,63]

Since O-6-methylguanine-DNA methyltransferase (MGMT) causes resistance to treatment with TMZ, Tumor suppressor gene (p53) is used to prevent the expression of MGMT.[65] WTP53 can negatively regulate the MGMT expression in cancer cells; consequently, wild-type p53 (wtp53) silences the MGMT.[65]

Several methods have been employed for gene therapy including suicide genes, virotherapy immunomodulatory genes, and tumor-suppressor genes.[25,63] In suicide genes approach, cytotoxicity is induced through prodrugs, while the tumor cells are lysing by using virus in virotherapy. On the one hand, immunomodulatory genes can improve the immune system's response, and in tumor suppressor genes procedure, presenting of them into the tumor can induce apoptosis.[25–27]

Genes carriers can be selected viral vectors namely adenovirus and retrovirus, non-viral vectors

like NPs, stem cells like neural stem cells (NSCs) and mesenchymal stem cells, and intelligent polymeric carriers such pH-sensitive systems. In this regard, nanocarriers, polymeric and non-polymeric were used as micelles, liposomes, PAMAM, silver NPs (Ag NPs), GNPs, SPIONs and multi-walled carbon nanotubes (MWCNTs).[25–27] Table 2 illustrates some studies that used from nanocarries for gene delivery.[62,66–82]

Meanwhile, liposomes are the most well-known nanocarriers, more commonly used in *in vitro* and in-vivo studies for gene therapy.[26] Incorporation of liposomes with PEG and presence of transferrin receptors on their surface will overcome their problems like short half-life and weak delivery of therapeutics.[25]

4.3. Hyperthermia

Due to the destructive effects of the thermotherapy (45- 41 °C) on the plasma membrane, damage to DNA and protein denaturation, and changes in micro-environmental pH, it induces apoptosis in the tumor cells.[14,83–85] For localized GBM hyperthermia, magnetic fields and laser were applied. GNPs and magnetic NPs (MNPs) are two main NPs that are used extensively in HT.[84] The first use of MNPs for cancer HT was done in 1957.[83,84,86] Three major classes of iron NPs, namely magnetite, maghemite and hematite especially SPIONs, are frequently used in HT due to biocompatibility and low toxicity.[84] On the other hand, utilization of the alternating magnetic field (AMF) as a heat inducer of NPs, IONs coated by aminosilane, dextran, and also magnetosome extraction from Magnetospirillum gryphiswaldense (MSR-1) bacteria coated by poly-L-lysine (PLL) can be useful for hyperthermia.[14,85] Generally, thermal energy is produced due to Néel and Brownian relaxations[85] and hysteresis loss.[83,85] The μ-oxo N,N'-bis(salicylidene)ethylenediamine iron [Fe(Salen)] NPs potentially increased the GBM cell death through reactive oxygen species (ROS) process.[14] Limitations of magnetic HT include optimization dose of MNPs, toxicity, inappropriate heat distribution, untargeted MNPs injected, and lack of device for measuring local temperature.[84] Carbon nanotubes (CNTs) with near-infrared radiation (NIR) can reduce the tumor size, and particularly eradicate the CSCs.[6]

HT with magnetite NPs was approved in Europe as an additional treatment alongside radiotherapy for rGBM.[83,84] One of the dilemmas facing HT is heat shock proteins (HSPs) that are resistant to hyperthermia and overexpression in glioma tumors.[83] In the first step, it seems that HSPs degradation and then HT have better effects than HT alone.

4.4. GBM tumor tracking

One of the major NPs advantages is tracking at the same time with treatment strategies using the MRI and fluorescence imaging.[26] GNPs and iron oxide nanoparticles (IONs) were proved to be a promising option in drug delivery, imaging, and therapeutic effects. In addition, SPIONs can improve endocytosis by activating the cancer cells in the site of metastasis. GNPs are anti-cancer agents due to low toxicity by increasing effective radiation dose due to the presence of propagated electron and free radicals. GNPs showed to be good contrast agents for tissue imaging, and a high number of gold atoms can empower X-rays. Combination of computed tomography (CT) and GNPs are able to do cell-based tracking.[87,88] FDA-approved poly-ethylene glycol-polycaprolactone (PEG-PCL), as a copolymer with amphipathic and biodegradable properties, were used to increase the systemic circulation time.[87] GNP (1.9 nm) and SPION (15 nm) were loaded to micelles and covered with PEG-PCL and injected intravenously; we used CT and MRIs to detect imaging.[87] SPIONs with other nanocarriers or alone were applied to treat GBM and cell tracking, using MRI system and HT with AMF system, respectively.[14] The other system employed for theranostic of GBM are micelles including SPIONs and GNPs, gadolinium NPs, selenium NPs loaded with Cd/Te quantum dots (QDs) and ruthenium, PLGA NPs loaded with TMZ and iron oxide, mesoporous silica nanoparticles (MSNs) loaded with sunitinib (inhibit from RTK) and surface functionalized with $VEGF_{121}$ and ^{64}Cu.[14]

5. Future perspective

Up to now, the most important works for the treatment of GBM are shown in Figure 2. Although the current strategies for GBM therapy are able to improve the overall survival a few more months, another method should be replaced in order to get better outcome. Probably, advanced methods in combination with standard therapies can be beneficial in the treatment of tumors. Nanotechnology, in terms of nanoparticles and nanocarriers, is an option for targeting treatment-based drug delivery, gene therapy, HT, and tracking. Given the recent satisfactory results in *in vitro* and preclinical studies, we are expecting that sciences based on nanotechnology can be used in clinical studies as soon. Certainly, smart nanoparticles

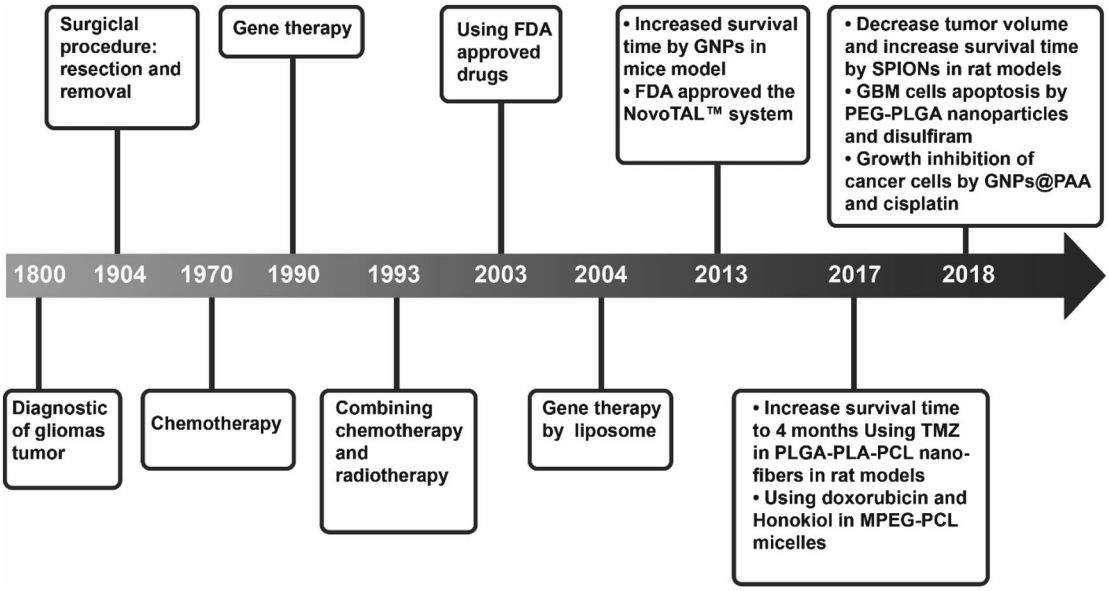

Figure 2. Timeline of glioblastoma; from diagnostic to present.

and nanocarriers have a powerful effect on drug delivery and gene therapy.

6. Conclusion

GBM is the most malignant brain tumor, and standard therapy cannot completely eradicate it. Thanks to FDA approval therapeutic agents and strategies, overall survival has been possible for several months. In addition, nanotechnology had significant results in the treatment of tumor cell lines; hence, scientists can improve the overall survival and treat complex tumors via NPs. The protective effect of NPs from drugs in the body, controlled release of therapeutics, and even the ability of treatment and simultaneous tracking of NPs were revealed. However, the unknown issues of NPs made limitations in clinical application. Because GBM has not shown a promising response to the current therapeutic approaches, there is a need to discover and solve the unknowns of advanced technology to be found with the most ideal results.

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References

1 Phillips KA, Fadul CE, Schiff D. Neurologic and medical management of brain tumors. Neurol Clin. 2018;36:449–466.
2 Komori T. The 2016 WHO Classification of tumours of the central nervous system: The major points of revision. Neurol Med Chir (Tokyo). 2017;57:301–311.
3 Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, et al, On behalf of the Brain Tumor Epidemiology Consortium. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer. 2008;113:1953–1968.
4 Rajesh Y, Pal I, Banik P, Chakraborty S, Borkar SA, Dey G, et al. Insights into molecular therapy of glioma: current challenges and next generation blueprint. Acta Pharmacol Sin. 2017;38:591–613.
5 Clarke J, Butowski N, Chang S. Recent advances in therapy for glioblastoma. Arch Neurol. 2010;67:279–283.
6 Glaser T, Han I, Wu L, Zeng X. Targeted nanotechnology in glioblastoma multiforme. Front Pharmacol. 2017;8:166.
7 Baklaushev VP, Nukolova NN, Khalansky AS, Gurina OI, Yusubalieva GM, Grinenko NP, et al. Treatment of glioma by cisplatin-loaded nanogels conjugated with monoclonal antibodies against Cx43 and BSAT1. Drug Del. 2015;22:276–285.
8 Zhou M, Zhang Z, Zhao H, Bao S, Cheng L, Sun J. An immune-related six-lncRNA signature to improve prognosis prediction of glioblastoma multiforme. Mol Neurobiol. 2018;55:3684–3697.
9 Ferronato MJ, Alonso EN, Salomon DG, Fermento ME, Gandini NA, Quevedo MA, et al. Antitumoral effects of the alkynylphosphonate analogue of calcitriol EM1 on glioblastoma multiforme cells. J Steroid Biochem Mol Biol. 2018;178:22–35.
10 Ostrom QT, Cote DJ, Ascha M, Kruchko C, Barnholtz-Sloan JS. Adult glioma incidence and survival by race or ethnicity in the United States from 2000 to 2014. JAMA Oncol. 2018;4:1254–1262.
11 Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev. 2014;23:1985–1996.
12 Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee Sh U. Glioblastoma multiforme: A review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pacific J Cancer Prev. 2017;18:3–9.
13 Franco T, Roque C, Khorasanizadeh S, McCullough LD. A 25-year-old man with progressive left-sided weakness and a mass lesion on brain imaging. J Postgrad Med. 2009;55:214–219.
14 Nam L, Coll C, Erthal LCS, de la Torre C, Serrano D, Martinez-Manez R, et al. Drug delivery nanosystems for the localized treatment of glioblastoma multiforme. Mater (Basel, Switzerland). 2018;11(5):779.
15 Bansal K, Liang ML, Rutka JT. Molecular biology of human gliomas. Technol Cancer Res Treat. 2006;5:185–194.
16 Myong NH, Park BJ. Malignant glioma arising at the site of an excised cerebellar hemangioblastoma after irradiation in a von Hippel-Lindau disease patient. Yonsei Med J. 2009;50:576–581.

17 Davis ME. Glioblastoma: Overview of disease and treatment. Clin J Oncol Nursing. 2016;20:S2–S8.
18 Little RB, Madden MH, Thompson RC, Olson JJ, Larocca RV, Pan E, et al. Anthropometric factors in relation to risk of glioma. Cancer Causes Control. 2013;24:1025–1031.
19 Bradshaw A, Wickremsekera A, Tan ST, Peng L, Davis PF, Itinteang T. Cancer stem cell hierarchy in glioblastoma multiforme. Front Surg. 2016;3:21.
20 Jawhari S, Ratinaud MH, Verdier M. Glioblastoma, hypoxia and autophagy: a survival-prone 'menage-a-trois. Cell Death Dis. 2016;7:e2434.
21 Yi Y, Hsieh IY, Huang X, Li J, Zhao W. Glioblastoma stem-like cells: Characteristics, microenvironment, and therapy. Front Pharmacol. 2016;7:477.
22 Ramachandran R, Junnuthula VR, Gowd GS, Ashokan A, Thomas J, Peethambaran R, et al. Theranostic 3-Dimensional nano brain-implant for prolonged and localized treatment of recurrent glioma. Sci Rep. 2017;7:43271.
23 Pearson JRD, Regad T. Targeting cellular pathways in glioblastoma multiforme. Sig Transduct Target Ther. 2017;2:17040.
24 Tseng YY, Huang YC, Yang TC, Yang ST, Liu SC, Chang TM, et al. Concurrent chemotherapy of malignant glioma in rats by using multidrug-loaded biodegradable nanofibrous membranes. Sci Rep. 2016;6:30630.
25 Kane JR, Miska J, Young JS, Kanojia D, Kim JW, Lesniak MS. Sui generis: gene therapy and delivery systems for the treatment of glioblastoma. Neuro-Oncol. 2015;17:ii24–ii36.
26 Kwiatkowska A, Nandhu MS, Behera P, Chiocca EA, Viapiano MS. Strategies in gene therapy for glioblastoma. Cancers. 2013;5:1271–1305.
27 Caffery B, Lee JS, Alexander-Bryant AA. Vectors for glioblastoma gene therapy: Viral & non-viral delivery strategies. Nanomater (Basel, Switzerland). 2019;9:105.
28 Gutkin A, Cohen ZR, Peer D. Harnessing nanomedicine for therapeutic intervention in glioblastoma. Expert Opin Drug Del. 2016;13:1573–1582.
29 Qian L, Zheng J, Wang K, Tang Y, Zhang X, Zhang H, et al. Cationic core-shell nanoparticles with Carmustine contained within O(6)-benzylguanine shell for glioma therapy. Biomater. 2013;34:8968–8978.
30 Lim WM, Rajinikanth PS, Mallikarjun C, Kang YB. Formulation and delivery of itraconazole to the brain using a nanolipid carrier system. Int J Nanomedicine. 2014;9:2117–2126.
31 Setua S, Ouberai M, Piccirillo SG, Watts C, Welland M. Cisplatin-tethered gold nanospheres for multimodal chemo-radiotherapy of glioblastoma. Nanoscale. 2014;6:10865–10873.
32 Ebrahimi Shahmabadi H, Movahedi F, Koohi Moftakhari Esfahani M, Alavi SE, Eslamifar A, Mohammadi Anaraki G, et al. Efficacy of Cisplatin-loaded polybutyl cyanoacrylate nanoparticles on the glioblastoma. Tumor Biol. 2014;35:4799–4806.
33 Nance E, Zhang C, Shih TY, Xu Q, Schuster BS, Hanes J. Brain-penetrating nanoparticles improve paclitaxel efficacy in malignant glioma following local administration. ACS Nano. 2014;8:10655–10664.
34 Wang B, Lv L, Wang Z, Jiang Y, Lv W, Liu X, et al. Improved anti-glioblastoma efficacy by IL-13Ralpha2 mediated copolymer nanoparticles loaded with paclitaxel. Sci Rep. 2015;5:16589.
35 Wu M, Fan Y, Lv S, Xiao B, Ye M, Zhu X. Vincristine and temozolomide combined chemotherapy for the treatment of glioma: a comparison of solid lipid nanoparticles and nanostructured lipid carriers for dual drugs delivery. Drug Del. 2016;23:2720–2725.
36 Kuo Y-C, Lee I-H. Delivery of doxorubicin to glioblastoma multiforme in vitro using solid lipid nanoparticles with surface aprotinin and melanotransferrin antibody for enhanced chemotherapy. J Taiwan Institute Chem Eng. 2016;61:32–45.
37 Fisusi FA, Siew A, Chooi KW, Okubanjo O, Garrett N, Lalatsa K, et al. Lomustine nanoparticles enable both bone marrow sparing and high brain drug levels - A strategy for brain cancer treatments. Pharm Res. 2016;33:1289–1303.
38 Mu Q, Jeon M, Hsiao MH, Patton VK, Wang K, Press OW, et al. Stable and efficient Paclitaxel nanoparticles for targeted glioblastoma therapy. Adv Healthcare Mater. 2015;4:1236–1245.
39 Shaw TK, Mandal D, Dey G, Pal MM, Paul P, Chakraborty S, et al. Successful delivery of docetaxel to rat brain using experimentally developed nanoliposome: a treatment strategy for brain tumor. Drug Del. 2017;24:346–357.
40 Gao X, Yu T, Xu G, Guo G, Liu X, Hu X, et al. Enhancing the anti-glioma therapy of doxorubicin by honokiol with biodegradable self-assembling micelles through multiple evaluations. Sci Rep. 2017;7:43501.
41 Maleki H, Dorkoosh F, Adabi M, Khosravani M, Arzani H, Kamali M. Methotrexate-loaded PLGA nanoparticles: Preparation, characterization and their cytotoxicity effect on human glioblastoma U87MG cells. Int J Med Nano Res. 2017;4:20.
42 Battaglia L, Muntoni E, Chirio D, Peira E, Annovazzi L, Schiffer D, et al. Solid lipid nanoparticles by coacervation loaded with a methotrexate prodrug: preliminary study for glioma treatment. Nanomed (London, England). 2017;12:639–656.
43 Wang Y, Ying X, Xu H, Yan H, Li X, Tang H. The functional curcumin liposomes induce apoptosis in C6 glioblastoma cells and C6 glioblastoma stem cells in vitro and in animals. Int J Nanomed. 2017;12:1369–1384.
44 Irani M, Sadeghi GMM, Haririan I. The sustained delivery of temozolomide from electrospun PCL-Diol-b-PU/gold nanocompsite nanofibers to treat glioblastoma tumors. Mater Sci Eng C, Mater Biol Appl. 2017;75:165–174.
45 Hua H, Zhang X, Mu H, Meng Q, Jiang Y, Wang Y, et al. RVG29-modified docetaxel-loaded nanoparticles for brain-targeted glioma therapy. Int J Pharmac. 2018;543:179–189.
46 Coluccia D, Figueiredo CA, Wu MY, Riemenschneider AN, Diaz R, Luck A, et al. Enhancing glioblastoma treatment using cisplatin-gold-nanoparticle conjugates and targeted delivery with magnetic resonance-guided focused ultrasound. Nanomed: Nanotechnol, Biol Med. 2018;14:1137–1148.
47 Madala HR, Punganuru SR, Ali-Osman F, Zhang R, Srivenugopal KS. Brain- and brain tumor-penetrating disulfiram nanoparticles: Sequence of cytotoxic events and efficacy in human glioma cell lines and intracranial xenografts. Oncotarget. 2018;9:3459–3482.
48 Shirvalilou S, Khoei S, Khoee S, Raoufi NJ, Karimi MR, Shakeri-Zadeh A. Development of a magnetic nano-graphene oxide carrier for improved glioma-targeted drug delivery and imaging: In vitro and in vivo evaluations. Chemico-Biol Interact. 2018;295:97–108.
49 Li X, Tsibouklis J, Weng T, Zhang B, Yin G, Feng G, et al. Nano carriers for drug transport across the blood-brain barrier. J Drug Target. 2017;25:17–28.
50 Zhao J, Zhang B, Shen S, Chen J, Zhang Q, Jiang X, et al. CREKA peptide-conjugated dendrimer nanoparticles for glioblastoma multiforme delivery. J Colloid Interface Sci. 2015;450:396–403.
51 Jiang Y, Lv L, Shi H, Hua Y, Lv W, Wang X, et al. PEGylated Polyamidoamine dendrimer conjugated with tumor homing peptide as a potential targeted delivery system for glioma. Colloids Surf B, Biointerf. 2016;147:242–249.
52 Singh I, Swami R, Pooja D, Jeengar MK, Khan W, Sistla R. Lactoferrin bioconjugated solid lipid nanoparticles: a new drug delivery system for potential brain targeting. J Drug Target. 2016;24:212–223.
53 rosina G. Nanoparticle-mediated drug delivery to high-grade gliomas. Nanomed: Nanotechnol, Biol Med. 2016;12:1083–1093.
54 Borran AA, Aghanejad A, Farajollahi A, Barar J, Omidi Y. Gold nanoparticles for radiosensitizing and imaging of cancer cells. Radiat Phys Chem. 2018;152:137–144.
55 Thakor AS, Jokerst J, Zavaleta C, Massoud TF, Gambhir SS. Gold nanoparticles: a revival in precious metal administration to patients. Nano Lett. 2011;11:4029–4036.
56 Dimitriou NM, Tsekenis G, Balanikas EC, Pavlopoulou A, Mitsiogianni M, Mantso T, et al. Gold nanoparticles, radiations and the immune system: Current insights into the physical mechanisms and the biological interactions of this new alliance towards cancer therapy. Pharmacol Therapeutics. 2017;178:1–17.
57 Meola A, Rao J, Chaudhary N, Sharma M, Chang SD. Gold nanoparticles for brain tumor imaging: A systematic review. Front Neurol. 2018;9:328.
58 Kunz-Schughart LA, Dubrovska A, Peitzsch C, Ewe A, Aigner A, Schellenburg S, et al. Nanoparticles for radiooncology: Mission, vision, challenges. Biomaterials. 2017;120:155–184.
59 Mokhtarzadeh A, Hassanpour S, Vahid ZF, Hejazi M, Hashemi M, Ranjbari J, et al. Nano-delivery system targeting

to cancer stem cell cluster of differentiation biomarkers. J Control Release. 2017;266:166–186.
60 Bahrami B, Hojjat-Farsangi M, Mohammadi H, Anvari E, Ghalamfarsa G, Yousefi M, et al. Nanoparticles and targeted drug delivery in cancer therapy. Immunol Lett. 2017;190:64–83.
61 Shevtsov MA, Nikolaev BP, Yakovleva LY, Marchenko YY, Dobrodumov AV, Mikhrina AL, et al. Superparamagnetic iron oxide nanoparticles conjugated with epidermal growth factor (SPION-EGF) for targeting brain tumors. Int J Nanomedicine. 2014;9:273–287.
62 Reszka RC, Jacobs A, Voges J. Liposome-mediated suicide gene therapy in humans. Meth Enzymol. 2005;391:200–208.
63 Cai X, Sughrue ME. Glioblastoma: new therapeutic strategies to address cellular and genomic complexity. Oncotarget. 2018; 9:9540–9554.
64 Aldape K, Zadeh G, Mansouri S, Reifenberger G, von Deimling A. Glioblastoma: pathology, molecular mechanisms and markers. Acta Neuropathol. 2015;129:829–848.
65 Kim SS, Rait A, Kim E, Pirollo KF, Nishida M, Farkas N, et al. A nanoparticle carrying the p53 gene targets tumors including cancer stem cells, sensitizes glioblastoma to chemotherapy and improves survival. ACS Nano. 2014;8:5494–5514.
66 Choi E, Han J, Tan X, Oh J, Lee D, Rhim T, et al. Combined delivery of temozolomide and the thymidine kinase gene for treatment of glioblastoma. J Drug Targeting. 2017;25:156–162.
67 Li AJ, Zheng YH, Liu GD, Liu WS, Cao PC, Bu ZF. Efficient delivery of docetaxel for the treatment of brain tumors by cyclic RGD-tagged polymeric micelles. Mol Med Rep. 2015;11: 3078–3086.
68 Tan X, Kim G, Lee D, Oh J, Kim M, Piao C, et al. A curcumin-loaded polymeric micelle as a carrier of a microRNA-21 antisense-oligonucleotide for enhanced anti-tumor effects in a glioblastoma animal model. Biomater Sci. 2018;6:407–417.
69 Jiao X, Yu Y, Meng J, He M, Zhang CJ, Geng W, et al. Dual-targeting and microenvironment-responsive micelles as a gene delivery system to improve the sensitivity of glioma to radiotherapy. Acta Pharmaceut Sin B. 2019;9:381–396.
70 Yoshida J, Mizuno M, Fujii M, Kajita Y, Nakahara N, Hatano M, et al. Human gene therapy for malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) by in vivo transduction with human interferon beta gene using cationic liposomes. Human Gene Ther. 2004;15:77–86.
71 Sun X, Pang Z, Ye H, Qiu B, Guo L, Li J, et al. Co-delivery of pEGFP-hTRAIL and paclitaxel to brain glioma mediated by an angiopep-conjugated liposome. Biomaterials. 2012;33: 916–924.
72 Ito A, Shinkai M, Honda H, Kobayashi T. Heat-inducible TNF-alpha gene therapy combined with hyperthermia using magnetic nanoparticles as a novel tumor-targeted therapy. Cancer Gene Ther. 2001;8:649–654.
73 Kato T, Natsume A, Toda H, Iwamizu H, Sugita T, Hachisu R, et al. Efficient delivery of liposome-mediated MGMT-siRNA reinforces the cytotoxity of temozolomide in GBM-initiating cells. Gene Ther. 2010;17:1363–1371.
74 Costa PM, Cardoso AL, Custodia C, Cunha P, Pereira de Almeida L, Pedroso de Lima MC. MiRNA-21 silencing mediated by tumor-targeted nanoparticles combined with sunitinib: A new multimodal gene therapy approach for glioblastoma. J Control Release. 2015;207:31–39.
75 Bai CZ, Choi S, Nam K, An S, Park JS. Arginine modified PAMAM dendrimer for interferon beta gene delivery to malignant glioma. Int J Pharmaceut. 2013;445:79–87.
76 Han L, Zhang A, Wang H, Pu P, Jiang X, Kang C, et al. Tat-BMPs-PAMAM conjugates enhance therapeutic effect of small interference RNA on U251 glioma cells in vitro and in vivo. Human Gene Therapy. 2010;21:417–426.
77 Bae Y, Thuy LT, Lee YH, Ko KS, Han J, Choi JS. Polyplexes of functional PAMAM dendrimer/apoptin gene induce apoptosis of human primary glioma cells in vitro. Polymers. 2019;11: 296.
78 Kang C, Yuan X, Li F, Pu P, Yu S, Shen C, et al. Evaluation of folate-PAMAM for the delivery of antisense oligonucleotides to rat C6 glioma cells in vitro and in vivo. J Biomed Mater Res. 2010;93:585–594.
79 Gao S, Li J, Jiang C, Hong B, Hao B. Plasmid pORF-hTRAIL targeting to glioma using transferrin-modified polyamidoamine dendrimer. Drug Des Devel Ther. 2016;10:1–11.
80 Grabowska M, Grześkowiak BF, Szutkowski K, Wawrzyniak D, Głodowicz P, Barciszewski J, et al. Nano-mediated delivery of double-stranded RNA for gene therapy of glioblastoma multiforme. PLoS One. 2019;14:e0213852.
81 Kievit FM, Veiseh O, Fang C, Bhattarai N, Lee D, Ellenbogen RG, et al. Chlorotoxin labeled magnetic nanovectors for targeted gene delivery to glioma. ACS Nano. 2010;4:4587–4594.
82 Long L, Wang W, Cai XD, Cheng D, Shuai X, Peng Y. PinX1-siRNA/mPEG-PEI-SPION combined with doxorubicin enhances the inhibition of glioma growth. Exper Therap Med. 2014;7: 1170–1176.
83 Mahmoudi K, Bouras A, Bozec D, Ivkov R, Hadjipanayis C. Magnetic hyperthermia therapy for the treatment of glioblastoma: a review of the therapy's history, efficacy and application in humans. Int J Hyperthermia. 2018;34:1316–1328.
84 Pinel S, Thomas N, Boura C, Barberi-Heyob M. Approaches to physical stimulation of metallic nanoparticles for glioblastoma treatment. Adv Drug Del Rev. 2019;138:344–357.
85 Wankhede M, Bouras A, Kaluzova M, Hadjipanayis CG. Magnetic nanoparticles: an emerging technology for malignant brain tumor imaging and therapy. Expert Rev Clin Pharmacol. 2012;5:173–186.
86 Gupta R, Sharma D. Evolution of magnetic hyperthermia for glioblastoma multiforme therapy. ACS Chem Neurosci. 2019; 10:1157–1172.
87 Sun L, Joh DY, Al-Zaki A, Stangl M, Murty S, Davis JJ, et al. Theranostic application of mixed gold and superparamagnetic iron oxide nanoparticle micelles in glioblastoma multiforme. J Biomed Nanotechnol. 2016;12:347–356.
88 Meir R, Betzer O, Motiei M, Kronfeld N, Brodie C, Popovtzer R. Design principles for noninvasive, longitudinal and quantitative cell tracking with nanoparticle-based CT imaging. Nanomed: Nanotechnol Biol Med. 2017;13:421–429.