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Current Perspectives on Therapies, Including Drug Delivery Systems, for Managing Glioblastoma Multiforme

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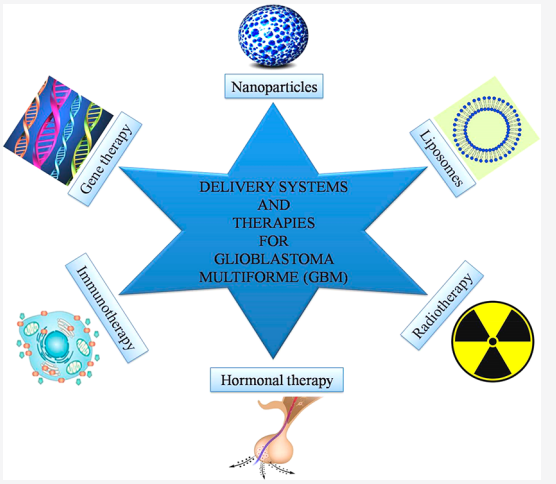
ABSTRACT: Glioblastoma multiforme (GBM), a standout among the most dangerous class of central nervous system (CNS) cancer, is most common and is an aggressive malignant brain tumor in adults. In spite of developments in modality therapy, it remains mostly incurable. Consequently, the need for novel systems, strategies, or therapeutic approaches for enhancing the assortment of active agents meant for GBM becomes an important criterion. Currently, cancer research focuses mainly on improving the treatment of GBM via diverse novel drug delivery systems. The treatment options at diagnosis are multimodal and include radiation therapy. Moreover, significant advances in understanding the molecular pathology of GBM and associated cell signaling pathways have opened opportunities for new therapies. Innovative treatment such as immunotherapy also gives hope for enhanced survival. The objective of this work was to collect and report the recent research findings to manage GBM. The present review includes existing novel drug delivery systems and therapies intended for managing GBM. Reported novel drug delivery systems and diverse therapies seem to be precise, secure, and relatively effective, which could lead to a new track for the obliteration of GBM.



KEYWORDS: *Glioblastoma multiforme, epidemiology, pathogenesis, delivery systems, therapies, drug targets*

1. INTRODUCTION

Glioma, the term generally used to describe primary brain tumors, is classified according to the presumed cell of origin, which include astrocytic tumors (such as astrocytoma, anaplastic astrocytoma, and glioblastoma), ependymomas, oligodendrogliomas, and mixed gliomas.[1−4] These are the most frequently occurring tumors of the central nervous system (CNS), accounting for nearly 80% of all malignant primary brain tumors.[3−5]

Glioblastoma multiforme (GBM), the most malignant and commonly occurring type of primary astrocytoma, accounts for more than 60% of all brain tumors in adults.[6] It is still a fatal disease with an extremely poor prognosis even after the availability of varied modern therapies. Usually, patients have a median survival of 14−15 months (approximately) from the diagnosis.[7,8] The World Health Organization (WHO) classifies gliomas as grade I to grade IV, based on the level of malignancy determined by histopathological criteria. Grade I gliomas have lesions with low proliferative potential and are curable by surgical procedures. Grade II−IV gliomas are highly malignant and invasive, and GBM is the most invasive, aggressive, and undifferentiated type of tumor, which WHO has designated as grade IV.[9,10]

An average age-adjusted incidence rate per 100,000 people is 3.2.[11,12] While GBM occurs exclusively in the brain, it can appear in the brain stem, cerebellum, and spinal cord also. Generally, 61% percent of all primary gliomas occur in the four lobes of the brain comprising frontal lobe (25%), temporal lobe (20%), parietal lobe (13%), and occipital lobe (3%).[13] Initially, GBM was thought to be derived from glial cells solely, but per the evidence, it may arise from the multiple cell types with neural stem cell-like properties. These cells are at multiple stages of differentiation (stem cell to neuron to glia), with phenotypic variations determined in large part by molecular alterations in the signaling pathways rather than by differences in the cell type of origin.[14−16]

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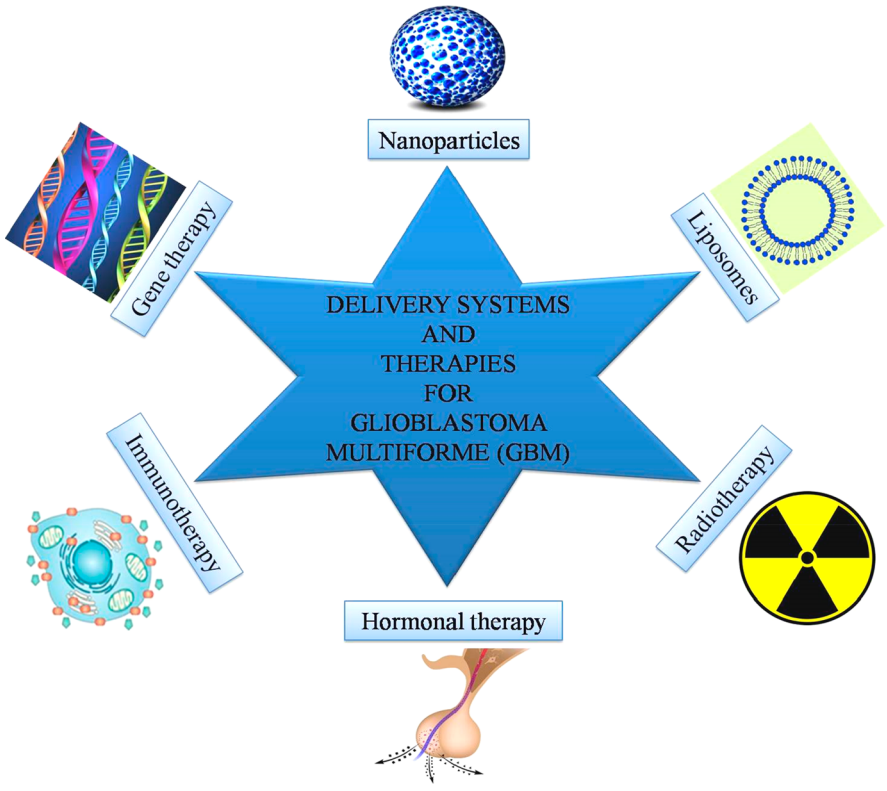

Figure 1. Delivery systems and therapies for GBM.

Hence, the latest updates on diverse conclusions as well as crucial findings of GBM treatments are required to be broadly spread to research, medical, and other scientific societies. In this review, we have focused on and covered some novel drug delivery systems and various therapies available for managing GBM, as indicated in Figure 1.

2. EPIDEMIOLOGY AND ETIOLOGY

Even though the global incidence of GBM is less than 10 per 100,000 people, the poor prognosis with the lowest survival rate after diagnosis makes it a decisive public health issue.[17] It accounts for almost 60% of all gliomas in all age groups,[6] but the peak incidence is between 55 and 60 years.[18] The reason behind 2.5% of deaths due to cancers is malignant gliomas, which are also the third leading cause of cancer death in the 15−34 year old population.[19] The ratio of GBM incidence is slightly higher in men compared to women (1.6:1),[8,18] and also in the Western world as compared to less developed countries, which could be due to lower reporting of cases of glioma, limited access to health care, and differences in diagnostic practice.[20,21] Some studies have also reported that blacks are less prone to GBM as compared to other ethnic groups, such as whites, Latinos, and Asians.[17] This may be because of genetics as it more likely to tip the scale of etiology.

2.1. Risk Factors. Identification of any possible relationship between GBM and environmental or occupational exposure has largely been uncertain. Ionizing radiation is one of the known risk factors for glioma development, and radiation-induced GBM can be seen long after radiation therapy (RT) previously for another tumor or condition.[15,22] Other environmental exposures to pesticides, vinyl chloride, synthetic rubber manufacturing, and petroleum refining have been loosely associated with glioma development. Electromagnetic fields and nonionizing radiation from cell phones have not been proven to cause GBM.[23] The risk of glioma development is seen increasingly in several definite genetic diseases like retinoblastoma, tuberous sclerosis, neurofibromatosis 1 and 2, Li−Fraumeni syndrome, and Turcot syndrome. However, less than 1% of patients with a glioma possess known hereditary disease.[15]

2.2. Clinical Presentation. Generally, over half of GBM patients have a short clinical history ranging between 3 and 6 months. However, if the source of the tumor is a low-grade astrocytoma, the clinical history spans over several years.[24] Presentation of a newly diagnosed GBM patient may greatly vary depending on the size as well as the location of the tumor and also the anatomic structures of the brain involved.[25,26] Mostly, the patients present with symptoms of increased intracranial pressure, along with the headache and focal or progressive neurologic deficits. The presenting symptom in 25% of the patients is a seizure, which can occur again at a later stage in as many as 50% of the patients.[27] In nearly 13% of cases, GBM may present as multifocal (more than two lesions), distant (secondary lesion noncontiguous with primary), or diffuse disease.

Initial diagnostic imaging includes computed tomography (CT) or magnetic resonance imaging (MRI). In the case of MRI, detection of nearly all GBMs is enhanced with gadolinium contrast. Moreover, they show an irregularly shaped mass with a dense ring of enhancement and hypointense center of necrosis. Necrosis is a hallmark feature of GBM, and the presence of necrosis is required for a brain tumor to be grade IV or to be classified as GBM based on the WHO classification system.[13] Furthermore, surrounding vasogenic edema, hemorrhage, and ventricular distortion may also be present on the diagnostic imaging.[15,22]

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3. PATHOGENESIS

3.1. Site. Cerebral hemispheres are the most common location for GBM with 95% of these tumors arising in the supratentorial region, while very many fewer tumors occur in the brain stem, cerebellum, and spinal cord.[28]

3.2. Macroscopic and Histological Features. GBM is quite heterogeneous macroscopically, mainly featuring necrosis, multifocal hemorrhage, and cystic and gelatinous areas.[29] Variation in gross appearance of the tumor from one region to another is a characteristic feature of GBM. Some of the regions, owing to the tissue necrosis, appear as soft and yellow in color, whereas other tumor areas appear firm and white in color, and some regions indicate marked cystic degeneration and hemorrhage.

The tumor usually presents as a single, relatively large, and irregularly shaped lesion that arises usually in the white matter. Histologically, GBM is similar to anaplastic astrocytoma demonstrating a pleomorphic cell population ranging from small poorly differentiated tumor cells to large multinucleate cells, with multifocal necrosis with pseudopalisading nuclei and prevalent mitotic activity.[30] The proliferation of vascular endothelial cells with the glomeruloid structure is also one of the major characteristic features.[29]

3.3. Genetic Pathogenesis. GBM can be classified as primary (de novo), arising with no known precursor, or as secondary, wherein a low-grade tumor transforms into GBM over time. The majority of GBM tumors are primary, and such patients tend to be older and have poorer prognosis compared to secondary GBM patients.[16] In the case of genetic pathogenesis of GBM, primary glioblastoma arises from direct transformation of glioma precursor cells, typically involving concurrent mutations in several genes such as EGFR and VEGFR. However, secondary glioblastoma arises from a progressive series of the pathological events with each progression step associated with genes such as p53, CDK4, P13K, and others. Figure 2 summarizes the pathogenesis of GBM.

4. NOVEL DRUG DELIVERY SYSTEMS

Diverse novel drug delivery systems have been used to treat various types of cancer. Many researchers have also reported current perspectives and updates on novel drug delivery for different cancers as well as other fatal diseases.[31−35]

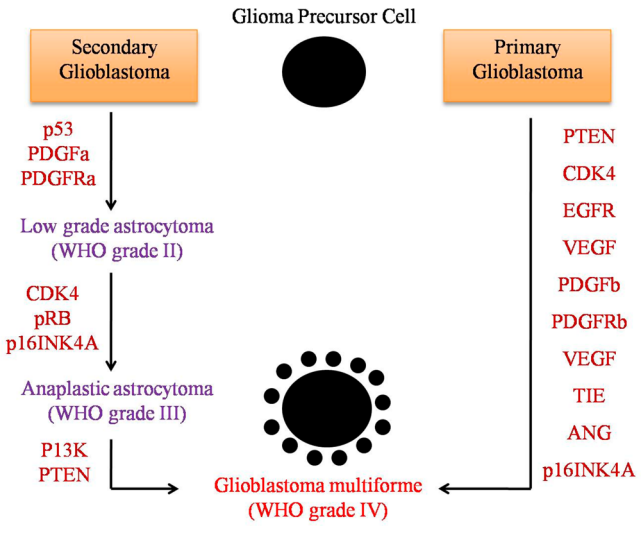

Figure 2. Pathogenesis of GBM.

4.1. Nanoparticles (NPs). GBM being among the most encountered gliomas of central nervous system (CNS), there is a pressing need to investigate novel drug delivery systems especially intended to target GBM. Nanoparticles (NPs) can be employed for various purposes like gene therapy, diagnosis, treatment, and imaging. Surface charge is one of the important features of NPs. While neutral NPs and a lesser concentration of anionic NPs have no impact on blood−brain barrier (BBB) integrity, high centralization of anionic NPs and cationic NPs is harmful to the BBB.[36]

Generally, brain tolerance of anionic NPs at low concentrations is more noteworthy than that of neutral or cationic NPs.[37] Therefore, surface charges of NPs ought to be considered for lethality and mind dissemination diagrams. The smaller size of NPs less than 100 nm facilitates their penetration even into small vessels and cells thereby favoring targeted drug delivery. However, a larger size of NPs builds their immunogenicity and prompts their release by the reticular endothelial system (RES). Formulating the NPs with polysorbate (Tween) surfactants encourages their transmission through the BBB. The utilization of biodegradable NPs prompts stable medication (drug) release during days or even weeks.[38] Different mechanisms of transporting therapeutic medicaments through different *in vitro* and *in vivo* BBB models have exhibited essential preclinical characteristics for controlling CNS conditions, for example, brain cancer, which include transportation by receptor mediated transcytosis as well as endocytosis.[39]

NPs can equally reduce the potency of some active medications. NPs protect medications from enzymatic and synthetic degradation. They also have the capacity to accomplish tissue targeting for several active medications, for example, cytostatics, antitoxins, proteins, nucleic acids, and peptides. Furthermore, NPs can be administered by various routes including oral, transdermal, intraocular, nasal, and intravascular.[40]

Novel theranostic nanocarriers enable treatment of illnesses while providing real-time imaging of the diseased site. The advancement of such theranostic agents is still complicated. A multifunctional dendrimer-based theranostic nanosystem was created for malignant tumor cell chemotherapy and computed tomography (CT) imaging focusing on specificity. Fifth generation (G5) polyamidoamine (PAMAM) dendrimer was developed with doxorubicin (DOX), a model antitumor drug, linked via acid-sensitive *cis*-aconityl (NHAc), and folic acid (FA) was prefunctionalized to obtain the G5 dendrimer. Further, NHAc−FA−DOX conjugated mixtures were entrapped using gold nanoparticles (Au NPs) to develop Au NP dendrimers (Au DENPs). The developed DOX−Au DENPs have a Au core size of 2.8 nm, have 9.0 DOX molecules conjugated onto each dendrimer, and are a stable colloid under various conditions. The developed DOX−Au DENPs display a pH-responsive discharge profile of DOX because of the *cis*-aconityl linkage, having a burst DOX release rate under slightly more acidic pH conditions than physiological pH. Significantly, because of the conjunction focusing on ligand FA and core Au NPs as CT imaging agents, the multifunctional DOX-stacked Au DENPs manage the cost of explicit chemotherapy and CT imaging of FA receptors (FAR) over communicating malignancy cells. The DOX-conjugated Au DENPs have

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favorable potential to be used for concurrent chemotherapy and CT imaging of different classes of malignant tumor cells.[41]

Different types of metal−organic (MO) compounds have been shown to be effective antitumor agents, but these compounds were limited in clinical application because they lack and efficient route of administration due to insolubility or poor solubility. The current strategy to overcome their administration problem is to formulate MO nanoparticles (MONPs) containing metal complex compounds.

A simple synthesis of MO nanoparticles consisting of bovine serum albumin (BSA), Cu^{2+}, and an antitumor compound, 5-nitro-8-hydroxyquinoline (NQ), with albumin as nanoreactors was completed. The resultant BSA/Cu/NQ nanoparticle was stable at physiological pH and could target tumors through the EPR effect and receptor-mediated cellular uptake. Since BSA/Cu/NQ NPs could be freely and effectively taken up by tumor cells, they produced much higher cytotoxicity of diseased cells than a NQ + Cu(II) complex and NQ. In this way, treatment with BSA/Cu/NQ NPs perceptibly improved the anticancer activity without causing systemic toxicity, suggesting that this simple synthesis technique can develop other MONPs for anticancer therapy.[42]

Higher systemic toxicity, lack of specific targeting to cancer cells, and poor BBB penetration are the limitations of anticancer drugs in glioblastoma treatment. To overcome these limitations, solid lipid nanoparticles (SLNPs) have been employed because of their lower systemic toxicity and proven biocompatibility compared to other classes of existing anticancer drugs and conventional drug delivery for the treatment of GBM. The surface of solid lipid nanoparticles was conjugated with lipoprotein receptor-related protein 1 (LRP1) and angiopep-2 (a ligand that is present in the endothelial cells of both brain and glioma) for the docetaxel (DTX) delivery. The Angiopep-2 conjugated solid lipid nanoparticles (A-SLN) resulted in improved cytotoxicity, better cellular internalization, and promising apoptosis compared to the blank (unconjugated SLNPs) against U87MG human glioblastoma and GL261 mouse glioma cells. Furthermore, the results of *in vivo* characterization through real-time fluorescence imaging tests in a C57BL/6 mice model of glioblastoma confirmed the significant dual targeting effect of A-SLN ($p < 0.0001$). Additionally, A-SLN showed specific targeting and higher accumulation in the brain compared to commercially available DTX injection (Taxotere) confirmed by tissue distribution and pharmacokinetic studies. These studies concluded that A-SLN could be a tremendous choice for the treatment of GBM.[43]

Glioblastoma is the deadliest brain cancer, and the existing therapies can only extend the patient's survival to approximately one year. Chemotherapy treatment for GBM using temozolomide (TMZ), an alkylating compound, is the preferred first-line therapy. TMZ has various disadvantages like lower bioavailability and higher systemic toxicity than other chemotherapy drugs. Nanoparticles of TMZ (TMZ NPs) were developed employing poly(lactic-*co*-glycolic acid) (PLGA) for the delivery of temozolomide, and TMZ-NPs stabilized with a monoclonal antibody (OX26) for transferrin receptor were formulated to target GBM cancer cells, since these GBM cells are well-known for overexpressing this receptor. The release profile of TMZ from the NPs was studied by mimicking various pH conditions and also the effect on cellular internalization was determined. An *in vitro* cell viability assay was carried out using GBM cell lines (U215 and U87) to evaluate the cytotoxicity of the TMZ. These studies concluded that the formulated TMZ nanocarriers along with the monoclonal antibody enhanced the anticancer activity and improved cellular internalization in glioblastoma cells.[44]

Based on surface characterization, zinc oxide (ZnO) NPs exhibited potential as a drug for cancer therapy. In one of the investigations, the most abundant blood proteins, albumin, fibrinogen, and apo-transferrin, were covalently bound to ZnO NPs (c-ZnO NPs) followed by nonspecific adsorption (n-ZnO NPs) onto ZnO NPs to estimate the role of these alternative routes in the protein structure and their consequences for GBM cells. The accomplishment of alteration and the structures of the proteins on ZnO NPs were analyzed spectroscopically with Fourier-transform infrared spectroscopy (FTIR). FTIR analysis revealed that the secondary structure of proteins compared to those covalently attached to the ZnO NPs was significantly affected by the noncovalent interaction. Further, a cell viability assay was carried to investigate the effect of altered ZnO nanoparticles on GBM (U373) cells, and the n-ZnO NPs were found to have higher systemic toxicity compared to pristine and c-ZnO NPs. Nevertheless, both albumin with c-ZnO NPs and apo-transferrin disturbed the cell cycle function and reduced the necrotic cell death rate of U373 cells at lower toxic concentration, thus signifying the potential therapeutic effect on GBM cells.[45]

Chemical therapy and radiation techniques are different types of therapeutic methodologies for the treatment of neuropathology. Manganese oxide (MnO), one of the metal oxide derivatives, with the application of X-ray radiation was studied for cytopathogenic effect on human GBM cells (U87). Accordingly, doses of 0.5, 4, 40, and 100 Gy of X-ray radiation in the combination with NPs at a concentration of 0.5 ng/mL were utilized. The synchrotron radiation source VEPP-4 was used for the irradiation of glioma cells. The glioma cells were treated with NPs for approximately 24 h and radiation; the results were evaluated using MTT assay at 10^6 cells/mL densities. It was confirmed that preincubation of GBM cell lines (U87) with MnO NPs permits a decreased dose of radiation. The NP and X-ray radiation combinations can deliver various new opportunities for the treatment of brain cancers.[46]

Various investigations on glioblastoma cells have revealed that the cells display upregulated low-density lipoprotein receptors (LDLRs). In contrast, communal neurons have comparatively fewer LDLRs. Hence, targeting LDLRs could offer a promising therapeutic methodology in chemotherapeutic drug delivery.[47,48] Accordingly, some investigations have employed plasma-derived low-density lipoprotein (LDL) as a targeting agent for glioblastoma cancer cells. Due to the difficulty of purification of natural LDL, synthetic forms of LDL have been employed in therapeutic methodologies. Synthetic LDL-conjugated NPs have successfully delivered paclitaxel for the treatment of glioblastoma cancer cells.[49,50]

Celecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor, acts by inducing apoptosis and altering cell growth.[51] Celecoxib-conjugated poly(lactic-*co*-glycolic acid) (PLGA) has been shown to have significant anticancer activity against glioma cells (U87MG and C6) in a dose-dependent manner. The results of these studies conclude that celecoxib-conjugated PLGA NPs are an effective drug delivery system for the treatment of GBM.[52]

Angiopep (ANG) conjugated NPs (ANG-NPs) was supplemented with enhancing peptide or proteins for delivery

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across the BBB and cancer targeting through lipoprotein receptor-mediated endocytosis.[53] Furthermore, paclitaxel-loaded ANG-NPs may prevent the proliferation of glioma cells (U87MG) and enhance their cell death (apoptosis). Moreover, the utilization of these NPs improved the accumulation of the drug in the CNS and decreased the viability of glioblastoma cell lines (U87).[54]

Curcumin is a curcuminoid derivative, derived from turmeric (an Indian spice). Various works have reported that curcumin compounds can be used as anticancer agents through various mechanisms, such as anti-inflammatory effects, pro-apoptotic effects, antimitogenic effects, antiangiogenic effects, and immune modulation.[55] Curcumin also could influence different factors like signal transducers, the activator of transcription 3 (STAT3), insulin-like growth factor (IGF), mitogen-activated protein kinase (MAPK), serine−threonine protein kinase (Akt), nuclear factor-kappa β (NF-$\kappa\beta$), and Notch.[56] As all of these pathways are thought to be active in lethal brain cancer, it appears that curcumin might be compelling in the treatment of GBM. An anticancer drug like curcumin drug-loaded magnetic NPs (MNPs) can act as a novel drug delivery system that may suppress the proliferation of GBM tumor cells. The combination of curcumin and MNP formulations were compared to individual drug formulations and showed improved cytotoxic effects.[57,58]

Further, other studies have reported that magnetic iron oxide NPs have been altered by PEGylation and also conjugated using cyclodextrin and loading cholera toxin (CTX), pertussis toxin (PTX), and fluorescein. These alterations could lead to improved NP engulfment by glioblastoma cells; accordingly, PTX can improve efficiency in reducing lethal resistance of the drugs by glioblastoma cells.

In another investigation, PTX loaded multiwalled carbon nanotubes (MWCNTs) were utilized to interrupt microtubule activity by binding to tubulin which prevents cell division.[59]

Furthermore, lately, convection-enhanced delivery (CED) of NPs have been resulting in the improved chemotherapeutic drug delivery to the cancer bed, sustained release, and improving survival of animals with intracranial cancer. Gemcitabine, an antineoplastic chemotherapeutic drug used as a first line medication for the treatment of various classes of cancer, was contained within squalene-based nanoparticles (SQ-Gem NPs) using CED to rectify previously reported challenges for the treatment of GMB. Lower percentages of PEG drastically improved the distribution of SQ-Gem NPs in healthy and cancer-bearing animals after administration by CED. SQ-Gem-PEG NPs were tested on an orthotopic model of glioblastoma, the results demonstrated that the therapeutic efficacy was improved significantly when compared to pure gemcitabine, both as a chemotherapeutic drug and as a radiosensitizer. Additionally, the SQ-Gem-PEG NPs also incorporated MR contrast agents to track the NPs during infusion by a noninvasive method.[60]

The various chemotherapeutic drugs face the limitations for crossing the BBB in the treatment of brain cancer. Anticancer drug-loaded PLGA NPs and poloxamer 188 can overcome the problem of penetration across BBB in anticancer treatment. These formulations resulted in high antineoplastic effect against GBM in rats, as well as in human grade IV GBM. The main reason for surface-modified NPs along with receptor-mediated transcytosis followed by poloxamer 188-coating was to cross BBB to be adsorbed in blood apolipoproteins (ApoE). Human glioma cells (U87) were used to determine the intracellular fate of surface-modified NPs. The mechanism by which PLGA NPs entered human glioma cells (U87) was clathrin-mediated endocytosis. The pure doxorubicin drug was released from endosomes within 1 h and can reach its targeted site, DNA in the nuclei, without degradation, while the PLGA NPs, which were labeled with Cy5.5, were still detected in the endolysosomal compartment. The results of these experiments concluded that the core mechanism of action in the U87 cells is diffusive doxorubicin release from the NPs instead of intracellular degradation.[61]

Enzymes called histone deacetylases (HDACs) are the well-known factors in the development of cancer cells and improvement by their modulation of the structure of chromatin and the expression and post-translational modification of various proteins. The HDACs are significantly overexpressed in aggressive dedifferentiated cancers, such as GBM, and apoptosis, cellular differentiation, and cell arrest occurred upon HDAC enzyme inhibition. Though quisinostat (an inhibitor of numerous HDACs) is of interest in oncology owing to its effective *in vitro* efficacy, clinical study of quisinostat therapy against cancer showed poor drug delivery. Therefore, NPs of quisinostat-loaded poly(D,L-lactide)-*b*-methoxy-poly(ethylene glycol) were developed to treat orthotopic GBM. A pH-driven method for attaining over 9% (w/w) quisinostat loading was identified. Moreover, quisinostat-NPs were found to retain drug potency *in vitro* and efficiently reduced cancer cell growth *in vivo*, leading to an extended drug release compared to control mice.[62]

5. THERAPIES

Apart from the novel drug delivery, diverse therapies have also been used to treat the various types of cancer. Many researchers have also reported current perspectives and updates on therapies for different cancers as well as other fatal diseases.[31−35]

5.1. Radiotherapy. Radiotherapy (RT) uses high energy X-rays, commonly produced by linear accelerators. Radiotherapy promotes changes in normal as well as tumor cells, but tumor cells are highly sensitive to RT, and most of them get killed. Usually, human cells are able to repair themselves, and hence, the damage to normal human cells is mostly transient.

Since the first diagnostic X-ray carried out in the US on 3 Feb 1896, the application of ionizing radiation to the field of medicine has become increasingly important. Both in clinical medicine and in basic research, the use of X-rays for diagnostic imaging and radiotherapy is now widespread. Radiography, angiography, computerized axial tomography (CAT) and positron emission tomography (PET) scanning, mammography, and nuclear medicine are all examples of technologies developed to image human anatomy. For the treatment of cancer cells, both internal and external radiation sources have been utilized in therapeutic applications. The improvement of committed synchrotron radiation sources has enabled energizing advances to occur in a significant number of these applications. The new sources give tunable, high-power monochromatic shifts over a wide scope of energies, which can be custom fitted to explicit needs.[63]

GBM has terrible prognosis even with the best accessible treatment. Various investigations have suggested a possible effect of antiepileptic drugs (AEDs) on survival in patients with GBM. A recent mathematical analysis of newly classified AEDs has found a nonsignificant survival effect in the treatment of GBM patients. A total of 285 adult patients with GBM were

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involved in the reflective investigation. The main aim of these studies was to determine the influence of AED treatment on overall survival (OS), after adjusting for known prognostic factors (age, Karnofsky performance status, the extent of surgery, radio-chemotherapy). Out of 285 patients, 95 received an enzyme-inducing AED (EIAED) and 144 patients received a non-enzyme-inducing (NEIAED) one. The overall survival (OS) of GBM patients treated with antiepileptic drugs (AEDs) was not significantly different from that of patients who did not receive AED, as demonstrated in univariate analysis. Also, between EIAED and NEIAED treated patients no significant difference in OS was found. The mathematical (multivariate) analysis found improved survival rate (P = 0.15, 95% confidence interval [CI] 0.59 to 1.08 and hazard ratio [HR] = 0.8) in a patient with NEIAED treatment. Questions whether the treatment with AED might improve patient's OS in GBM remain unanswered and randomized clinical trial could reveal a potent impact of AEDs on GBM treatment. Meanwhile, the utilization of AEDs in GBM patients, in light of the assumed potential anticancer action, is not recommended.[64]

A group of investigators[65] conducted a PubMed search for literature published from 1938 to 2015 regarding cancer location, death (critical events), demographics, and treatment methodologies in GBM; 128 spinal GBM cases were selected for this study. The study results concluded that patient between ages 18 and 65 had an improved overall survival (OS) (14 months) compared with the "extreme" age groups (<18 years, 10.5 month survival, and >65 years, 2 month survival; log-rank P = 0.0005). In univariate analysis, patients between 18 and 65 years old (HR = 0.121; 95% CI= 0.04−0.37; P = 0.0005) and those receiving surgery with radiotherapy (HR = 3.71; 95% CI = 1.36−10.13; P = 0.01) had significantly different with OS. In multivariate analysis, cancer occurring in thoracic spine (odds ratio [OR] = 0.154; 95% CI = 0.033−0.717; P = 0.017) and conus (OR = 0.091; 95% CI = 0.010−0.798; P = 0.030) resulted in fewer critical issues at 6 months. The patients who were treated with adjuvant therapy had improved survival than those treated with surgery (log-rank P = 0.0005). For the treatment of spinal GBM, the review concluded that surgery followed by adjuvant therapy (radiotherapy, chemotherapy, or both) was found to significantly improve survival of the patients. Furthermore, OS was enhanced in middle age of 18−65 years (68 cases) compared with the extreme ranges (<18 years, 53 cases; >65 years, 4 cases).[65]

Radiation-induced tumors are well-known but rare complications of radiotherapy. Meningiomas are the most common radiation-induced (RI) cranial tumors, followed by the gliomas and sarcomas, while other tumors such as human glioblastomas remain extremely exceptional. Seven patients were presented with RI brain tumors diagnosed and treated between 1990 and 2006. All patients were irradiated during childhood as a treatment for another disease and fulfilled the criteria of RI neoplasia. Four patients developed meningiomas and three developed other tumors (one glioblastoma, one soft tissue sarcoma, and one human glioblastoma). In all cases, complete surgical removal was achieved. Preoperative assessment based on MRI supplied the correct diagnosis in six patients. The most important risk factors described in the literature for developing RI tumors are the age at which radiotherapy was administered and the dose of radiation applied. Differential diagnosis of RI tumors includes any tumor appearing after radiotherapy, especially recurrences of the primary disease, as RI neoplasias are a rare complication. Even in cases with complete surgical resection, the prognosis of this clinical entity is related to the histology of the RI tumor.[66]

The long-term survival of patients with high-grade gliomas remains extremely poor. The main reason for such an outcome is a local failure or recurrence after surgery and radiotherapy. Higher doses of radiation may result in decreased local failure rates provided that the location (and extent) of the gross tumor and microscopic disease can be defined accurately. The abnormalities appearing in images from diagnostic modalities, such as CT and MRI, are being used as a starting point and as a guide for the clinical definition of the tumor and its extensions. However, some recent studies on two-dimensional specimens, correlating histopathological findings to CT and MRI images, showed that the resulting definition of tumor cell extensions was unsatisfactory, different, and in need of ample margins.[15] A retrospective analysis was carried out to compare the target volumes that would have been defined by CT, T_2-weighted MRI, and T_1-weighted post-gadolinium MRI images of the same individual, and to explore the implications of the resulting volume definitions for radiotherapy. The results of this limited study, based on the margins used, indicate that the CT-defined target volume is consistently larger than that from either of the two MRI modalities and also suggest that non-coplanar approaches for its treatment and other local approaches for tumor boost should be considered. Hence, it was concluded that until more definitive histopathological guidelines correlated to image features have been formulated and agreed upon, one should try to make full use of all available diagnostic information in order to minimize the possibility of geographical miss of target extensions.[67]

In 1986 the EORTC Radiotherapy and Brain Tumor Groups initiated a prospective trial to compare early radiotherapy with delayed radiotherapy, and an interim analysis has been reported. After surgery, patients from 24 centers across Europe were randomly assigned to either early radiotherapy of 54 Gy in fractions of 1.8 Gy or deferred radiotherapy until the time of progression (control group). Patients with low-grade astrocytoma, oligodendroglioma, mixed oligoastrocytoma, and incompletely resected pilocytic astrocytoma with WHO performance status 0−2 were eligible. The analysis was by intention to treat, and primary end points were overall and progression-free survival; 157 patients were assigned early radiotherapy and 157 control. Median progression-free survival was 5.3 years in the early radiotherapy group and 3.4 years in the control group (hazard ratio 0.59, 95% CI 0.45−0.77; $p < 0.0001$). However, overall survival was similar between the groups: median survival in the radiotherapy group was 7.4 years compared with 7.2 years in the control group (hazard ratio 0.97, 95% CI 0.71−1.34; p = 0.872). In the control group, 65% of patients received radiotherapy at progression. At 1 year, seizures were better controlled in the early radiotherapy group. Hence, it was concluded that early radiotherapy after surgery lengthens the period without progression but does not affect overall survival. Because the quality of life was not studied, it is not known whether the time to progression reflects clinical deterioration. Radiotherapy could be deferred for patients with low-grade glioma who are in good condition, provided they are carefully monitored.[68]

Relapse is the main cause of mortality in patients with GBM. Treatment options involve surgical resection followed by a

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combination of radiotherapy and chemotherapy with temozolomide. Several genes and genetic pathways have been identified that contribute to therapeutic resistance, giving rise to the recurrence of the malignancy. In the last decades, glioma stem cells (GSCs) with the capacity of self-renewal have been demonstrated to maintain tumor propagation and treatment resistance. CD133-positive (CD133+) and CD133-negative (CD133−) cells were isolated from glioblastoma U98G and U87MG cell lines. The role of phosphoribosyl pyrophosphate synthetase 1 (PRPS1), which catalyzes the first step of the synthesis of nucleotides, in proliferation and apoptosis was investigated. It was found that PRPS1 had a remarkable effect on cell proliferation and sphere formation in both CD133+ and CD133− cells. Compared to CD133− cells, CD133+ cells exhibited more significant results in cell apoptosis assay. CD133+ T98G and U87MG cells were used in a xenograft mouse model of tumor formation. Interestingly, the mice implanted with PRPS1 knockdown T98G or U87MG stem cells exhibited prolonged survival time and reduced tumor volume. By immune staining caspase-3 in tumor tissues of these mice, it was demonstrated that the apoptotic activities in tumor cells were positively correlated to the survival time but negatively correlated to PRPS1 expression. Results have indicated that PRPS1 plays an important role in proliferation and apoptosis in GSCs and provides new clues for potential PRPS1-targeted therapy in GBM treatment.[69]

In another study, by using an orthotopic G7 glioblastoma (GBM) xenograft model the impact of four different radiotherapy plans was studied on tumor and normal tissue dosimetry. Plans were created using four different approaches (single beam, parallel opposed pair, single plane arcs, couch rotation arcs) and dose volume histograms (DVH) for the tumor and the relevant organs at risk (mouth, ipsilateral brain, contralateral brain, brain stem) were compared for a sample mouse subject. To evaluate the accuracy of delivery, treatment plans were recreated in solid−water phantoms and delivered to radiochromic film. Favorable tumor dosimetry was achieved by all plans. DVH analysis showed that different plans could be used to spare specific organs at risk depending on the objectives of the study. The delivery accuracy of the various treatments was better than 2%/2 mm (dose difference/distance to agreement) in terms of global gamma analysis. Consequently, small animal radiotherapy research platforms are an exciting addition to the preclinical research environment. Such systems improve the conformality of irradiation of tumors and organs at risk (OARs) while maintaining a high degree of accuracy and enable investigators to optimize experiments in terms of tumor coverage and inclusion or exclusion of relevant OARs.[70]

Pediatric GBM is a relatively rare brain tumor in children that has a dismal prognosis. Surgery followed by radiotherapy is the main treatment protocol used for older patients. The benefit of adjuvant chemotherapy is still limited due to a poor understanding of the underlying molecular and genetic changes that occur with irradiation of the tumor. In this study, total RNA sequencing was performed on an established stable radioresistant pediatric GBM cell line to identify mRNA expression changes following radiation. The expression of many genes was altered in the radioresistant pediatric GBM model. These genes have never before been reported to be associated with the development of radioresistant GBM. In addition to exhibiting an accelerated growth rate, radioresistant GBM cells also have overexpression of the DNA synthesis-rate-limiting enzyme ribonucleotide reductase and pro-cathepsin B. These newly identified genes should be concertedly studied to better understand their role in pediatric GBM recurrence and progression after radiation. It was observed that changes in multiple biological pathways protected GBM cells against radiation and transformed them into a more malignant form. These changes emphasize the importance of developing a treatment regimen that consists of a multiple-agent cocktail that acts on multiple implicated pathways to effectively target irradiated pediatric GBM. An alternative to radiation or a novel therapy that targets differentially expressed genes, such as metalloproteases, growth factors, and oncogenes and aims to minimize oncogenic changes following radiation is necessary to improve recurrent GBM survival.[71]

Generally, natural isothiocyanates isolated from plants of the Cruciferae family are selectively cytotoxic to tumor cells. It has been demonstrated previously that diisothiocyanate-derived mercapturic acids are highly cytotoxic to colon cancer cells. In this study, the application of diisothiocyanate-derived mercapturic acids led to a decrease in the viability of an established glioblastoma cell line, primary patient-derived sphere-cultured stem cell-enriched cell populations (SCs), and cells differentiated from SCs. Consequently, targeting glioblastoma cells by diisothiocyanate-derived mercapturic acids is a promising approach to restrict tumor cell growth and may be a novel therapeutic intervention for the treatment of glioblastoma.[72]

An investigation was done in the survival outcomes and safety of hypofractionated stereotactic radiotherapy as a salvage treatment for recurrent high-grade glioma. Between March 2012 and March 2017, 32 consecutive patients (12 women, 20 men) treated in a single center were retrospectively included in this study. Grade III gliomas were diagnosed in 14 patients and grade IV in 18 patients. Thirty-four lesions were treated with hypofractionated stereotactic radiotherapy on the linear accelerator. Hypo fractionated stereotactic radiotherapy delivered a median dose of 30 Gy (27−30) in 6 fractions (3−6) of 5 Gy (5−9). The treatment plans were normalized to 100% at the isocenter and prescribed to the 80% isodose line. Clinical outcomes and prognostic factors were analyzed. The median follow-up was 20.9 months. Median overall survival following hypofractionated stereotactic radiotherapy was 15.6 months (median overall survival for patients with glioblastoma and grade III glioma was 8.2 and 19.5 months, respectively; P = 0.0496) and progression-free survival was 3.7 months (median progression-free survival for patients with glioblastoma and grade III glioma was 3.6 and 4.5 months, respectively; P = 0.2424). In multivariate analysis, tumor grade III (P = 0.0027), an Eastern Cooperative Oncology Group status <2 at the time of re-irradiation (P = 0.0023), and a mean dose >35 Gy (P = 0.0055) significantly improved overall survival. A maximum re-irradiation dose above 38 Gy (P = 0.0179) was significantly associated with longer progression-free survival. Hypofractionated stereotactic radiotherapy is well tolerated and offers an effective salvage option for the treatment of recurrent high-grade gliomas with encouraging overall survival. Our results suggest that the dose distribution had an impact on survival.[73]

High-grade gliomas (HGGs) are a heterogeneous disease group, with variable prognosis, inevitably causing deterioration of quality of life. The estimated 2-year overall survival is 20%, despite the best trimodality treatment consisting of surgery, chemotherapy, and radiotherapy. To evaluate long-term

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survival outcomes and factors influencing the survival of patients with high-grade gliomas treated with radiotherapy, data from 47 patients diagnosed with high-grade gliomas between 2009 and 2014 and treated with three-dimensional radiotherapy (3DRT) or intensity-modulated radiotherapy (IMRT) were analyzed. Median survival was 16.6 months; 29 patients (62%) died before the time of analysis. IMRT was employed in 68% of cases. The mean duration of radiotherapy was 56 days, and the mean delay to the start of radiotherapy was 61.7 days (range, 27−123 days). There were no statistically significant effects of the duration of radiotherapy or delay to the start of radiotherapy on patient outcomes.[74]

Anticancer drugs that target both cancer cells and angiogenesis are possible options for the treatment of GBM. One such drug is sorafenib (SFN), a tyrosine kinase inhibitor. Nevertheless, clinical application has been limited by its adverse effects, poor water solubility, and requirement for local treatment. To overcome these disadvantages lipid nanocapsules (LNCs) were developed for encapsulating SFN. The developed SFN-LNC formulations showed an average diameter particle size of 54 ± 1 nm and great encapsulation efficiency (>90%), and drug loading was 2.11 ± 0.03 mg/g of LNC dispersion. The SFN-LNCs restrained *in vitro* angiogenesis and diminished human glioblastoma (U87MG) cell viability also compared to free SFN. *In vivo* investigations demonstrated that the intratumoral SFN-LNCs or free SFN administration in naked mice bearing an orthotopic U87MG human GBM xenograft diminished the extent of multiplying cells in the tumor compared to control groups. SFN-LNCs were more successful than free SFN for inducing early tumor vascular standardization, described by increments in the tumor bloodstream and diminished tumor vessel area. These outcomes emphasize the ability of LNCs to be used as a novel delivery for SFN. The vascular standardization initiated by SFN-LNCs could be utilized to improve the viability of chemotherapy or radiotherapy for treating GBM.[75]

5.2. Hormonal Therapy. Gliomas, which include astrocytomas, oligodendrogliomas, and ependymomas, are one of the most common types of primary malignant brain tumors.[76] Gliomas originate from brain glial cells, that is, astrocytes and oligodendrocytes.[77] GBM is the highest grade of glioma, and it is the most common and aggressive type of malignant glioma.[78] Approximately 90% of cases of GBM are referred to as "primary glioblastoma multiforme".[79] The etiology of GBM is due to high-dose ionizing radiation and abnormal genetic conditions.[80] In addition, endogenous ovarian steroid hormones are also contributing factors to the progress of glioma.[81] Steroid hormones contribute vital roles in brain development and differentiation.[82] Especially endogenous estrogens and other estrogenic compounds are identified as neuroprotective agents for a variety of neurologic disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, and ischemic stroke via improvement of myelination, reduction of edema, alteration of abnormal apoptosis and necrosis, and decrease of neuroinflammation.[83] In contrast, steroid hormones may play a role in the progress of brain tumors via ligand-activated transcription factors of steroid hormone receptors and the acceleration of the oncogenic pathway.[84]

Steroid receptors are located in the plasma membrane, cytosol, and nucleus of the cells. The receptor ligands make the receptor dimerization and interact with enhancer or repressor elements in target genes via multiple cytosolic messengers.[85] The target gene elements cause changes in the gene transcription process over hours to days.[86] Estrogens have a higher affinity to these receptors (called estrogen receptors, ERs) and alter signal transduction for control of cell growth and mitogenic activity.[87] In addition, the numerous co-activators and co-repressors can also modulate these receptor functions. Furthermore, estradiol, other steroid hormones, and selective estrogen receptor modulators (SERMs) also function via nonclassical (not directly through ER) pathways.[88] The expressions of classical ER, progestin, glucocorticoid, and androgen receptors have been identified in normal glial cells.[89] Thus, the expression of ER is substantial in gliomas, glioblastomas, and astrocytomas.[90] One-third of glioblastomas have ERα expression. The treatment with steroid hormone receptor agonists and antagonists, tibolone and 2-methoxyestradiol, has been shown to induce glioma cell death in humans and in rats.[83] In addition, melatonin inhibits the local production of estrogens and also inhibits the growth of glioma cells.[91] Furthermore, a variety of other estrogenic agents, like genistein, bind to ERβ, inhibit protein tyrosine kinases and topoisomerase II, and rapidly inhibit DNA synthesis in human glioma cells.[92] The SERM tamoxifen has estrogenic and antiestrogenic effects. It also inhibits glioma cell proliferation and induces apoptosis *in vitro*.[93] Interestingly, tamoxifen and benzopyranone induce apoptosis in glioma cells. Tamoxifen is an antagonist for ERβ, and it also has agonist activity on ERβ when the estrogen response is mediated through non-estrogen response elements (EREs).[94] Another possibility of ER-related protein expression in glioblastoma is mediated thorough tamoxifen actions.[83] At high doses of tamoxifen may act via a non-estrogen-mediated steroid receptor and its influence on the action on calmodulin, various kinases, intracellular calcium, and protein kinase C signal transduction pathways.[95] In addition to that, glucocorticoid receptor antagonist mifepristone (RU486) suppressed malignant glioma cell proliferation.[96]

The preclinical and clinical studies, as well as cell culture studies, provide evidence that the steroid hormones play a role in the development of glioma.[81] Further, the rate of GBM incident is higher in females than males. In the female, it occurs during the premenopausal years.[97] Practically, the expression of estrogen receptors (ERs, especially ERβ) and aromatase levels are higher in gliomas and glioblastoma cells.[98] These factors are responsible for the conversion of testosterone to estradiol and other steroid hormone production. The agonists and antagonists of steroid hormone receptors act via receptor-dependent and independent actions on glioblastoma.[99] Hormone replacement therapy (HRT) is one of the choices for the management of glioblastoma, intracranial meningioma, and other brain tumors.[100] Three major HRT prescriptions are used for the treatment of GBM, estrogen only, progestin-only, and combined estrogen−progestin preparations.[101,102] However, the risk for glioma of chronic usage of HRT remains a debate.[103] Some reports revealed that steroidal therapy has a significant role in the management of glioblastoma.[104] Therefore, hormonal approaches are one of the targets for the treatment of GBM.[105]

5.3. Immunotherapy. In the central nervous system, glial cells, astrocytes, and oligodendrocytes are neuroimmune cells.[106] The most aggressive type of primary brain tumor cells is glial cell, and they enhances the progress of glioblastoma via alteration of cellular microenvironment and immunosuppressive actions.[107] Conventional treatments like chemotherapy, radiation therapy, hormonal therapy, and

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surgical therapies continue to demonstrate poor efficacy compared with immunotherapy.[108] The recent studies revealed that immunotherapy for glioblastoma has a promising role in the management of early and later complications of glioblastoma.[107] The current advancement of immunotherapy has been successful with vaccine therapy for multiple forms of glioblastoma.[109]

The major action of immunological agents targets specialized immune cells. They may be peripheral (T cells, B cells, etc.) or local to the central nervous system (like glial cells).[110] Further, these agents induce discrimination between self and nonself (recognizing foreign invaders and defending against them).[111] The immune defense system becomes ready to fight the glioblastoma.[112] The primary innate immune system is the first line of defense, and it recognizes pathogen-associated changes of cellular and molecular events like alteration of endoplasmic, mitochondrial, and nuclear functions and toll-like receptor (TLR) and other pattern recognition receptors (PRR) mediated actions.[113] Another part is an adaptive immune system that is activated by antigens via T lymphocytes, B lymphocytes, and antigen-presenting cells.[114] T-cells are predominately involved in the management of glioblastoma due to their potential cytotoxic actions. In addition, most active antigen-presenting cells are dendritic cells that interfere with pathogen entry and continuous antigen release sites.[115] Furthermore, dendritic cells up-regulate the cytokine receptors and chemokine receptors, and trafficking to the lymph nodes leads to enhancement of the induction of T cell responses.[116] Thereafter, monocytes recruit an abundant quantity of macrophages and dendritic cells in perivascular zones, choroid plexus, and meninges.[117] These events are mostly regulated by vaccine therapy, and this approach has been successfully used for the treatment of high-grade gliomas.[118] Also, glioblastoma patients are treated with systemic immune suppressive agents. However, the micro-environment of glioblastomas has higher immunosuppressive factors that are secreted by gliomas.[119] Such factors include transforming growth factor beta (TGF-β) and vascular endothelial growth factors (VEGFs), which suppress the proliferation of T cells, cytotoxic action, and maturation of dendritic cells.[120] Therefore, the enhancement of immunosuppressive factors can reduce the progress of glioblastoma.[121] Such factors are tumor factors (i.e., TGF-β, prostaglandin E2, interleukin-10 (IL-10) and VEGF). exogenous factors (like age, exogenous steroids and chemotherapy), and immune factors (i.e., regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs)). Therefore, vaccine therapy is targeted to regulate these factors to treat glioblastoma[122]

Immunotherapy has ample scope to treat GBM. Generally, immunization techniques are used for infectious disorders.[123] However, it also can treat various other conditions. Theoretically, it occurs in the form of active and passive immunotherapy. Active immunotherapy boosts the patient's natural immune system.[124] Passive immunotherapy provides immune cell or antibody delivery targeted to the glioma cells and suppresses the progress of glioblastoma.[125] Bevacizumab is a humanized IgG1 monoclonal antibody, and it neutralizes VEGF. The administration of bevacizumab regulates the angiogenesis process in glioblastoma cells via binding to complement cascade proteins and the Fc receptor of glioma cells.[126] In addition, it also dilates the afferent blood vessels and constricts the efferent blood vessels in glioma cells.[127] Therefore, it has additional benefits to treat the glioblastoma cells by inhibiting the angiogenesis as well as the reduction of micronutrient supply.[128] In addition, various vaccines are under clinical trials for the treatment of glioblastoma. Such agents are dendritic cell eluted peptides, dendritic cell lysate, and dendritic cell glioma fusion.[129]

However, there are some challenges for the treatment of glioblastoma with immunotherapy,[130] including enhancing antigen presentation capabilities, tumor-induced immune tolerance, activation of tumor-specific cytolysis effects, and the scale up of production of cell-based therapy. In addition, further boosting the immunological response leads to increased serious adverse events like induction of secondary brain tumors and autoimmunity.[131] Similarly, prolonged activation of antitumor T cell response with dendritic cell lysate-based immunotherapy is effective in glioblastoma,[132] but there is still controversy over conditions to obtain the most activated and potent dendritic cells.[133] An ongoing clinical trial is testing the fusion of dendritic and glioma cells with recombinant human interleukin 12 (rhIL-12) for the treatment of malignant glioma with monitoring of side effect profiles.[124] Therefore, immunological therapy-based approaches can be newer medicine for the treatment of GBM.[134]

5.4. Gene Therapy. Gene therapy is one approach for the treatment of various genetic disorders. Gene therapy involves the introduction of the therapeutic gene or manipulation of the disease-related gene.[135] Mainly this approach is accomplished by using vectors like viruses and bacteriophage. Genetic factors play key roles in the progress of glioblastoma.[136] There are some gene modifications documented in the progress of glioblastoma.[137] Different methods are used for the delivery of genetic materials, including viral vectors, cellular carriers (i.e., neural stem cells, mesenchymal stem cells, or embryonic stem cells), and nanotechnology-based synthetic vectors (like nanoparticles and cationic liposomes).[138] Stem cells also act as vehicles in gene therapy. A virus interaction with recombinant deoxyribonucleic acid (DNA) is used for the treatment of glioblastoma.[139] Clinically, a synthetic vector (cationic liposome) has only been used for the treatment of glioblastoma as a small molecule carrier. However, liposome based delivery of genetic materials is considered a safer and efficacious method.[140] In addition, two types of viral vectors have been used for antiglioma therapy, replication-deficient viruses and oncolytic viruses. Currently, adenovirus (AV), retrovirus, herpes simplex virus (HSV), and adeno-associated virus (AAV) have been used for the delivery of genetic materials to the glioma cells.[141]

The primary genetic material for the treatment of cancer disorders is called a suicide gene. Herpes simplex virus thymidine kinase (HSV-TK) and cytosine deaminase 5-fluorocytosine (CD/5-FC) genes are widely used suicide genes for glioblastoma cells.[142] A possible mechanism of HSV-TK gene therapy is catalyzed phosphorylation of nucleoside analogs like ganciclovir (GCV). In glioblastoma cells, the HSV-TK gene supports conversion of GCV to a toxic metabolite, GCV-triphosphate.[143] Further, GCV-triphosphate blocks DNA replication and cell division of glioblastoma via enhancement of the apoptosis process.[144] In addition, it also induces the accumulation of phosphorylated nucleoside analogs in neighboring glioblastoma cells, which leads to enhanced apoptosis of nontransduced cells.[145] Furthermore, it also enhances the phagocytosis process neighboring transduced cells leading to the apoptotic vesicle formation.[146] The following genetic modifying agents are under clinical trials

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for the management of glioblastoma cells: CD/5-FC; carcinogenic embryonic antigen; cytosine deaminase; fms-like tyrosine kinase-3 ligand; interleukin; and thymidine kinase. Furthermore, certain oncolytic genes are also used for the treatment of glioblastoma.[147] Mainly virus replicating in glioblastoma cells leads to control and arrest of glioblastoma cell replication.[148] Such oncolytic agents are HSV, adenovirus, measles virus, poliovirus, Newcastle disease virus, parvovirus, and reovirus.[149]

The mechanism of oncolytic gene therapy is mainly due to the replication of competent viral vectors in targeted cancer cells.[150] In addition, it spreads the new adjacent progeny cells via the host cell lysis process and releases the progeny virus to the next cell.[151] But this replication is poor and slower due to host cell defense mechanisms. The viral infection causes suppression of host cell protein synthesis via protein kinase R (PKR) factor,[152] and it inactivates the autophosphorylation of eukaryotic initiation factor-2 alpha (EIF-2α), which is required for the translation and initiation of protein synthesis. The specialized vector HSV-1 is an enveloped double strand DNA virus with neurotrophic factors.[153] It also has potential replication properties in dividing and nondividing cells.[154] However, wild-type HSV-1 undergoes a lytic cycle or remains in the intranuclear episome without the integration of the host genome.[155] Thus, it is also sensitive to acyclovir and GCV. Therefore, these vectors are safer for the treatment of glioblastoma cells. The mutant vector of HSV, G207, replicates in a conditioned manner. A genetically engineered HSV-1 (F) strain lacks the genes necessary for viral replication in normal cells.[156] Therefore, it targets only the glioblastoma cells. Clinical trials revealed that the administration of G207 decreased glioma growth with a high safety profile.[157] Stem cells are also used as carriers for oncolytic viruses and have a promising role for the infiltration of solid tumors. In addition, neural stem cells or mesenchymal stem cells are employed in the delivery of conditionally replicating HSV and AV.[158] Intra-arterial delivery of mesenchymal stem cells with Ad5Delta24-RGD results in selective release of the genetic materials in human gliomas leading to enhanced eradication in glioma and improving patient survival.[159]

Cytokines demonstrate pleiotropic actions in a biological system. They have immunological as well as gene regulating actions.[160] Cytokines mediated gene therapy is focused on tumor-selective gene transfer and selective in situ expression of various cytokine genes like interleukins (ILs, IL-2, IL-4, and IL-12) and interferons (IFNs, IFN-β and -γ).[161] These cytokines have restricted the antigens for specific glioma cells. However, these agents also interfere with inflammatory pathways.[162] Some cytokines influence lack of production of an anti-inflammatory mediator like transforming growth factor (TGF)-β, weaker expression of major histocompatibility complex (MHC) class I and II, and the existence of BBB.[163] Therefore, cytokine based gene therapy has a challenging task to develop an effective antitumor response in glioblastoma.[164] Crucially, tumor suppressor gene therapy is also one of the approaches for the treatment of glioblastoma.[165] It has multiple cellular activities like the interaction with cell-cycle checkpoints, detection and repair of DNA damage, cell proliferation, and apoptosis.[166] The primary tumor suppressor gene, p53, is located on chromosome 17p and encodes a 393 amino acid protein. Inactivated p53 is one of the most commonly mutated tumor suppressor genes in glioma.[167] The p53 gene directly interferes with DNA and initiates the DNA repair process, inhibition of angiogenesis, and inhibition of abnormal cell growth.[168] Recently, a more specific variant of tumor suppressor gene therapy was identified, $p16^{INK4A}$. It arrests the cell cycle at the G1−S transition point via stabilizing hypophosphorylated retinoblastoma protein (Rb) protein.[169] The overexpression of the p16 gene using a recombinant replication-deficient adenovirus was reported to reduce glioma cell invasion leading to a decrease in the activity of matrix metalloprotease-2.[170] Moreover, the phosphatase and tensin homologue (PTEN) gene is also employed in the central catalytic action of the phosphatase core domain and initiates the negative regulation of phosphoinositide 3-kinases (PI_3K).[171] About 40−50% of glioblastoma cells show inactivation of PTEN with aberrant PI_3K activity.[172] The expression of PTEN in glioblastoma cells can enhance cellular apoptosis and decrease glioma cell proliferation.[173] Experimentally, an adenovirus with PTEN produces an antiangiogenic response in glioblastoma cells.[174] Based on the above literature reports, the delivery of mutated gene therapy can be used as medicine for the treatment of GBM.[175]

6. CLINICAL TRIALS

Investigations are being done within clinical trials for the cellular regulatory pathways with tyrosine kinase and signal transduction inhibitors. Immunotherapy research is also ongoing along with the applications of monoclonal antibodies as well as vaccines.

Rindopepimut (Rintega), an immunotherapy vaccine targeting EGFR variant III, was tested in the patients with newly diagnosed GBM, but it failed to produce any survival benefit, consequently leading to termination of the clinical trial.[176]

Generally, a promising target in recurrent GBM is an immune checkpoint blockade. Drugs targeting programmed cell death protein 1 (PD-1) receptor, its ligand PD-L1, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) receptors have been shown to have antitumor activity in other cancers, such as melanoma. Therefore, research in patients with recurrent GBM is underway.

Manipulating the BBB for enhancing targeted drug delivery is also being investigated. With a bit of luck, the outcomes of these trials may lead to improved survival for GBM patients.

7. CONCLUSION

The key function of any anticancer treatment is to knock down the cancer cells to the extent possible along with the highest safety. Currently, cancer research primarily highlights the management of GBM via diverse nanosystems as well as therapies that are discussed in the present work. Such delivery systems and therapeutic approaches have come forward with an enormous interest as a potential substitutes to overcome the numerous formerly encountered barriers to capably target several cancer cells types as they have shown abundant hopeful features. These miscellaneous novel drug delivery systems along with the therapeutic approaches seem to be specific, safe, and comparatively effective. Consequently, they could lead to a new track for the destruction of GBM.

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Mahendran Bhaskaran contributed to conceptualization, prepared the table of contents, and wrote, revised, and edited the manuscript. Vishakante Gowda Devegowda reviewed, edited, and revised the manuscript. Vishal Kumar Gupta reviewed, edited, and revised the manuscript. Amruthesh Shivachar Significantly contributed to the writing of manuscript. Rohit Rajendra Bhosale contributed to writing the manuscript and prepared images. Muthuraman Arunachalam significantly contributed to writing the immunotherapy and clinical trials parts. Thirumalaraju Vaishnavi contributed to rewriting and referencing.

Notes

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