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Nanotechnology in the Treatment of Glioblastoma Multiforme: Enhancing Radiotherapy and Chemotherapy with Nanoparticles

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Abstract

Introduction:

Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor, associated with poor prognosis despite standard treatment modalities including surgery, radiotherapy, and chemotherapy. The limited efficacy of these therapies is due, in part, to the difficulty of complete tumor resection, the blood-brain barrier (BBB) hindering drug penetration, and the tumor's resistance mechanisms to chemotherapy and radiotherapy. Nanoparticles (NPs) offer promising solutions for targeted drug delivery, potentially improving therapeutic outcomes. This review summarizes recent advances in nanoparticle-based therapies for GBM.

Methods:

A literature review was conducted by analyzing 38 scientific articles using PubMed and Google Scholar databases. Studies published within the last five years focusing on the application of nanoparticles in GBM treatment were included. Various types of nanoparticles, their mechanisms of action, and the potential benefits and limitations of their clinical use were discussed.

Results:

The literature indicates that nanoparticles enhance drug permeability across the BBB, improve tumor penetration, and increase treatment efficacy. Their use in GBM therapy enables more precise drug delivery, reduces systemic toxicity, and minimizes damage to healthy tissues. Furthermore, nanoparticles play a significant role in combination therapies, potentially leading to a synergistic therapeutic effect.

Conclusions:

Nanoparticles represent a novel and promising strategy for the treatment of GBM, offering targeted drug delivery and improved therapeutic outcomes. However, further research is

needed to optimize nanoparticle formulations and to evaluate their long-term safety and efficacy in clinical settings.

Keywords: *Glioblastoma multiforme, nanoparticles, drug delivery, blood-brain barrier, targeted therapy, nanomedicine, nanotechnology*

Introduction

Glioblastoma multiforme (GBM) is a primary brain tumor that can arise in any part of the central nervous system (CNS), although it most commonly occurs in the frontal or temporal lobes. It originates from glial tissue, specifically from astrocytes—star-shaped glial cells. GBM is characterized by a high rate of cellular division, extensive angiogenesis, and central areas of tumor necrosis. [1] Its annual incidence is estimated at 3–5 cases per 100,000 people. Moreover, it is more prevalent in men than in women (approximately 1.6 times more frequent), and the median age at diagnosis is 65 years. [1,4]

Classification

According to the WHO CNS5 (2021), glioblastoma (GBM, IDH-wildtype) is classified as a grade IV malignant brain tumor in adults, characterized by the absence of mutations in the IDH1, IDH2, and H3 genes. Unlike previous classifications, which emphasized histopathological features, the current approach incorporates molecular testing as both a diagnostic and supportive tool. The molecular criteria for diagnosis include the presence of a TERT promoter mutation, EGFR gene amplification, or a chromosomal aberration in the form of trisomy 7 and monosomy 10 (+7/–10). [2]

Clinical Symptoms

Patients may present with acute symptoms such as seizures (20–50%) and focal neurological deficits (10–40%), as well as gradually progressive complaints, including headaches (50%), personality changes, and cognitive impairments (30–40%). These symptoms are often the result of increased intracranial pressure, leading to nausea, vomiting, and fatigue. On physical examination, papilledema may be observed. Due to the nonspecific nature of these symptoms, early diagnosis of glioblastoma multiforme is challenging and often does not allow for clear differentiation from other neurological disorders. [3]

Diagnosis

Magnetic resonance imaging (MRI) is the primary diagnostic modality for glioblastoma multiforme. A typical radiological presentation includes a focal lesion with peripheral contrast enhancement on T1-weighted sequences, indicating disruption of the blood-brain barrier. T2-weighted imaging reveals central hypointensity suggestive of necrosis, while perilesional hyperintensity on T2-weighted and FLAIR images reflects vasogenic edema or tumor infiltration. [1] Definitive diagnosis of GBM usually requires biopsy or surgical resection, followed by histopathological and molecular analysis. Molecular testing not only confirms the diagnosis but also provides valuable prognostic information and allows for personalized therapy. [6]

Standard Treatment

The standard treatment of glioblastoma multiforme includes maximal safe surgical resection, which is a cornerstone of therapy. This is followed by radiotherapy in combination with concurrent and adjuvant chemotherapy using temozolomide (TMZ). [4]

However, conventional treatment of high-grade gliomas faces multiple limitations. Surgical tumor removal is often incomplete due to the infiltrative nature of the tumor, while extensive resection carries a risk of neurological deficits. Chemotherapy is limited by drug resistance, difficulty in crossing the blood-brain barrier, significant toxicity, and the activity of the MGMT enzyme, which reduces the efficacy of alkylating agents. Radiotherapy may impair neurocognitive function and face resistance challenges, particularly in hypoxic tumor environments. [4,5]

Despite the application of standard therapy, the prognosis for patients with glioblastoma multiforme remains poor, with a median survival time of only 15–23 months. [5]

Nanotechnology has the potential to significantly improve drug pharmacokinetics and facilitate penetration through the blood-brain barrier. Nanodelivery systems increase the selectivity of treatment by targeting active substances directly to tumor cells, allowing for the bypassing of resistance mechanisms and minimizing systemic side effects. [6]

Nanoparticles – Characteristics and Mechanisms of Action in GBM Chemotherapy

Properties of Nanoparticles

Nanoparticles (NPs) are particles with dimensions ranging from 1 to 100 nanometers (nm) in at least one dimension, characterized by unique physical, chemical, and biological properties

compared to their macroscopic counterparts. Their basic composition is relatively complex and includes a surface layer, a coating layer, and a core, which essentially constitutes the central part of the NPs. [7]

The size, shape, and surface functionalization of nanoparticles play a key role in their application in cancer therapy. The size of NPs significantly influences their biodistribution, cellular uptake, and ability to penetrate biological barriers, such as the blood-brain barrier (BBB). [8] Different shapes of NPs may affect their interactions with cells and their fate within the body. For example, elongated NPs may exhibit distinct pharmacokinetics and biodistribution compared to spherical NPs. [9] Surface functionalization is crucial for ensuring specific targeting to cancer cells, enhancing stability in biological fluids, preventing undesired uptake by the immune system, and facilitating the delivery of the therapeutic payload. [8]

NPs enable precise control over drug release in response to specific conditions in the tumor microenvironment. With their ability to respond to stimuli such as enzymes, pH, temperature, light, or magnetic fields, they serve as intelligent therapeutic systems. They can be designed so that their properties change under the influence of these factors, allowing controlled drug delivery directly to the tumor, thereby increasing local drug concentration and minimizing effects on healthy tissues. [7,10]

It is also important to note that upon contact with bodily fluids, proteins adsorb onto the surface of NPs, forming what is known as the protein corona (PC). This protein layer can significantly influence the in vivo fate of the nanoparticle by modifying its size, surface charge, interactions with cells, and recognition by the immune system. Therefore, the characterization and minimization of the undesirable protein corona is an important aspect of designing effective nanotechnology-based drug delivery systems. [11]

A key factor influencing the biodistribution of NPs is the coating of their surface with polyethylene glycol (PEG). [10] PEGylation creates a hydrophilic layer on the nanoparticle's surface, which minimizes the adsorption of plasma proteins (opsonization) and thus reduces uptake by the reticuloendothelial system (RES). [7] As a result, the circulation time of NPs in the bloodstream is significantly prolonged, increasing the likelihood of their reaching the tumor site through the enhanced permeability and retention (EPR) effect or active targeting. [8,10]

Due to their specific properties, nanoparticle drug carriers play a crucial role in modern chemotherapy, offering targeted drug delivery, reduced side effects, protection of the active substance, increased bioavailability, and new therapeutic and diagnostic opportunities. [9,11]

Mechanisms of Drug Delivery

The mechanisms of interaction between NPs and cancer cells include both passive and active targeting strategies.

Passive targeting is based on the enhanced permeability and retention (EPR) effect, which occurs in the tumor vasculature. The blood vessels in tumors are characterized by leakiness and pores ranging from 200 to 2000 nm, depending on the cancer type and tumor microenvironment. In addition, lymphatic drainage within the tumor is impaired, leading to the retention of NPs in the tumor region. Passive targeting does not utilize specific ligands for cancer cells but relies on the physicochemical properties of NPs, such as size and circulation time. [7] Examples of drugs based on passive targeting include Doxil® (liposomal doxorubicin) and Abraxane® (albumin-bound paclitaxel). [7,11]

Active targeting involves functionalizing the surface of NPs with specific ligands such as antibodies, peptides, aptamers, or small molecules (e.g., folic acid, transferrin). These ligands bind to specifically or overexpressed receptors on the surface of cancer cells (or on the endothelial cells of tumor vessels), thereby increasing nanoparticle uptake by these cells via receptor-mediated endocytosis. Active targeting aims to increase drug concentration in target cells while reducing off-target effects. [7,8]

Transport Across the Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB) is a microvascular network that separates the central nervous system (CNS) from the peripheral blood circulation, posing a significant challenge in delivering drugs to the CNS. Developing strategies that enable effective penetration of this barrier is crucial for treating brain tumors such as gliomas. Nanoparticles show promise as drug delivery systems capable of crossing the BBB and increasing therapeutic concentrations in brain tissue. [12]

Nanoparticles (NPs) cross the BBB via various transport mechanisms. One key mechanism is receptor-mediated transcytosis (RMT), in which NPs functionalized with ligands such as transferrin, lactoferrin, or the Angiopep-2 peptide bind to endothelial receptors, initiating endocytosis and subsequent transport across the barrier. [13] Similarly, adsorptive-mediated transcytosis, based on electrostatic interactions between NPs and the cell membrane, plays a role, although excessive positive charge can lead to toxicity and BBB disruption. [12,13] Another strategy is cell-mediated transcytosis, where drugs encapsulated in liposomes are transported to the brain by immune cells in response to inflammation. [13,14] NPs may also

utilize carrier-mediated transport (CMT), mimicking endogenous substances to cross the BBB via active membrane transporters. [12,14] In contrast, passive diffusion can occur for small, lipophilic molecules; however, in a healthy BBB, tight junctions significantly limit this pathway. [12] Under pathological conditions, such as in glioblastoma multiforme, the BBB often exhibits increased permeability (the EPR effect), facilitating easier nanoparticle penetration into the tumor. [14]

The efficiency of nanoparticle transport across the BBB depends on a range of factors, including size, shape, chemical composition, surface charge, and particle rigidity. [15] Surface modifications, such as conjugation with specific ligands, surfactants, or cell-penetrating peptides (CPPs), can significantly enhance their ability to traverse the barrier. [12,13] Additionally, strategies for temporarily opening the BBB, such as focused ultrasound (FUS) or appropriate chemical agents, may support the efficacy of transport. At the same time, potential neurotoxicity of certain nanomaterials must be taken into account, underscoring the need for further research into their safety. [12]

Examples of Nanoparticles in GBM Chemotherapy

Nanoparticles represent a promising strategy in the treatment of glioblastoma multiforme (GBM), enabling selective drug delivery and improving therapeutic efficacy. Several major types of nanoparticles are distinguished by their different mechanisms of action.

Liposomal Nanoparticles

Liposomes are spherical vesicles with a structure similar to cellular membranes, composed of a bilayer of amphiphilic phospholipids surrounding an aqueous core. [16] The phospholipid bilayer consists of hydrophilic heads oriented outward and hydrophobic fatty acid chains forming the inner, non-polar layer. This structure allows liposomes to encapsulate both hydrophilic drugs in the aqueous core and lipophilic drugs within the lipid bilayer, thus expanding their therapeutic applicability. [17]

Liposomes are considered biocompatible and biodegradable, contributing to their low toxicity and minimal in vivo immunogenicity. PEGylation (surface modification with polyethylene glycol) can further improve their stability and prolong blood circulation time by reducing immune system uptake—these are known as "stealth liposomes". [16,18]

Preclinical studies have demonstrated the effectiveness of liposomes in delivering various chemotherapeutic agents to glioblastoma, including:

- Doxorubicin (DOX): Liposomal doxorubicin, often PEGylated, has shown reduced systemic toxicity and enhanced drug delivery to brain tumors. Modifications using cell-penetrating peptides (CPPs) or transferrin (TF) further increase efficacy. [16,18] Studies are also underway on pH-sensitive liposomes that release doxorubicin in a controlled manner within the tumor microenvironment. [38]
- Paclitaxel (PTX): Encapsulation of paclitaxel in liposomes can enhance its solubility and BBB penetration. [16,38] Ligand modifications using glucose, RGD peptides, or dNP2 peptides improve targeting and therapeutic efficiency. [16]
- Temozolomide (TMZ): Liposomal formulations of temozolomide can enhance tumor concentration and reduce systemic toxicity. The combination of liposomes with ultrasound technology may further increase BBB permeability and TMZ delivery. [18,38]

Moreover, liposomes can effectively deliver natural anticancer compounds such as acteoside and curcumin, often showing greater cytotoxicity than free compounds and inducing apoptosis in glioma cells. [17]

Polymeric Nanoparticles

Polymeric nanoparticles serve as drug carriers composed of a core made from biocompatible and biodegradable polymers, which help reduce toxicity and accumulation in the body. Therapeutic substances can be surface-attached or encapsulated within the particle. [19,20] Properties such as molecular weight, crystallinity, and stability are carefully analyzed to develop carriers with desired features. [20]

Key polymers used in brain cancer treatment include:

- Polyanhydrides: Gliadel® wafer, a polyanhydride-based implant releasing carmustine (BCNU), is FDA-approved for recurrent GBM treatment. [19]
- Poly(lactic-co-glycolic acid) (PLGA): An FDA- and EMA-approved anionic polymer widely used for drug encapsulation. It features easy synthesis, modifiability, and controlled drug release. An example is PLGA nanoparticles coated with Poloxamer 188 (Dox-PLGA), which have demonstrated BBB penetration and tumor inhibition. [35]
- Poly(β-amino esters) (PBAEs): Easily synthesized, biodegradable, and biocompatible cationic polymers used for delivering polynucleotides. Their pH-buffering capacity facilitates endosomal escape. Though blood instability is a limitation, surface modifications aim to overcome this. [19]

- Chitosan: Used as a nanoparticle coating or in hybrid delivery systems. Chitosan-dextran hybrid nanoparticles have shown increased glioma cell internalization and in vivo tumor accumulation. [19,20]
- Poly(ε-caprolactone) (PCL): Known for versatility, PCL can be blended with other polymers. For example, PCL nanoparticles loaded with docetaxel (DOC) and modified with methoxy-PEG (mePEG-PCL), dispersed in a bioadhesive film, showed prolonged drug release and higher cytotoxicity compared to free docetaxel. [20]
- Poly(alkyl cyanoacrylate) (PACA): Promising for BBB drug delivery and solid tumor infiltration. Their degradation enables sustained drug release, and they may overcome multidrug resistance (MDR) through ionic interaction with agents like doxorubicin. [19]

Gold Nanoparticles (Metallic)

Gold nanoparticles (AuNPs) are among the most versatile and extensively studied materials in nanomedicine. They are typically synthesized in solution via reduction of chloroauric acid, yielding particles ranging from 5 to 100 nm in diameter. Their optical and electrochemical properties make them valuable tools in cancer therapy, including for GBM. [21]

The surface of AuNPs can be functionalized with various ligands to enhance targeting specificity, stability, and reduce toxicity. Drug delivery via AuNPs can be achieved through covalent or electrostatic conjugation to the particle surface or encapsulation within porous structures. [22]

In vivo studies in animal models of glioblastoma have shown that both unmodified and functionalized AuNPs can cross the BBB, especially when aided by MRI-guided focused ultrasound (FUS). Accumulation of AuNPs within tumors contributed to tumor volume reduction and prolonged survival. [34] However, their clinical use in GBM patients remains limited and requires further investigation.

Magnetic Nanoparticles

Magnetic nanoparticles (MNPs), particularly superparamagnetic iron oxide nanoparticles (SPIONs), are a promising class of materials used in GBM therapy. Their main advantage is the ability to be directed and controlled by external magnetic fields. The magnetic core, usually iron oxide (Fe_3O_4), imparts unique magnetic properties suitable for magnetic therapy and medical imaging as contrast agents. [23]

Additionally, magnetic nanoparticles can be used in magnetic hyperthermia. Under an alternating magnetic field, MNPs generate heat, raising the temperature in the tumor area.

This hyperthermia damages tumor cells—especially glioma cells—and significantly enhances the efficacy of chemotherapy. [25]

NanoTherm® (MagForce Nanotechnologies AG), which uses SPIONs coated with aminosilane, is an example of a nanodrug approved in Europe for hyperthermia therapy in recurrent GBM. Clinical studies have shown that its combination with radiotherapy is safe and effective, leading to improved overall survival. [35]

Enhancing Radiotherapy with Nanoparticles

Glioblastoma multiforme (GBM) resistance to radiotherapy is a key factor contributing to treatment failure and remains a significant clinical challenge. Despite the use of radiotherapy (RT) as one of the main components of standard GBM treatment, patient prognosis remains poor. [26]

Limitations of Radiotherapy

GBM cells, characterized by significant heterogeneity, often exhibit innate or acquired resistance to radiation-induced DNA damage. [27] Only about 2% of this damage results in cytotoxic double-strand breaks. [26] Furthermore, the high activity of DNA repair mechanisms allows tumor cells to survive treatment. [28] Hypoxia in the tumor microenvironment further impairs radiotherapy efficacy, as oxygen plays a critical role in fixing DNA damage. [26,29] The degree of hypoxia in malignant gliomas is an important prognostic factor for patient survival. [29] Increasing radiation dose is limited by the need to spare healthy tissue, and the invasive nature of GBM complicates complete eradication of cancer cells. In response to these challenges, new therapeutic strategies, including nanomedicine and nanoparticle-based radiosensitizers, are being intensively explored to enhance the effectiveness of radiotherapy. [26]

Mechanisms of Radiosensitizers

Nanoparticles can enhance tumor cell susceptibility to ionizing radiation through various mechanisms. One key process is the stimulation of reactive oxygen species (ROS) production, leading to intensified cellular damage. [28] Nanoparticles can also serve as drug carriers that inhibit DNA repair mechanisms or other processes responsible for radioresistance. Additionally, they can modulate the tumor microenvironment, influencing cancer cell invasiveness. [30]

Metallic Nanoparticles as Radiosensitizers

High atomic number (Z) nanoparticles, such as gold (Au) or gadolinium (Gd), can absorb higher levels of radiation energy and emit secondary electrons, increasing the local radiation dose within tumor cells. [31] Gold nanoparticles (AuNPs) are especially well-studied due to their low toxicity, ease of synthesis, and surface functionalization. [28] Both preclinical and clinical studies have shown the potential of AuNPs to enhance GBM radiotherapy efficacy. [26]

Gadolinium nanoparticles (GdNPs), which serve both as MRI contrast agents and radiosensitizers, have also gained attention. [28] Phase I studies in patients with brain metastases demonstrated safety and tumor response when combined with whole-brain radiotherapy (WBRT), with nanoparticles retained in tumors for up to one week. [26]

Notably, studies suggest that silver nanoparticles (AgNPs) may exhibit superior radiosensitizing properties compared to gold. AgNPs effectively inhibit proliferation, promote apoptosis, and induce autophagy in cancer cells. [28]

Although research on nanoparticles in GBM radiotherapy is promising, further clinical studies are necessary to confirm the safety and efficacy of these innovative strategies in primary GBM treatment.

Nanoparticles in Combined Therapy

Combined therapy involves the simultaneous or sequential use of two or more therapeutic modalities targeting different aspects of tumor biology and the tumor microenvironment to achieve a synergistic anticancer effect. In the context of nanoparticles, combined therapy in GBM most commonly integrates chemotherapy with radiotherapy, though several other modalities are also under investigation.

Immunotherapy

Nanoparticles can be designed to deliver both chemotherapeutic and immunotherapeutic agents simultaneously. For instance, a neutrophil-based delivery system loaded with ZGO@TiO_2 nanosensors carrying PD-1 antibodies and liposomal paclitaxel (PTX) can be activated by ultrasound, which triggers ROS release and liposome rupture. [32] Another example involves a nanoparticle targeting CD47/PD-L1 and loaded with a STING agonist to enhance immune response and radiotherapy in GBM treatment. [24]

Photothermal Therapy (PTT)

Nanoparticles play a key role in PTT by being engineered to absorb near-infrared (NIR) light and convert it into heat, selectively accumulating in tumor tissue to destroy cancer cells. Examples include noble metal-based nanoparticles (gold, silver, palladium), copper, carbon materials, organic polymers, and polydopamine (PDA) nanoparticles, which show high photothermal conversion efficiency. [33,36]

Photodynamic Therapy (PDT)

PDT relies on the interaction of three components: a photosensitizer, light of a specific wavelength, and oxygen. Upon light exposure, the photosensitizer transfers energy to oxygen, generating ROS toxic to cancer cells. Nanoparticles enhance PDT by improving the delivery of photosensitizers to tumors, increasing local concentration and minimizing toxicity to healthy tissues. [32,33]

Tumor microenvironment (TME) hypoxia can limit PDT effectiveness due to oxygen dependence for ROS generation. Strategies are being developed to overcome hypoxia, such as oxygen-releasing nanoparticles or the use of oxygen-independent photosensitizers. [33]

An example is mesoporous nanoparticles loaded with a photosensitizer (RBT), modified with aptamer AS1411 and transferrin. These particles showed enhanced glioma cell uptake, tumor volume reduction, and apoptosis under light exposure, resulting in prolonged survival in U-87 MG glioma mouse models. [34]

PTT + PDT Combinations

Thanks to their complementary mechanisms, combining PTT and PDT can lead to synergistic effects in glioma treatment. PDA nanoparticles can act as platforms for dual therapy by loading both photothermal agents and photosensitizers. [32]

Huang et al. developed ICG-PDA-TPZ nanoparticles, which exhibited photothermal and photodynamic effects under NIR laser exposure. These synergized with a hypoxia-activated drug (TPZ), leading to effective inhibition of glioma growth in vitro and in vivo with minimal side effects. [33]

Gene Therapy

Nanoparticles can serve as carriers for both chemotherapeutic drugs and genetic material, such as siRNA, to simultaneously target multiple mechanisms in GBM cells. [24,25] For

example, nanoparticles co-delivering temozolomide (TMZ) and si-PD-L1 to TMZ-resistant GBM cells led to PD-L1 silencing and enhanced T-cell cytotoxicity. [25]

Theranostics

Nanoparticles play a promising role in the theranostics of glioblastoma multiforme (GBM), combining diagnostic imaging with therapy. They can be engineered as contrast agents for various imaging modalities, including magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and fluorescence imaging. [32]

Superparamagnetic iron oxide nanoparticles (SPIONs) are used in MRI for brain tumor visualization. In MRI, SPIONs induce stronger proton relaxation compared to paramagnetic contrast agents, allowing effective imaging even with smaller amounts of contrast material. [24,32]

Gold nanoparticles can be functionalized and used in imaging due to their unique optical properties [24,37]. For example, AuNPs labeled with chlorotoxin peptides have been used for glioma imaging via SPECT/CT. [21]

Polydopamine (PDA) nanoparticles demonstrate potential in photoacoustic imaging (PAI) and can be combined with other contrast agents, such as iron oxides, for multimodal imaging. [33]

Liposomes containing nanoparticles can be equipped with PET and MRI tracers to enable monitoring of their biodistribution and tumor interactions. [32]

Nanoparticle-based theranostics offer a promising approach for GBM treatment by integrating diagnosis, targeted therapy delivery, and real-time monitoring of therapeutic outcomes.

Limitations of Nanoparticles

The limitations and challenges associated with the application of nanotechnology in GBM therapy represent a significant barrier to translating promising preclinical findings into effective clinical treatments.

Challenges in Bioavailability and Metabolism

One of the primary challenges in nanoparticle-based GBM therapy is ensuring effective bioavailability within the brain tumor while overcoming the blood-brain barrier (BBB). Although the BBB may be disrupted within tumors—creating the so-called blood-tumor barrier (BTB)—its permeability is heterogeneous, and some regions may remain intact, which still hampers drug delivery. [32] Additionally, nanoparticle metabolism and clearance significantly affect their availability at the target site. Particles smaller than 10 nm may be

rapidly eliminated by renal filtration, reducing circulation time and therapeutic effectiveness. In contrast, larger particles (>150 nm) are more prone to rapid uptake by the reticuloendothelial system (RES), limiting tumor accumulation. Surface PEGylation is a strategy used to prolong nanoparticle circulation by reducing RES uptake. [24,34] However, even PEGylation does not guarantee consistent and efficient drug delivery to all tumor regions. [35]

Potential Side Effects and Toxicity

The safety of nanoparticles in GBM therapy remains a critical consideration. Adverse effects and toxicity may arise due to their physicochemical properties, including size, shape, surface charge, and chemical composition. [24,32] Positively charged nanoparticles can interact more efficiently with negatively charged cell membranes, potentially increasing tumor cell uptake but also promoting reactive oxygen species (ROS) production and cytotoxicity. [34] Nanoparticles may accumulate in organs such as the liver and spleen, posing risks of organ-specific toxicity with prolonged exposure. [33,34]

There are also concerns regarding potential neurotoxicity of nanomaterials and their impact on BBB integrity. Temporary BBB disruption by nanoparticles may increase the risk of unwanted substances or pathogens entering the brain. [25,32,34]

Preclinical and Clinical Research Limitations

Translating promising preclinical results in nanoparticle-based GBM therapies into effective clinical applications is challenging. In vitro and animal models do not fully replicate the tumor's biological complexity, microenvironment, or interactions with the immune system, nor do they accurately represent BBB permeability and nanoparticle biodistribution across species. [32]

The number of completed clinical trials is limited, with many still in early phases (I/II) and often showing no significant improvement in patient survival over standard therapy. [24,34] Additional obstacles include patient heterogeneity, insufficient control over drug distribution in the brain, potential toxicity, and regulatory and ethical barriers that slow the clinical implementation of nanotechnology. [32]

Costs and Implementation in Standard Therapy

The high costs of developing, producing, and characterizing nanoparticles represent a major challenge to integrating nanotechnology into standard GBM treatment. Complex synthesis

processes, the need to meet stringent quality standards, and regulatory requirements can significantly increase the cost of nanoparticle-based therapies, potentially limiting patient access to these innovations. [32,33]

Conclusions

Nanotechnology opens new perspectives in the treatment of glioblastoma multiforme (GBM), offering innovative strategies to support conventional therapies. A review of the literature indicates that nanoparticles can significantly enhance the effectiveness of chemotherapy and radiotherapy by improving drug bioavailability, facilitating transport across the blood-brain barrier, and enabling precise delivery of active compounds to cancer cells. In particular, lipid-based, polymeric, metallic, and magnetic nanoparticles demonstrate strong therapeutic potential by minimizing systemic toxicity and reducing the risk of tumor resistance to treatment.

The potential applications of nanotechnology in GBM therapy are extensive and include not only improvements in drug pharmacokinetics but also the use of nanoparticles in photothermal therapy, immunotherapy, and gene therapy. Nanotechnology also enables the development of advanced diagnostic methods, allowing for more accurate tumor imaging and real-time monitoring of therapeutic efficacy. Despite these promising results, most research on nanoparticles in GBM therapy remains at the preclinical or early clinical trial stages.

Future research should focus on optimizing the composition and properties of nanoparticles to enhance their efficacy and safety. A key challenge remains the development of strategies for precise control over drug delivery and the elimination of long-term side effects associated with nanotechnology-based therapies. Continued advancement in this field, supported by robust clinical studies, may ultimately lead to a breakthrough in GBM treatment—substantially improving patient outcomes and paving the way for more personalized oncology care.

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Authors do not report any disclosures.

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All authors contributed to the article.

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