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Glioblastoma Multiforme: Current Developments in Molecular Pathways, Magnetic Field-Based Interventions, and Personalized Therapy

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and aggressive brain cancer in adults. It is also one of the most aggressive tumors of the central nervous system and is associated with the worst prognosis. Developing an effective treatment method is complicated by the disease: its resistance to treatment, a high recurrence rate, and genetic and histological heterogeneity. This review provides a detailed assessment of GBM diagnostic methods, molecular pathogenesis, histopathological features, and current treatment approaches. IDH mutations, together with molecular markers such as PTEN, EGFR, TP53, and MGMT promoter methylation, play a significant role in predicting the course of glioblastoma multiforme and determining treatment response. Personalized medicine and immunotherapies, together with routine treatments, represent noteworthy approaches to GBM treatment in the near future. Recent studies report that magnetic field-based interventions are a promising approach and that applications of low-frequency magnetic fields suppress glioma cell proliferation. Studies conducted with the OM-100 device have shown a significant reduction in tumor growth in both in vivo and in vitro models and have demonstrated synergistic effects when the device was combined with anti-PD-1 therapy. Furthermore, static magnetic fields have been reported to increase apoptosis, inhibit proliferation, and may offer a complementary treatment with low toxicity. These findings suggest that magnetic-field-based approaches offer an innovative strategy for GBM treatment.

Keywords: Glioblastoma multiforme, immunotherapy, magnetic fields, mutations, precision medicine, therapeutics.

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common type of aggressive brain cancer in adults. It is also one of the most aggressive and worst-prognosis tumors of the central nervous system. Developing an effective treatment method for the disease is complicated by its resistance to treatment and high recurrence rate, and its genetic and histological heterogeneity. Grade 4 malignant gliomas, as classified by the World Health Organization (WHO), are usually located in the supratentorial area. Histopathologically, it is characterized by both astrocytic and necrotic

Table 1. Epidemiological characteristics of glioblastoma multiforme

Epidemiological characteristics	Information / value	Reference
Frequency of occurrence (Incidence)	Approximately 3.2–4.3 cases per 100,000 people per year	Ostrom et al., 2023[3]
Age group	Most commonly between the ages of 55 and 75	Ostrom et al., 2023[3]
Gender distribution	More common in men than in women (ratio of 1.6:1)	Ostrom et al., 2023[3]
Peak age of onset	around 64 years old	Ostrom et al., 2023[3]
Percentage of all primary brain tumors	Approximately 15–17%	Ostrom et al., 2023[3]
Proportion in high-grade gliomas	Approximately 45–50%	Ostrom et al., 2023[3]
Ethnic distribution	Higher in Caucasians; lower in Blacks and Asians	Ostrom et al., 2023[3]
Risk factors	Ionizing radiation, age, male gender, genetic predisposition	Ostrom et al., 2023[3]
Primary/secondary GBM ratio	Primary GBM ≈ 90%; Secondary GBM ≈ 10%	Nakajima et al., 2018[4]
Survival time (average)	Surgery + Radiotherapy + Chemotherapy for 12–18 months	Stupp et al., 2005[20]
5-year survival rate	Approximately 5–7%	Stupp et al., 2005[20]

GBM: Glioblastoma multiforme.

core-like cells and diffuse neoplastic infiltration of GBM into nerve tissue (e.g., angular nuclei and eukaryotic nuclei).[1] The high heterogeneity of GBM, combined with the blood-brain barrier (BBB) structure, creates an environment conducive to tumor cell survival.[2] In glioblastoma multiforme, difficulty in defining tumor margins during surgical intervention stems from its rapid invasion into surrounding brain tissue. This makes it very difficult to completely remove the tumor and often results in residual tumor tissue. Epidemiological findings indicate that glioblastoma multiforme is more common in men over the age of 50. In these patients, survival time generally ranges from 12 and 18 months despite the addition of radiotherapy and chemotherapy to the surgical intervention. In this context, the basic epidemiological and molecular characteristics of Glioblastoma Multiforme are summarized in Table 1.[1,3]

In recent years, studies, particularly in molecular biology and genetic analyses, have provided a more comprehensive understanding of the disease's pathogenesis. In addition, new treatment options have been developed, and the biological basis of the disease has been established.[3]

CLINICAL AND RESEARCH RESULTS

A literature review was conducted systematically and in detail on glioblastoma multiforme using the PubMed, Web of Science, and Scopus databases between May and August 2025. The search was designed to include studies focusing on human subjects and examining molecular mechanisms, signaling pathways, or treatment strategies in glioblastoma. Appropriate studies were identified through a detailed evaluation of the titles, abstracts, and full texts of the articles.

HISTOPATHOLOGICAL FEATURES

The diagnosis of GBM relies heavily on its histopathological features. Histologically, GBM is characterized by necrotic areas, microvascular proliferation, pleomorphic cells, and high mitotic activity. Glioblastoma multiforme tumor cells exhibit high nuclear atypia (irregularity and enlargement of the nucleus) as well as highly intense mitotic divisions, indicating both uncontrolled cell division and invasive spread to surrounding tissues.[1] Circumscribed gliomas are mostly benign. In contrast, diffuse (spreading) gliomas can infiltrate the surrounding normal brain parenchyma and recur even after complete tumor resection. Diffuse gliomas are the most common type of intrinsic primary brain tumor. Diffuse gliomas are classified into three groups according to malignancy levels: WHO grades 2, 3, and 4. WHO grade 4 diffuse glioma is synonymous with glioblastoma multiforme (GBM). Astrocytoma with GBM is the most common histological subtype of WHO grade 4 diffuse gliomas. In addition, it accounts for almost 50% of all primary malignant brain tumors. Palisade-like necrosis, a commonly observed and distinctive histological finding in GBM, forms as areas of necrosis resulting from depletion of oxygen and nutrients associated with the rapid growth of tumor cells. Microvascular proliferation, known as the abnormal proliferation of small blood vessels, provides the tumor with the blood supply needed to continue its progression. At the same time, this process also paves the way for GBM to become resistant to treatment.[4]

Molecular Markers

In addition to histopathological studies, Both molecular biology techniques and defined genetic and epigenetic parameters play a role in identifying subtypes of GBM. The

Table 2. Clinical significance of prominent molecular markers in glioblastoma multiforme

Molecular marker	Clinical role	Prognostic/predictive value	Relationship to treatment	References
MGMT promoter methylation	DNA repair	Predictive in predicting response to treatment	Temozolomide sensitivity increases	Hegi et al., 2005[6]
EGFR amplification / EGFRvIII	Cell proliferation and invasion	Poor prognosis	EGFR inhibitors (Erlotinib, Gefitinib)	An et al., 2018[11]
PTEN loss	Activation of the PI3K/AKT/mTOR pathway	Associated with tumor progression	Resistance to mTOR inhibitors develops	Bonneau & Longy, 2000[17]
TP53 mutation	Tumor suppressor gene	Poor prognosis, resistant structure	Little effect on standard treatment	Yin et al., 2002[18]
IDH1/2 mutation	Cell metabolism, epigenetic regulation	Good prognosis (especially in secondary GBM)	Targeted therapies potential	Yan et al., 2009[19]

GBM: Glioblastoma multiforme; IDH: Isocitrate dehydrogenase; MGMT: O6-methylguanine-DNA methyltransferase; EGFR: Epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog; TP53: Tumor protein p53; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin.

molecular parameters that have contributed most to the clinical application of GBM are IDH1, MGMT, and EGFR.[5] MGMT (O-6-methylguanine-DNA methyltransferase) promoter methylation is directly related to the efficacy of temozolomide treatment. This methylation is removed by an enzyme that repairs methylated bases in DNA and can eliminate DNA damage caused by temozolomide. In short, it has been emphasized that temozolomide causes cancer cell death by increasing the effectiveness of the structural damage it creates in DNA.[6] Among patients receiving temozolomide treatment, those with methylation of this promoter generally have better outcomes, whereas those without methylation may develop resistance to treatment. Therefore, MGMT methylation status plays an important role in personalizing treatment methods and provides clinically meaningful prognostic guidance regarding how patients will respond to treatment.[7] IDH (isocitrate dehydrogenase) mutation has been widely associated with a better prognosis in patients with GBM. These mutations are mostly found in younger patients (secondary GBM) with a high number of mutations in the TP53 gene.[6] In addition, EGFR can serve as a primary therapeutic target. Tyrosine kinase inhibitors, such as erlotinib and gefitinib, are among the treatment methods aimed at inhibiting EGFR activity. This method has been evaluated in clinical trials to block downstream signaling pathways by inhibiting EGFR phosphorylation.[8] The relationship between the most frequently studied molecular markers in GBM and treatment, as well as their clinical significance, are presented in Table 2.[5,7]

Molecular Pathogenesis

The development of GBM stems from numerous genetic and epigenetic alterations. Recent studies have shown that GBM is associated with multiple molecular pathways and that these alterations determine the invasive nature of the tumor. Molecular-level abnormalities encompass multiple processes, such as excessive expression of growth factors, disruption of DNA repair mechanisms, and mutations in genetic factors that regulate the cell cycle. Glioblastoma multiforme (GBM) is a common type of primary brain tumor. Despite ongoing standard treatment, the average survival time is approximately 15 months, and it is a clinically aggressive tumor. Studies have suggested that the molecular pathogenesis of GBM has a highly complex and layered structure.[5] This review provides a detailed assessment of the tumor microenvironment, epigenetic and genetic alterations driving GBM pathogenesis, signaling pathways, and glioma stem cells. These epigenetic and genetic alterations that occur at the molecular level in GBM determine not only the biological behavior of tumor cells, but also the formation of the tumor microenvironment and the shaping of the immune response.

Tumor Microenvironment and Immune Suppression

Mutations in TP53, EGFR, NF1, PTEN, IDH1/2, and the TERT promoter are among the genetic abnormalities that shape the molecular profile of GBM. EGFR amplification, which causes permanent activation of the receptor even without ligand interaction, and especially the EGFRvIII mutation trigger cell proliferation and activate anti-apoptotic mechanisms. Losses in the PTEN gene, which cause disinhibition of the PI3K/AKT/mTOR pathway, promote tumor progression.[9]

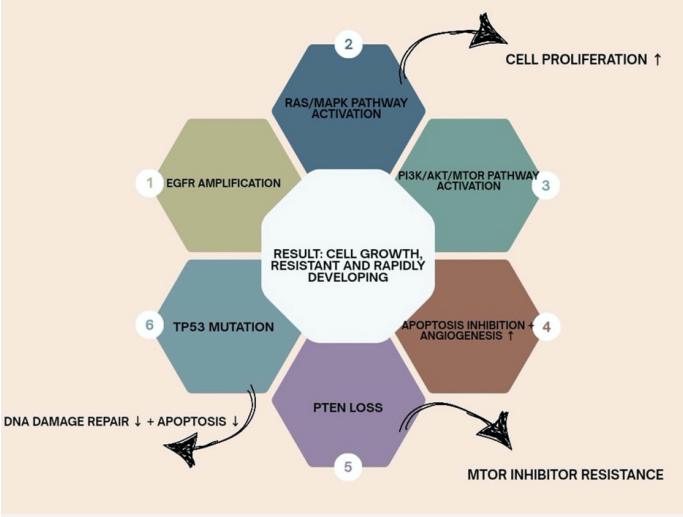

Figure 1. Key signaling pathways involved in the molecular pathogenesis of GBM, including EGFR amplification, RAS/MAPK activation, PI3K/AKT/mTOR signaling, PTEN loss, TP53 mutation, and apoptosis/angiogenesis regulation.

TP53 mutations trigger the disruption of fundamental tumor suppressor mechanisms, such as cell cycle control, DNA repair, and apoptosis. Epigenetic reprogramming occurs as a result of IDH1 mutations, which are frequently seen in secondary GBMs, through the formation of 2-hydroxyglutarate.[5]

Epigenetic Changes

Epigenetic regulation enables control of gene expression without altering the DNA sequence. MGMT promoter methylation is one of the most common epigenetic modifications observed in GBM. Methylation in this gene promoter region reduces DNA repair activity and enhances the drug response of tumor cells to alkylating agents such as temozolomide. Epigenetic mechanisms such as microRNA modulation and histone modifications also play a role in tumor progression. MicroRNAs such as miR-21 and miR-10b have been implicated in the activation of anti-apoptotic signaling pathways and the enhancement of the invasive phenotype.[9]

Genetic Alterations and Mutations

The tumor microenvironment plays a significant role in both the acquisition of invasive properties and the development of resistance to treatment in glioblastoma multiforme. Immune-suppressive cytokines (TGF-β, IL-10), macrophages (TAMs), astrocytes, and microglia associated with the tumor are used to create an immune-suppressive environment.[10] This environment suppresses T cell activation, preventing the elimination of tumor cells by the immune system. In addition, increased PD-L1 expression in GBM prevents effective the therapeutic suppression of immune checkpoints, thereby facilitating protection from the immune system. Consequently, this situation limits both the immune system's ability to recognize tumor cells and its potential to eliminate them.[9]

Signaling Pathways and Intracellular Communication

Various cellular signaling pathways play an important role in both the tumorigenesis and progression of GBM. Figure 1 depicts a pathway diagram summarizing the relationships among the signaling pathways involved in GBM pathogenesis. Among these pathways, the best-characterized are as follows:

The PI3K/AKT/mTOR pathway, activated by PTEN loss, promotes cell proliferation and inhibits apoptosis. PTEN (Phosphatase and Tensin Homolog), a protein-coding gene, is a multifunctional tumor suppressor.[5,7]

EGFR mutations activate proliferation via the RAS/MAPK pathway. The most amplified receptor tyrosine kinase (RTK) in GBM is the epidermal growth factor receptor (EGFR). EGFR gene amplification, which is specific to the basic subtype of glioma, was detected in 57.4% of patients with primary GBM This situation leads to high EGFR protein levels triggering not only tumor formation but also its progression.[11]

The Notch and Wnt/β-catenin pathways promote the regeneration of glioma stem cells. The Notch and Wnt/β-catenin signaling pathways, which are evolutionarily conserved and fundamental, modulate key biological mechanisms such as cell differentiation, proliferation, and stem cell regeneration. In addition to tumor invasiveness, the preservation of tumor stem cells, dysregulation of these pathways, and the development of treatment resistance are also associated with highly malignant gliomas such as glioblastoma multiforme (GBM).[12]

STAT3 (Signal Transducer and Activator of Transcription 3), a transcription factor that plays a key role in the pathogenesis of glioblastoma (GBM), is essential for both the maintenance of neural stem cells and the development of astrocytes. It has also been found to be continuously active in both GBM and GBM-derived cell lines, compared with normal tissues. Consequently, it has been observed to stimulate tumor growth, angiogenesis, and immune effects.[13]

Glioma Stem Cells (GSCs)

Glioma stem cells are a subpopulation with both regenerative and tumor-forming potential. GSCs possess structural features that enable them to resist radiotherapy and chemotherapy. These cells cause the Notch and Hedgehog pathways to remain constantly active, while the hypoxic microenvironment also supports the phenotype of these cells.[14]

Angiogenesis and Hypoxia

Glioblastoma multiforme (GBM) is characterized by both adaptation to hypoxia and a dense vascular structure. VEGF expression supports new blood vessel formation by enhancing the hypoxia-inducible factor-1 alpha (HIF-1α) response. This not only increases tumor size but also hinders the effective delivery of chemotherapy agents to tumor tissue.[15]

Primary Genetic Alterations

EGFR Amplification

EGFR amplification and mutations are key oncogenic drivers in several cancers, including non-small cell lung cancer (NSCLC), breast cancer, and glioblastoma. Approximately two-thirds of primary GBMs exhibit EGFR amplification, and nearly half of these cases harbor concurrent EGFRvIII mutations and single-nucleotide variants. This alteration enhances tumor cell proliferation, invasion, and therapeutic resistance by activating major signaling pathways such as PI3K/AKT, RAS/MAPK and JAK/STAT.[16]

PTEN Loss

PTEN (Phosphatase and Tensin Homolog) is a gene that encodes a protein. In addition to being a multifunctional tumor suppressor, it is very common in human cancers. It is observed to varying degrees in cancers such as glioblastoma, endometrial cancer, prostate cancer, lung cancer, and breast cancer. It has been determined that this gene carries various structural abnormalities, such as mutations or deletions, in a large number of sporadic human tumors.[17]

TP53 Mutations

TP53 encodes the tumor suppressor protein p53, whose stability and activity are negatively regulated by the oncogene product MDM2 through proteasomal degradation. p53 plays a central role in DNA repair, cell cycle control, and inhibition of angiogenesis. TP53 mutations, which are common across multiple cancer types, contribute to glioblastoma development by promoting uncontrolled cellular proliferation.[18]

IDH Mutation

Isocitrate dehydrogenase (IDH) enzymes are key regulators of cellular metabolism, including the Krebs cycle and redox balance. IDH1 is localized in the cytoplasm and peroxisomes, whereas IDH2 and IDH3 are mitochondrial. Mutations in IDH1 and IDH2 define a distinct molecular subtype of glioblastoma by reprogramming cellular metabolism and promoting genomic instability. These alterations are commonly observed in human malignancies and are associated with a more favorable prognosis. According to WHO classification, IDH mutations are present in approximately 80% of grade II/III gliomas.[19]

MGMT Promoter Methylation

MGMT is an important DNA repair enzyme that protects cells against the carcinogenic and cytotoxic effects of alkylating chemotherapy agents. Epigenetic silencing of this gene through methylation of its promoter region reduces DNA repair capacity in glioblastoma cells and weakens the resistance developed against alkylating agents.[20] Furthermore, this promoter methylation is directly related to the efficacy of temozolomide used in treatment.[6]

DIAGNOSTIC METHODS

Accurate diagnosis and classification of GBM play a critical role in both predicting its progression and determining appropriate treatment methods.[21] The diagnosis usually begins with neuroimaging followed by biopsy and histopathological examination.

Neuroimaging

Magnetic resonance imaging (MRI) is the primary diagnostic modality for glioblastoma. Contrast-enhanced T1-weighted sequences are essential for assessing tumor size, margins, and peritumoral edema. Advanced techniques such as magnetic resonance spectroscopy (MRS) further characterize tumor biology and treatment response by analyzing metabolites including choline, creatine, and N-acetylaspartate.[22]

Histopathology and Biopsy

Biopsy is the most reliable method for diagnosing GBM. In the histopathological examination of tissue samples, characteristic findings of glioblastoma such as microvascular proliferation, pleomorphism, and necrosis are examined.[19] These morphological features, characteristic of GBM, both increase diagnostic accuracy and have prognostic significance.

Molecular Analyses

Recently, molecular markers have decisively influenced the identification of GBM subtypes and the development of personalized treatments. Promoter methylation of the MGMT (O6-methylguanine-DNA methyltransferase) gene is a strong predictive biomarker of response to temozolomide chemotherapy. Patients with MGMT methylation tend to respond better to alkylating agents and also exhibit a noticeable increase in overall survival.[6,21] IDH1/IDH2 mutations are commonly found, especially in secondary GBM cases, and correlate with a better prognosis. Both changes in tumor biological behavior and, in most cases, slower-growing tumors are associated with these mutations.[19]

Treatment Methods

Treatment for GBM is highly challenging and usually involves multiple treatment modalities.

Surgical Intervention

In GBM treatment, surgical resection is the initial and most important therapeutic step. The main goal of surgical resection is to relieve mass effect and obtain brain tissue for pathological examination by removing as much of the tumor as possible. Numerous prospective studies have shown that "gross total resection" of glioblastomas provides a better survival advantage than subtotal/partial resection.[23] The combination of techniques, including intraoperative MRI, neuronavigation, ultrasound, and fluorescence-guided surgery, has led to better survival outcomes and postoperative functional improvement by enabling safe and maximal surgical resection.[24] Numerous studies have demonstrated the importance of aggressive surgical resection, when possible, and have reported trends toward better outcomes in patients with greater resection volumes. Various studies have shown statistically significant associations between greater resection extent and longer progression-free survival and overall survival.[25]

Radiotherapy and Chemotherapy

Radiotherapy, which is frequently used in GBM treatment, is typically administered at a dose of 60 Gy, while chemotherapy is administered using chemotherapeutic agents such as temozolomide. Temozolomide, which inhibits DNA repair mechanisms, causes the death of tumor cells.[20] The average survival times of GBM patients by treatment method are shown in Figure 2.

Targeted Therapies

Recent studies indicate that targeted therapies, such as EGFR and VEGF inhibitors (e.g., bevacizumab), have shown positive results. Bevacizumab targets the tumor's blood vessels and also attempts to inhibit its growth.[26]

Immunotherapies

PD-1/PD-L1 immune checkpoint inhibitors, a promising approach in GBM treatment, are being investigated. However, because the GBM tumor microenvironment is immunosuppressive and heterogeneous, the efficacy of these treatments remains limited. A systematic review published by Baskaran and colleagues in 2024 examined clinical trials of PD-1/PD-L1 inhibitors for the treatment of GBM and concluded that these therapies generally provide limited benefit. However, it was emphasized that more positive results could be achieved in patient subgroups with specific biomarkers.[27]

Magnetic Field-Based Approaches and Their Use in GBM Treatment

In recent years, therapies based primarily on magnetic fields have emerged as promising alternatives for the treatment of neurological malignancies, such as glioblastoma multiforme

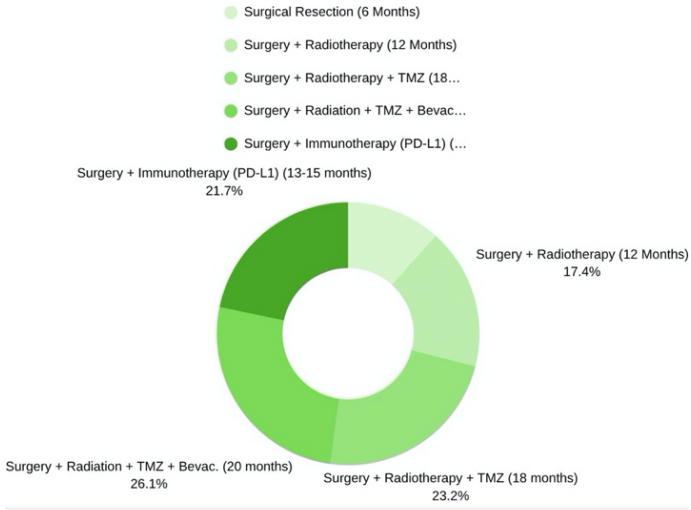

Figure 2. Average survival times observed in glioblastoma multiforme(GBM)patients according to different treatment approaches.

(GBM). These approaches generally include low-frequency magnetic fields (LF-MF), static magnetic fields (SMF), and tumor-treating fields (TTFields).

Low-Frequency Magnetic Fields (LF-MF)

In recent years, it has been demonstrated that low-frequency magnetic fields (LF-MF) have the potential to modulate the tumor microenvironment of glioblastoma multiforme (GBM) cells to favor the immune response, and to inhibit their proliferation. Studies using OM-100, an experimental tumor treatment device evaluated in GBM in both in vivo and in vitro models, report significant suppression of tumor growth. However, current data on the OM-100 device are largely limited to preclinical studies, and studies into clinical applications are still ongoing. In particular, it has been shown that LF-MF applied at a frequency of 100 kHz modulates PD-L1 expression in GBM cells. Furthermore, when combined with anti-PD-1 immunotherapy, it exhibits pronounced synergistic antitumor effects compared with standalone applications. These findings suggest that the integrated use of magnetic field-based approaches with immunotherapy may be a promising strategy in GBM treatment.[28]

Static Magnetic Fields (SMF)

The effects of SMF on GBM are related to mechanisms such as inhibition of cell proliferation, induction of apoptosis, and regulation of the tumor microenvironment. Research shows that SMF reduces the invasion and migration abilities of glioma cells and increases apoptosis, and does so by inhibiting TGF-β1-induced epithelial-mesenchymal transition (EMT).[29]

Tumor Treatment Fields (TTFields)

TTFields target cell division through the application of low-intensity electric fields. In GBM treatment, TTFields have been shown to suppress tumor growth by inhibiting cell division and to prolong patient survival. The NovoTTF-100A device is approved by the FDA and the European Medicines Agency (EMA) and is used in clinical applications.[30]

Glioblastoma multiforme is a significant focus of medical research, but it is also characterized by poor prognosis and resistance to treatment. Years of genetic and molecular research have led to new insights into the development of GBM and to new approaches to treatment. However, the heterogeneous and treatment-resistant nature of GBM complicates the development of effective treatment strategies. In the future, personalized treatment approaches, along with advances in genetic markers and immuno-oncology, will pave the way for significant steps forward in the treatment of GBM.

A meta-analysis evaluated the efficacy and safety of adjuvant temozolomide with radiotherapy for the treatment of glioblastoma. Analysis of randomized controlled trials showed that adding temozolomide to treatment significantly increased overall survival and progression-free survival. Furthermore, the incidence of serious treatment-related side effects was low, and they were tolerable to patients. These findings support the safe use of combined temozolomide therapy with radiotherapy as a standard treatment approach for GBM.[31]

A review examined glioblastoma treatment from a broad perspective, ranging from traditional methods to current multidisciplinary and innovative approaches. Due to the limitations of standard chemoradiotherapy and surgical protocols, novel targeted therapies, nanotherapies, immunotherapies, and non-invasive energy-based approaches are critically important. Furthermore, this study concluded that treatments applied alone are insufficient due to GBM's immune escape mechanisms and adaptive nature; therefore, combination-based treatment strategies may offer more effective solutions in the future.[32]

In a retrospective study, the efficacy and safety of temozolomide treatment, administered during and after radiotherapy, in patients with newly diagnosed glioblastoma were investigated. Based on ten years' experience, this study demonstrates that temozolomide improves tumor control and that treatment-related side effects are acceptable. Consequently, it is demonstrated that radiotherapy supported by temozolomide is appropriate for widespread use in glioblastoma treatment.[33]

A Phase I clinical trial investigated the safety, pharmacokinetics, and tolerability of the WEE1 kinase inhibitor adavosertib in combination with radiotherapy and temozolomide in patients with newly diagnosed glioblastoma. The study examined the drug's penetration into tumor tissue by measuring intratumoral drug levels during the treatment protocol. The results showed that the concurrent treatment had an acceptable toxicity profile and that intratumoral adavosertib concentrations were sufficient to achieve therapeutic efficacy. This study demonstrates the potential for concurrent use of adavosertib with radiotherapy and chemotherapy in glioblastoma treatment.[34]

The OLA-TMZ-RTE-01 Phase I study investigated the feasibility and safety of the combination of temozolomide, olaparib, and concurrent radiotherapy in newly diagnosed glioblastoma (GBM) patients who had undergone biopsy or partial resection. In the study, patients received different dose levels of the treatment protocol, and adverse events, treatment responses, and overall tolerability were examined. The findings indicate that combination therapy has an acceptable safety profile within the specified dose ranges and is clinically feasible.[35]

The study comprehensively examined applications of radiotherapy in patients with WHO Grade 4 adult-type diffuse glioma and evaluated dosing procedures and current clinical protocols. Based on the ASTRO clinical guidelines, the safety and efficacy of radiotherapy were analyzed, and the challenges encountered during the treatment period, as well as methods for optimization, were investigated. The data obtained within the findings contributed to the development of standard radiotherapy protocols for the treatment of high-grade gliomas.[36]

In this study, low-frequency repetitive transcranial magnetic stimulation (rTMS) produced tumor-suppressive effects on glioblastoma (GBM) progression. Experiments conducted in vitro and in vivo revealed that application of low-frequency rTMS limited GBM invasion, reduced cell proliferation, and activated apoptotic mechanisms. On the other hand, rTMS was evaluated for safety and tolerability and was found to have low toxicity and to be well tolerated. The findings suggest that rTMS may be a clinically feasible complementary treatment option that can be included in current standard protocols for GBM treatment.[37]

A study was conducted in China to investigate the efficacy and safety of chemoradiotherapy alone or in combination with Tumor Treating Fields (TTFields) in patients with newly diagnosed glioblastoma (GBM). In this study, patients were divided into two groups: the first group received the standard chemoradiotherapy protocol, while the second group received TTFields therapy in addition to this. Response rates, overall survival (OS), progression-free survival(PFS),and adverse events were evaluated. The findings showed that survival outcomes improved significantly in the group receiving TTFields and that the treatment demonstrated an acceptable safety profile.[38]

Another study evaluated the frequency-dependent effects of magnetic fields on tumor and non-tumor neural cell models. Cellular functions, proliferation, and viability were compared across different exposure frequencies. The results demonstrated that specific frequencies suppressed glioblastoma cell growth while exerting more limited effects on normal neural cells. These findings indicate that frequency-specific magnetic field modulation may represent a selective and complementary therapeutic strategy for glioblastoma.[39]

CONCLUSION

The challenging nature of glioblastoma multiforme stems from its aggressive behavior and resistance to treatment. Findings in the literature suggest that temozolomide-based radiotherapy is the standard approach for glioblastoma treatment. Additionally, innovative strategies such as PARP and WEE1 inhibitors, TTFields, and magnetic field-based methods offer potential for enhancing treatment efficacy. These findings suggest that combination approaches and personalized treatment plans may play a critical role in GBM management. In the future, integrating low-frequency magnetic field-based treatment approaches with personalized medicine strategies could create a significant paradigm shift in glioblastoma treatment. Within the scope of individualized approaches that take into account the characteristics of the tumor immune microenvironment, molecular profile, and patient-specific treatment responses, it may be possible to optimize the frequency, duration, and combination protocols for magnetic field applications, such as OM-100. When used in combination with immune checkpoint inhibitors and targeted agents, magnetic field therapies that are adapted according to patient-specific biomarkers (e.g., PD-L1 expression) may increase treatment efficacy while reducing side effects. In this regard, biomarker-based clinical trials and advanced preclinical studies will provide critical data to support the integration of magnetic field therapies into personalized GBM treatment algorithms.

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