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Diagnosis, Treatment, and Future Perspectives of Glioblastoma Multiforme

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Abstract: Currently, glioblastoma multiforme (GBM), the most malignant glial tumor of the central nervous system, stands out globally with its high mortality rate and significant prevalence among the adult population. Accordingly, issues related to the diagnosis, treatment, chemotherapy, complications, and outcomes of GBM are highly relevant today.Unfortunately, glioblastoma remains the impregnable fortress of modern neurooncology, as no effective therapeutic agent or treatment regimen has yet been developed that can fully cure the disease. Magnetic resonance imaging (MRI) and biopsy remain as the gold standards for diagnosis. Treatment involves neurosurgical intervention, radiotherapy, and chemotherapy.In current chemotherapy protocols for glioblastoma, new-generation medications are employed, particularly temozolomide, carmustine, and bevacizumab. However, their efficacy is not fully established, and their use is associated with various side effects and toxicities. The rapid proliferative nature of tumor cells, acquired resistance during chemotherapy, and the side effects of drugs present significant challenges in the management ofGBM.Due to these factors, the search for effective cures for glioblastoma remains as one of the top priorities in modern medicine.At present, available data and evidence regarding effective therapeutic regimens and chemotherapeutic agents for glioblastoma multiforme remain limited.Contemporary medical research focuses intensively on the prevention of chemotherapy-induced side effects and toxicities, as well as exploring innovative avenues for potential curative treatments for glioblastoma.

Keywords: Glioblastoma, Temozolomide, Chemotherapy, Carmustine, Bevacizumab

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Introduction

Glioblastoma multiforme (GBM) represents the most malignant and prevalent subtype of gliomas. It is the most common primary brain tumor in adults. High mitotic activity, microvascular proliferation, and necrosisare characteristic features of GBM [10].It is marked by rapid growth and invasiveness, often leading to a poor prognosis despite aggressive treatment. Histopathologically, GBM is characterized by diffuse neoplastic infiltration of neural tissue, central necrosis, and tumor cells displaying astroglial features such as angular nuclei and euchromatin [16].Despite current multimodal treatment strategies—including completely safe surgical resection followed by combined radiotherapy and/or chemotherapy—median survival remains limited [1].According to the WHO classification, glioblastoma multiforme (GBM) is a grade IV glioma and simultaneously the most common malignant primary brain tumor.Recent years have witnessed significant progress in GBM treatment: besides advanced surgical resection methods such as fluorescence-guided surgery, three-dimensional imaging, tomoradiotherapy, moderate electro-hyperthermia, and adjunctive postoperative temozolomide chemotherapy, major breakthroughs have occurred in the fields of immunology, molecular biology, and virotherapy.Modern therapeutic approaches are emerging for GBM, integrating innovative techniques such as immunotherapy and virotherapy, emphasizing personalized oncological treatment based on individual tumorcharacteristics[2].This article primarily focuses on contemporary chemotherapeutic strategies for glioblastoma multiforme, the challenges encountered during treatment, and highlights future perspectives supported by various research studies, including gene therapy, virotherapy, and tumor vaccines.

Epidemiology

Each year, approximately 5–6 out of every 100,000 people are diagnosed with a primary malignant brain tumor, about 80% of which are malignant gliomas (MG) [1]. Glioblastoma (GBM) accounts for 45.2% of primary malignant tumors of the brain and central nervous system. In the United States, the incidence is 3.19 cases per 100,000 people, with an average age of 64 years. It is rare in children. The incidence is 1.6 times higher in men than in women and 2.0 times higher in Caucasians compared to Africans and African Americans, with lower rates among Asians and American Indians [22]. Glioblastoma multiforme remains an incurable disease, with an average survival time of 15 months. Only 5.5% of patients survive an average of 5 years. GBM is classified into isocitrate dehydrogenase (IDH) wild-type and mutant variants [10].The annual incidence of glioblastoma is approximately 35 cases per million individuals, with a male-to-female ratio of 6:1. Glioblastoma multiforme is mainly diagnosed in adults with an average age of 64 years. The incidence increases with age, peaking between 75 and 84 years, and declines after 85 years. Among cohorts older than 65 years, the incidence rises to 130 per million individuals. The number of tumor cases is expected to rise as the global population of people over 65 continues to increase due to advances in modern medicine and living conditions [11].

Etiology

several risk factors are associated with the development of GBM. Environmental risk factors mainly include exposure to therapeutic ionizing radiation and factors such as contact with vinyl chloride or pesticides, smoking, work involving petroleum processing or production, and work in the production of synthetic rubber [1].The only confirmed causative factor linked to the development of glioblastoma multiforme is exposure to high doses of ionizing radiation. Studies have shown a high prevalence (17%) in patients with a history of prior therapeutic radiation. The latent period between radiation exposure and

glioblastoma development ranges from several years to several decades. Studies have also shown that people with allergies and atopic diseases have a lower risk of gliomas. There is no strong evidence linking glioblastoma to lifestyle factors such as smoking, alcohol or drug use, or exposure to N-nitroso compounds. Based on existing evidence, mobile phone use does not increase the risk of glioblastoma, although further large-scale studies are needed to establish associations with long-term use.

Recent studies have also identified acorelationof glioblastoma risk and varicella-zoster virus (VZV) infection.It is known that GBM involves changes and/or increased activity in signaling pathways, particularly in the following inflammatory cytokines: Wnt, TGF-β, VEGF, EGFR, CDKN2A, NF-κB, and PI3K/AKT/mTOR, which are believed to play a significant role in the disease's pathogenesis and contribute to tumor aggressiveness [16].

Diagnosis

Clinically, patients with GBM may present with headache, focal neurological deficits, confusion, memory loss, personality changes, or seizures [1]. GBM is usually located in the supratentorial region (frontal, temporal, parietal, and occipital lobes) and is rarely found in the cerebellum [22].The typical radiologic appearance of GBM is a large heterogeneous mass in the supratentorial white matter, demonstrating significant mass effect. Rarely, GBM may develop near the dura mater, in the corpus callosum, the posterior fossa, or the spinal cord. GBM usually contains central areas of necrosis, has thick irregular walls, and is surrounded by extensive vasogenic edema; however, the tumor may occasionally have thin, rounded walls, minimal edema, or a cystic appearance with a mural nodule.GBM most commonly metastasizes from its original location by direct spread along white matter tracts. Nevertheless, cerebrospinal fluid dissemination, subependymal, and hematogenous spread can also occur. Given the rapidly expanding knowledge about GBM, the radiologist’s role has become more crucial than ever for accurate and timely diagnosis [18].On radiological analysis during the disease, poorly defined marginal enhancement is often seen. Characteristic MRI features include central hypointensity on T1-weighted imaging due to necrosis and peripheral hyperintensity on T2/FLAIR sequences due to edema.Magnetic resonance spectroscopy (MRS) during the disease shows a choline peak.The final diagnosis is established by histopathological examination, which reveals poorly differentiated pleomorphic cells with predominant astrocytic differentiation.Testing for glial fibrillary acidic protein (GFAP) presence, IDH mutation, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is recommended in GBM.IDH-wildtype GBMs, arising de novo, account for nearly 90% of all GBMs. They are typically observed in individuals over the age of 55. Histologically, they include giant cells, gliosarcomas, and epithelioid cells, often associated with epidermal growth factor receptor (EGFR) amplification, telomerase reverse transcriptase (TERT) gene mutations, or MGMT alterations.IDH-mutant GBMs develop from a precursor diffuse or anaplastic astrocytoma. They are associated with ATRX and TP53 mutations and usually affect younger patients, who tend to have relatively better median survival rates [10].

Treatment/Management

Developing a treatment plan requires a multidisciplinary team, including neurosurgeons, medical oncologists, and radiation oncologists.The gold standard for treating glioblastoma multiforme involves surgical resection followed by adjuvant radiotherapy and chemotherapy.

Surgical Treatment: Surgical resection enables cytoreduction for final histologic diagnosis and tumor genotyping; when possible, a Gliadel wafer containing carmustine can be used.

Gross total resection (GTR) is recommended over subtotal resection (STR). Compared to STR, GTR improves 1-year survival by nearly 60%, progression-free survival at 1 year by 50%, and 2-year survival by about 20%.Maximal tumor resection (removing at least more than 89% of the tumor) leads to a better prognosis.According to literature sources, a significant correlation exists between the extent of resection and positive outcomes in patients.Surgical resection of glioblastoma improved overall survival by up to 6 months compared to biopsy alone.Gross total resection can be achieved in almost 80% of cohorts with the

assistance of intraoperative visualization. Improved or stable functional status is achieved in nearly 80% of cases.Fluorescence-guided resection aids in increasing the extent of resection (EOR).

Radiotherapy: Radiotherapy options include laser interstitial thermal therapy, brachytherapy, Gamma Knife (GK), stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT), and proton beam therapy. The “Stupp protocol” refers to radiotherapy combined with temozolomide (TMZ).Proton therapy (PT) has been shown to have survival advantages.SRS is mainly justified when surgical intervention is contraindicated. Brachytherapy is also used to manage recurrent glioblastoma multiforme. Hypofractionated radiotherapy (HFRT) reduces the chances of cell repopulation and improves tumor control but carries an increased risk of radionecrosis (RN).The American Society for Radiation Oncology (ASTRO) recommends HFRT in elderly patients and in cohorts with poorprognosis and focal recurrences.According to the National Comprehensive Cancer Network (NCCN) guidelines, patients are categorized into those over and under 70 years of age.Each category is further divided based on good or poor functional status to guide treatment planning.For patients over 70 with a poor prognosis, hypofractionated radiotherapy may be preferred over the standard 6-week course with chemotherapy.In patients with a methylated MGMT promoter status, treatment slightly differs, as they derive maximum benefit from the alkylating agent temozolomide [11].

Chemotherapy of Glioblastoma

Glioblastoma multiforme (GBM) represents the most aggressive and malignant tumor of the central nervous system, and its treatment remains a significant clinical challenge. A combination of surgical resection, radiotherapy, and chemotherapy is considered the current standard of care. Among chemotherapeutic agents, temozolomide (TMZ), carmustine, and bevacizumab are the most commonly prescribed drugs, with temozolomide recognized as the "gold standard" for initial treatment of GBM [9].

Pharmacology of Temozolomide Temozolomide (TMZ) is a prodrug of an alkylating agent.It undergoes hydrolysis in blood and tissue fluids, converting into its active form — 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) [24]. The active metabolite transfers a methyl group to purine bases of DNA (O6-guanine, N7-guanine, and N3-adenine). The primary cytotoxic lesion, O6-methylguanine (O6-MeG), can be neutralized by the enzyme O6-methylguanine-DNA methyltransferase (MGMT), with MGMT expression in tumors contributing to TMZ resistance [21,24].Temozolomide is efficiently absorbed into the bloodstream following oral administration and is capable of crossing the blood-brain barrier (BBB). The drug was approved for the treatment of GBM in 2005 and is also utilized for the treatment of various other neoplasms, including neuroendocrine tumors [9].

Temozolomide in the Treatment and Therapeutic Regimens of Glioblastoma Multiforme:

Currently, the most widely used therapeutic protocol for GBM is the "Stupp protocol," which involves a combination of radiotherapy and TMZ chemotherapy following surgical tumor resection. The Stupp trial demonstrated that the addition of TMZ to radiotherapy prolonged survival by 2.5 months compared to radiotherapy alone, with the median overall survival increasing from 12.1 months to 14.6 months. Furthermore, the two-year overall survival (OS) rate increased from 10.4% to 26.5%.Despite standard combined chemoradiotherapy and adjuvant chemotherapy, most patients experience recurrence within six months. There is currently no universally accepted systemic regimen for second-line therapy; however, alkylating chemotherapy is frequently employed. Lomustine, carmustine, and retreatment with TMZ are potential options, although benefits are modest and likely limited to patients with MGMT promoter methylation.TMZ remains the primary agent for monotherapy. Nevertheless, studies have compared its efficacy when used alone versus in combination with carmustine. Some authors have reported a slight increase in overall survival following local implantation of carmustine wafers into the resection cavity.

Temozolomide in Patients Over 65 Years Old: A randomized trial demonstrated that, in elderly patients with glioblastoma multiforme, adding temozolomide to hypofractionated radiotherapy (40 Gy in 15 fractions) led to better outcomes compared to radiotherapy alone. A total of 562 patients with a

median age of 73 years were enrolled. The median overall survival was longer in the combined therapy group compared to radiotherapy alone (9.3 months vs. 7.6 months). One- and two-year survival rates were also higher in the chemoradiotherapy group (37.8% and 10.4%, respectively) compared to radiotherapy alone (22.2% and 2.8%).Prolonged TMZ therapy (>6 cycles) may further improve survival in patients with GBM without a significant increase in the frequency of hematologic adverse events; however, evidence remains limited [9].

Side Effects of Temozolomide: Temozolomide is generally well tolerated, and adverse effects are usually mild to moderate. Only about 15% of patients discontinue treatment due to intolerable side effects. The most commonly reported side effects are fatigue, nausea, vomiting, and myelosuppression. Severe adverse events mainly involve hematologic complications, including neutropenia, thrombocytopenia, lymphopenia, and leukopenia. Consequently, comprehensive hematologic monitoring is recommended during therapy, with frequency adjusted according to the treatment regimen. Temozolomide may also cause hepatotoxicity, albeit rarely, thus periodic monitoring of liver function is advised.Patients receiving TMZ-based chemotherapy, particularly those with prolonged lymphopenia, are at increased risk for pneumonia caused by Pneumocystis jiroveci, a potentially life-threatening opportunistic infection. In such cases, prophylactic antibiotics, such as trimethoprim-sulfamethoxazole, may be indicated.Gastrointestinal side effects, including nausea, vomiting, and anorexia, are frequent and can significantly impact patients' nutritional status, hydration, and overall well-being, sometimes necessitating dose modifications or treatment discontinuation [9].

Resistance to Temozolomide: Although TMZ remains the first-line chemotherapeutic agent for glioblastoma (GBM), approximately half of the patients develop resistance to the treatment. The most well-known mechanism underlying this resistance is related to the activity of O6-methylguanine-DNA methyltransferase (MGMT). This enzyme plays a critical role in DNA repair and the formation of uniquely resistant glioma stem cell populations. Downregulation of MGMT prior to chemotherapy with alkylating agents prevents the repair of O6-MeG lesions. Defects in the repair system lead to the persistence of potentially lethal methylated N7- and N3-purine residues, significantly contributing to TMZ cytotoxicity, especially when O6-MeG lesions are either repaired or tolerated [24].

In recent years, several other potential mechanisms influencing GBM resistance to TMZ have been identified. These include alternative DNA repair pathways such as mismatch repair (MMR) and base excision repair (BER), abnormal signaling pathways, autophagy, epigenetic modifications, microRNAs, and extracellular vesicle production. Additionally, some specific genes associated with GBM cell resistance have been discovered. Among them is the KDM5A gene, encoding a histone demethylase. Various studies have demonstrated a clear correlation between KDM5A expression and TMZ resistance. Another gene implicated is HDAC6, encoding a histone deacetylase. This enzyme regulates numerous biological processes, including carcinogenesis, through its deacetylase activity and ubiquitin-binding ability. Increased expression of HDAC6 has been detected in glioma cells, promoting cell proliferation and resistance to TMZ, primarily by stabilizing and activating EGFR. Conversely, other studies have shown that inhibition of HDAC6 is associated with increased levels of the key DNA repair proteins MSH2 and MSH6 and decreased MGMT expression.

In addition to biochemical changes, acquired resistance to TMZ in GBM cell populations may also be accompanied by morphological alterations. To investigate this, a study compared the in vitro phenotypes of two TMZ-resistant GBM cell lines with chemotherapy-sensitive control cells. The authors demonstrated that the development of resistance was associated with increased proliferation and migration, a higher frequency of chromosomal aberrations, and enhanced secretion of cytosolic lipids.

Acquired resistance to temozolomide appears to be a major reason for the poor effectiveness of GBM treatment. Therefore, understanding the mechanisms underlying this resistance is crucial for developing more effective therapies. Potential strategies to overcome GBM resistance include combination therapies with TMZ-sensitizing agents, targeted therapies against both the bulk tumor and tumor stem cells (which

play a critical role in recurrence), antiangiogenic therapies, and immunotherapies [9].

Carmustine or Gliadel Wafers

Carmustine or Gliadel wafers are biodegradable polymers containing 3.85% carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea). Carmustine inhibits DNA function in tumor cells through three main mechanisms. It alkylates DNA at the O6 and N7 positions of guanine residues, leading to the formation of DNA cross-links that prevent DNA strand separation, thereby inhibiting replication and transcription. It also impairs DNA repair by inhibiting the MGMT enzyme and affects RNA and protein synthesis via carbamoylation [4].Carmustine wafers are used intraoperatively, placed directly into the surgical cavity [15].The efficacy of carmustine wafer implantation has been demonstrated in mixed-age patient cohorts. However, it remains largely unknown whether this treatment method is equally effective in elderly patients compared to the general population. Characterizing the efficacy of carmustine wafers in elderly patients has become increasingly important, given that the incidence of glioblastoma multiforme (GBM) is higher in individuals over 65 years of age, and the global elderly population continues to grow thanks to advances in modern medicine and healthcare.

A retrospective study was conducted, including 133 patients aged over 65 years with GBM treated between 1997 and 2007. The aim of the study was to determine the efficacy of carmustine wafer implantation in this age group.Among the patients who underwent surgery with carmustine wafer implantation, 1 (1%) developed cerebral edema presenting with headache, and 1 (1%) reported increased fatigue/weakness. No perioperative deaths were recorded, and no patient required reoperation for wafer removal.Despite similar preoperative clinical status and treatment regimens, patients who received carmustine wafers during surgery demonstrated longer survival compared to those who did not receive wafers.The median survival for patients treated with carmustine wafers was 8.7 months, whereas it was 5.5 months for patients without wafer implantation. The 3-, 6-, 9-, and 12-month survival rates were 89%, 62%, 47%, and 33% respectively for patients with carmustine wafers, compared to 71%, 40%, 24%, and 9% for those without wafers.Additionally, studies focusing on patients aged over 70 and 75 years were conducted. Similar to patients over 65 years, individuals older than 70 years treated with carmustine wafers had longer survival compared to those not receiving wafer implantation.

In patients over 70 years, median survival was 9.1 months with carmustine wafers compared to 4.8 months without that. Their 3-, 6-, 9-, and 12-month survival rates were 89%, 61%, 50%, and 36%, respectively, while for those without wafers, these rates were 64%, 36%, 18%, and 3%.

Likewise, patients over 75 years of age who received carmustine wafers had significantly longer survival compared to those who did not.In this group, the median survival was 6.0 months with carmustinewafers and 4.7 months for patients treated without gliadel wafers. The 3-, 6-, 9-, and 12-month survival rates were 88%, 47%, 41%, and 24% for patients with carmustinewafers and 65%, 35%, 18%, and 6% for those without that.Overall, the use of carmustine wafers has been shown to increase median survival from 5.5 to 7.4 months in patients with recurrent GBM. Furthermore, the combination of carmustine wafers, radiation therapy, and temozolomide chemotherapy may increase median survival to 11.3 months in patients with recurrent GBM.

Additionally, in a randomized, placebo-controlled trial, the use of a carmustine wafer increased median survival from 10.0 to 14.5 months for patients with primary GBM. The median age of patients enrolled in this study was 53 years, and patients older than 65 years were not included. Although the peak incidence of glioblastoma multiforme is observed in individuals over 65 years of age, the benefit of the carmustine wafer in this patient population remains insufficiently studied. However, based on existing data, it is evident that the use of the carmustine wafer may be safe and effective in patients over 65 years of age [3].

Bevacizumab

Bevacizumab is a humanized monoclonal IgG1 antibody with anti-VEGF (vascular endothelial growth factor) properties [25]. Its antitumor effects are achieved by reducing blood supply, normalizing tumor

vasculature, and inhibiting tumor vascularization. It is noteworthy that resistance to bevacizumab may develop, leading to disease progression.Glioblastoma multiforme is a highly vascular tumor characterized by overexpression of VEGF. It is widely believed that VEGF is the primary growth factor responsible for tumor angiogenesis. New blood vessels form from pre-existing vessels, providing tumor cells with access to nutrients and oxygen. VEGF is thought to be a prognostic marker — higher VEGF expression is associated with poor prognosis.VEGF inhibitors are anti-angiogenic agents acting through several mechanisms. Anti-VEGF therapy is believed to reduce tumor blood supply and may sensitize tumor endothelial cells to cytotoxins. Another potential mechanism of anti-VEGF therapy is the normalization of tumor vasculature, which enhances the efficacy of chemotherapy and radiotherapy. By normalizing tumor blood vessels, hydrostatic pressure changes have been shown to improve the transport of large molecules into tumor tissue. Synergistic cell destruction and inhibition of tumor growth have been observed in vivo when bevacizumab was combined with doxorubicin, topotecan, paclitaxel, and docetaxel. In vitro and in vivo models have demonstrated that delivering anti-angiogenic agents, including bevacizumab, alongside radiation promotes endothelial cell apoptosis and reduces the formation of tumor blood vessels.A third additional effect of anti-VEGF therapy is the sustained inhibition of tumor vascularization.

In 2012, a study was conducted to determine the efficacy of combining bevacizumab with temozolomide in patients with recurrent glioblastoma multiforme. The study concluded that the combination therapy had acceptable tolerability, but the addition of temozolomide did not improve 6-month progression-free survival (PFS) compared to bevacizumab alone. Serious toxicity in this study included prolonged thrombocytopenia (likely due to temozolomide) and grade 4 pancreatitis.Another study aimed to assess the efficacy of combining bevacizumab with radiotherapy. In this study, 20 patients with recurrent GBM received bevacizumab along with 30 Gyhypofractionated stereotactic radiotherapy administered over five fractions. The 6-month PFS was 65% (95% CI: 40-82%), and the overall survival (OS) was 12.5 months. The study concluded that the combination of bevacizumab with hypofractionated stereotactic radiotherapy is safe and well-tolerated in patients with recurrent glioblastoma multiforme.

Resistance

In glioblastoma multiforme, inhibition of VEGF with bevacizumab has been considered one of the first promising steps toward targeted therapy for this disease. However, during the treatment of glioblastoma, acquired resistance to anti-angiogenic agents may develop, ultimately leading to a more invasive and difficult-to-treat tumor, as shown in mouse models. One mechanism that contributes to bevacizumab resistance is the acquired ability of the vasculature to develop independently of VEGF, although the exact mechanism behind this remains unclear. Upregulation of the receptor tyrosine kinase MET signaling pathway through VEGF inhibition may contribute to this complication. Anti-angiogenic resistance can also arise through other mechanisms [8]. While tumor vascular growth is typically controlled by angiogenesis, tumor cells subjected to VEGF inhibition may still grow by developing alternative vascular channels through a process called angiogenic mimicry [13]. Based on scientific assumptions, glioma stem cells promote the development of angiogenic mimicry. Although the precise mechanism is unknown, glioma stem cells (CD133-positive cells) are believed to play a major role in promoting vascular mimicry. Glioma stem cells not only contribute to angiogenic mimicry but also have the potential to differentiate into endothelial cells, facilitating tumor progression and growth. Both in vitro and in vivo studies have shown that glioma stem cells can transform into endothelial cells, which may or may not be VEGF-dependent [8].

Side Effects

The most common complications associated with bevacizumab include fatigue, hypertension, and proteinuria [12]. Interestingly, the development of hypertension during bevacizumab therapy has been associated with better outcomes. A study showed that patients who remained normotensive had a median PFS (progression-free survival) of 2.5 months, while those who developed hypertension had a median

PFS of 6.7 months. Hematologic side effects associated with bevacizumab monotherapy include thrombocytopenia in 12.5% of cases; however, this is more frequently linked to long-term use of the drug and a history of combination with other chemotherapeutic agents. Bevacizumab-related toxicity appears to be cumulative. The frequency of adverse events increases if the patient receives the drug for more than 24 months. Other common toxicities include hoarseness, dry skin, and joint pain. Overall, bevacizumab is well tolerated and can be administered alongside other chemotherapeutic agents.

Rare but serious side effects associated with bevacizumab may include: bleeding, epistaxis (nosebleeds), venous thromboembolism (deep vein thrombosis or pulmonary embolism), arterial thrombotic events (cardiovascular and cerebrovascular), congestive heart failure (left ventricular systolic dysfunction), wound dehiscence, and reversible posterior leukoencephalopathy syndrome. Special caution is necessary for patients with recurrent GBM receiving corticosteroids and bevacizumab simultaneously, as this combination can lead to ulcerative striae and gastrointestinal perforation or diverticulitis in the setting of peptic ulcer disease. Some patients may experience infusion-related reactions characterized by shortness of breath or clinically significant hypotension. Additionally, patients may develop allergic reactions/hypersensitivity, acute respiratory distress syndrome (ARDS), or bronchospasm.

During bevacizumab treatment, regular blood pressure monitoring is performed to maintain blood pressure within normal limits. Patients undergo urine dipstick or 24-hour urine collection tests at least every four weeks to monitor for proteinuria. If surgery is required, bevacizumab treatment should be discontinued at least six weeks before surgery. After surgery, bevacizumab therapy should not be initiated or resumed for at least four weeks. Bevacizumab therapy should not be started or restarted within six weeks of high-risk invasive procedures (e.g., neurosurgery, liver resection, or thoracotomy). It should also be noted that when bevacizumab is used with prothrombotic agents such as epoetin alfa and hormonal therapies, there is an additional risk of venous and arterial thrombosis.

It is unknown whether bevacizumab crosses the placenta or is excreted into human milk. However, teratogenic effects have been observed in animal studies with experimental bevacizumab treatment. No similar studies have been conducted in humans. Women of reproductive age should be informed about the increased risk of ovarian failure associated with bevacizumab therapy. The long-term impact on fertility remains unknown, but bevacizumab may irreversibly impair fertility. There is insufficient information to recommend bevacizumab use in pediatric patients. It is important to note that there tends to be a higher rate of side effects in patients over the age of 65 [8].

Future Perspectives

As outlined above, glioblastoma multiforme remains one of the deadliest diseases worldwide, primarily due to the lack of effective treatment options. Consequently, there is a pressing need to explore new therapeutic approaches.One modern strategy for curing the disease involves the use of agents that methylate the MGMT promoter or the combination of MGMT pseudosubstrates with temozolomide. MGMT pseudosubstrates such as O6-benzylguanine and lomeguatrib can sensitize tumors to TMZ, thereby allowing temozolomide to damage DNA while the DNA repair enzyme is rendered ineffective. This creates a disbalance between DNA damage and repair in favor of damage, ultimately leading to cell death. Moreover, this approach could significantly minimize the development of resistance to temozolomide.

Another potentially effective therapeutic method is the use of tumor vaccines [19]. Although not a new concept, research in this area remains highly active. The idea behind cancer vaccines is to extract surface (membrane) antigens from tumor cells and administer them intramuscularly. This is necessary because the immune system often fails to recognize tumor antigens due to the immunosuppressive environment surrounding the pathology. Artificially presenting these antigens helps the immune system identify the "foreign agent," promoting sensitization against the tumor and, theoretically, leading to its eradication. However, this vaccination method may also provoke allergic reactions (since the mutated protein is different from native ones, and vaccine components are antigenic themselves), which must be considered

in clinical practice [23].

A third therapeutic method for curing glioblastoma is oncolytic virotherapy. Oncolytic viruses selectively infect tumor cells and cause their destruction. Research in this field is ongoing, although, to date, only viral therapy for melanoma has been approved by the FDA. Developing such effective, targeted artificial viruses remains highly challenging. Oncolytic viruses could also serve as an alternative to chemotherapy, potentially being applied intraoperatively at the site of tumor removal. Theoretically, DNA-based oncolytic viruses may integrate into tumorcell DNA, further increasing mutation rates. To prevent this, it is crucial to use viruses that do not integrate into the tumor genome. The feasibility of this idea was reaffirmed last year when virologist Beta Halasi successfully cured herself of breast cancer using a laboratory-modified oncolytic virus. Therefore, oncolytic viruses represent a truly promising frontier in oncology [5, 7, 14, 20].

Conclusion

Based on the literature discussed in this article, we can conclude that glioblastoma multiforme is a highly malignant tumor that readily develops resistance even against modern aggressive therapies. Finally, it must be emphasized that expanding treatment strategies, particularly in immunotherapy, virotherapy, and gene therapy, is essential. Broader research and resulting advancements in these fields could significantly reduce lethality and help prevent various complications.

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