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Review Article

Recent Advances in the Therapeutic Approaches of Glioblastoma Multiforme

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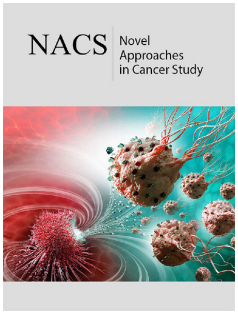

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Abstract

Glioblastoma Multiforme (GBM, WHO grade IV) is one of the most aggressive, invasive, and lethal intracranial neoplasms, with a low post-diagnosis survival rate. Standard-of-care treatment regimens involving maximal surgical resection, radiotherapy, and genetic anti-tumor compounds like Temozolomide have only been marginally effective in improving overall survival and quality of life. Cell fusion, autophagy, and other complex biological processes affecting GBM pathophysiology are being studied to improve GBM treatment. This paper therefore focuses on oncolytic virus therapy combined with surgical resection, photodynamic therapy, and novel gene therapy, demonstrating how GBM treatment for patients could result in immediate and authentic tumor cytotoxicity and removal, rather than treatment of recurrent GBM. Standard therapy for GBM, including surgery, radiotherapy, and chemotherapy, is called the Stupp regime with the inclusion of Temozolomide (TMZ). It is extremely difficult to design new and effective therapeutic approaches because of the numerous complex biological pathways involved in GBM pathogenesis. Even Stupp regime clinical outcomes have only shown modest benefits with less than 10% of overall 5-year survivorship. A major contributing factor in GBM development is also its interaction with the patient's host immune system.

Introduction

The prevalence of Glioblastoma Multiforme (GBM) is attributed to limited effective therapy and the late diagnosis of the condition. GBM, a long-term, rapid, and invasive disease in adults, is associated with an average survival time of less than 15 months. Brain tumors or tumors originating in the glial cells denote a GBM and are classified as grade IV according to the World Health Organization's (WHO) international criteria [1-3]. It has a high energetic requirement of the human body with a high rate, for various cellular activities. Typically, patients are treated with surgical removal of an accessible tumor to preserve some functional brain regions, based on clinical examination findings. The most serious health problems that follow the growth and irritating areas of the brain stem from spread to other areas. As GBM has a poor prognosis with old-fashioned drugs, it doesn't answer too well in patients. However, in some patients, this treatment helps to prolong life and reduce the devastating signs and neurological signs [4-6].Therefore, a significant number of scientists have concentrated their interest in the identification of the therapeutic value of GBM of survivors because of these drugs and have defined various metabolic targets according to their marking preferences, acting on different metabolic processes of energy production. In particular, the repression of metabolic-based PPAR expression has been investigated in relation to the development of drugs with anti-tumor effects [7,8].

Understanding Glioblastoma Multiforme

Glioblastoma Multiforme, commonly known as GBM, is the most common and aggressive type of primary brain tumor belonging to the grade IV subspecies of gliomas. The worldwide incidence of GBM is around 3.19%, constituting up to 60-70% of all gliomas and 15.6% of all brain tumors [9,10]. The median survival of GBM, regardless of its location and combined surgical, radiotherapeutic, and chemotherapy, is dismal and lies around 15 months, with a 5-year relative survival of only 6.8%. The molecular pathogenesis of GBM is very complex and has been attributed to various critical point mutations in the gene encoding for tumor suppressor protein, i.e., p53, Retinoblastoma protein (Rb), and PTEN [1,11]. In addition, GBM harbors mutations in Receptor Tyrosine Kinase (RTK) such as Epidermal Growth Factor Receptor (EGFR), PDGFR, VEGFR, and deletion or mutation of IDH1 or IDH2 and map kinase pathway, to name a few [12]. The core hallmarks of GBM are proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, and tissue invasion and metastasis, all of which are considered as the major force behind its high-grade malignancy. GBM also has an intact Blood-Brain Barrier (BBB), and up to date, all studies on therapeutic agents have failed to effectively cross and reach the core of the lesions. The standard therapy of GBM includes surgical resection followed by concomitant radiotherapy and chemotherapy (temozolomide) over 6 weeks [13-15]. The maximum safe surgical resection is the standard for GBM. In some instances, where GBM is surgically inaccessible, the molecular profile of the tumor is high-risk gross total surgical resection, followed by radiation therapy. In addition to the standard therapy, some therapies are used in research, including nimotuzumab, bevacizumab, tumor-treating fields, TTFields, modulated electro-hyperthermia, photodynamic therapy, and laser-induced thermal therapy, etc., in clinical as well as in vitro cell lines [16-18]. The overall survival benefit provided by radiotherapy over best supportive care is 4.9 months for high-grade astrocytomas and the 2.5-3 months absolute survival benefit in GBM due to chemoradiotherapy. GGKIs generally possess a significant potency to kill malignant glioma cells. Owing to the urgent unmet need in medical purposes for the development of novel therapeutic approaches, thus a multifaceted approach is adopted to treat GBM [19-21].

Epidemiology and Pathophysiology

Glioblastoma Multiforme (GBM) or grade IV astrocytoma is the most common and aggressive type of primary malignant brain tumor in humans. Each year, approximately 3-5 of every 100,000 people are diagnosed with this disease. Glioblastoma multiforme progresses aggressively and spreads in the brain, resulting in a dismal prognosis and short life expectancy in patients, even after appropriate therapy. The molecular pathogenesis of GBM is complex and associated with various genetic, chromosomal, and physiological alterations, such as abnormalities in cell signaling pathways regulating cell proliferation, angiogenesis, apoptosis, invasion, metastasis, and DNA repair. GBM microvascular proliferation and necrosis serve as pathological hallmarks. A reliable and robust biomarker that can reflect new changes over time and tumor progression should be considered. Approximately 90% of de novo GBMs harbor mutations in either of the isocitrate dehydrogenase (IDH) genes (e.g., IDH1 and 2), implying that these neoplasms show changes in epigenetic functions [22-24]. Radiotherapy and surgical resection followed by the alkylating agent, Temozolomide (TMZ), are the most common therapeutic strategies. However, the median Overall Survival (OS) does not exceed 15 months, even though the patient receives the best management. Recurrence and chemo- and radio-resistance are the common complications in GBM, which mainly depend on the evolution of Glioma Stem-like Cells (GSCs). In addition, the presence of the Blood-Brain Barrier (BBB), tumor microenvironment, epigenetic changes, and molecular heterogeneity also contribute tremendously to resistance. In a recent report from the Food and Drug Administration (FDA), approximately 70% of approximately 30 late-phase II-III studies have failed and resulted in unequivocal trials in GBM treatment. Hence, a shift is needed for the identification of new strategies in GBM treatment. This review summarizes the recent advances in therapeutic approaches for GBM [25-28].

Current Standard Treatments

One of the standard treatments for glioblastoma involves surgical resection, given that the initial neurosurgical intervention can provide symptomatic relief by decreasing the intracranial pressure. However, surgery is usually combined with adjuvant radiotherapy and temozolomide-based chemotherapy, as surgery alone is not sufficient. Moreover, due to the invasive and infiltrative nature of the GBM cells, most of the patients will recur locally and within two centimeters from the margins of the resection cavity. Patients can be divided into two general categories following resection [29-30]. Patients in category 1 are those with low-grade, non-enhancing, or otherwise resected tumors with a histologically confirmed diagnosis of GBM. Patients in category 2 are those with GBM that is beyond radiographically-defined resection. Thus far, it has been relatively well established that, after surgical removal of an enhancing region of the tumor on contrast-enhanced MR imaging, the current standard of care is to treat the residual infiltrating tumor with radiotherapy and temozolomide chemotherapy (TMZ/RT→TMZ) [31-33]. Radiation therapy and concomitant chemotherapy with temozolomide after surgical removal of glioblastoma are the conventional methods for managing this disease. Upon the completion of the initial treatment, the patient most likely stays on temozolomide (TMZ) for the remaining 11 months. The current National Comprehensive Cancer Network (NCCN) guidelines indicate that 60 Gy with precisely 2 Gy fractions is the standard dose to treat the majority of GBMs [34-36]. To assess the benefit of an advanced modern technique, several retrospective studies have shown that Intensity-Modulated Radiation Therapy (IMRT) is superior to the 3D Conformal Radiation Therapy (3DCRT) approach. Whether or not the utilization of proton therapy can minimize the comorbidities of GBM patients, such as neurocognitive impairment, or even increase the overall survival, has not yet been demonstrated. Crude response rates for TMZ alone

are poor, and recurrence is frequent. Thus, many researchers have at least initially pursued chemotherapeutic combination regimens, often with disappointing or mixed results. Many of these initial studies have been for relapsed GBM or newly diagnosed grade III gliomas [37-39].

Surgery

Surgery, an integral part of the multimodality treatment of glioblastoma, is performed to debulk the bulk of GBM growth with the aim of reducing intracranial pressure and increasing the patient's quality of life in addition to histopathological diagnosis. A notable portion of the patients undergo limited resection due to poor general status, deep tumor localization, no mass effect, and risk of impairment postoperatively. The use of Functional nuclear Magnetic Resonance Imaging (FMRI), Diffusion Tensor Imaging (DTI), and awake surgery provides a concurrent increase in the extent of resection and quality of life postoperatively. Stereotactic biopsy is indicated in deep-seated, unresectable, or biologically challenging brain masses when the diagnosis cannot be confirmed by noninvasive imaging. Isocitrate Dehydrogenase (IDH), TP53 mutation, and the MGMT promoter methylation status prediction by using new techniques can be useful to achieve maximal surgical resection (maximal safe resection, MSR) [40-42]. In the frame of the standard treatment of glioblastoma, maximal surgical resection (complete or subtotal) in young patients offers an average of three-month survival benefit; therefore, aggressive debulking resection seems to have a controversial survival benefit in the elderly. In order to clarify these findings, two phase III studies (in Austria and Germany) are now ongoing [17,43-45].

There are already some indications that surgery can activate the immune system. For instance, as shown in a smaller non-randomized phase II single-arm study by Weller and colleagues, a specific form of surgery, which involved taking the tissue and flushing it with DC, showed that survivors had a substantial increase in both PFS with a 6-month PFS of 94% and a median PFS of 72.8 months as well as an OS of 100% at 6 months. This amount of OS and PFS is unprecedented in the first-line treatment of glioblastoma. The surgical tumor material may also provide prognostic tissue for survival. Indeed, biomarkers, such as MissMatch Repair (MMR) mutations, can be valid biomaterials linked to recovery from glioblastoma [46-48]. Modified (complete) resections versus partial resections are linked with a better prognosis, albeit. The definition of a 'full resection' has been given by doubling the mean survival by patients in the city of Vienna, establishing a residence in the recent 1980s. In the meantime, this definition of 'full resection' should be preceded by the patient's initial size. Moreover, those with layers in Vienna noticed that if the operation was completed in a manner that lasted more than 90 minutes, it was then associated with a worse prognosis. In general, 95% of glioblastomas are bound to have residual diseases at the time of surgery. This is mainly because disorder cells can commute even from the contrast-enhanced zone of an MRI, which is frequently considered a standard surgery [49-51].

Recent Advances in Therapeutic Approaches

Recently, there have been advances in therapeutic approaches that improve and increase potential treatment alternatives. The discovery of new molecular pathways involved in the growth, evolution, and dissemination of glioblastoma multiforme disease, a highly aggressive brain tumor, led to the creation and development of targeted therapies. Unfortunately, all the advances that have occurred are not enough to improve patient survival. From here, the next step in tumor research was to begin to explore the possibility of the immune system to fight glioblastoma by developing immunotherapies [30,52]. Immunotherapies have the potential to be more targeted treatments than standard therapies. Given the standard of care that includes radiotherapy and chemotherapy of temozolomide, the immune system may not work correctly, and patients are thought to benefit more from immunotherapy treatments when they need them. Patients may experience tumor progression after immunotherapy with PD-1 and PD-L1 drugs, and, in some cases, they may have a clinical benefit while drug resistance is unknown. Therefore, tackling these resistance mechanisms is fundamental to achieving a truly applicable approach in patient treatment [53,54]. An important anti-aging gene Sirtuin 1 (SIRT1) may be important to the treatment of glioblastoma. SIRT1 is a member of the sirtuin family of proteins, which are involved in cellular regulation. Sirtuins are NAD+-dependent deacetylases, meaning they use nicotinamide adenine dinucleotide (NAD+) to remove acetyl groups from proteins. SIRT1, in particular, is involved in a variety of cellular processes including aging, transcription, apoptosis, inflammation, and stress resistance [55]. Functions of SIRT1 include Gene Regulation by deacetylating histones and various transcription factors, influencing gene expression. It plays a role in metabolic regulation by deacetylating key enzymes and coactivators involved in metabolic pathways. SIRT1 helps in the cellular response to stress by deacetylating proteins that are involved in oxidative stress response and DNA repair [55]. SIRT1 activity is associated with increased lifespan and delayed aging in various organisms. It is involved in protecting neurons from degeneration, and its activation is linked to beneficial effects in neurodegenerative diseases. The relationship between SIRT1 and glioblastoma is complex and involves various pathways [56]. SIRT1 has been shown to have both tumor-suppressive and oncogenic roles depending on the context. In some studies, SIRT1 overexpression is associated with reduced tumor growth and increased sensitivity to chemotherapy, suggesting a tumor-suppressive role. In other contexts, SIRT1 can promote tumor survival and proliferation, indicating an oncogenic role [57]. It deacetylates the tumor suppressor protein p53, which can influence cell cycle arrest and apoptosis. In glioblastoma, the regulation of p53 by SIRT1 can impact tumor cell survival and resistance to therapy. SIRT1 affects pathways that are critical for cell survival and proliferation [58]. In glioblastoma, SIRT1 can modulate the activity of pathways such as the PI3K/AKT/mTOR pathway, which is often dysregulated in cancers. It has been implicated in the development of resistance to chemotherapy in glioblastoma cells. Its role in DNA repair and

stress response can help tumor cells survive chemotherapy-induced damage [58,59]. SIRT1 may play a role in maintaining cancer stem cells, which are thought to contribute to tumor recurrence and resistance to conventional therapies.

Overall, the exact role of SIRT1 in glioblastoma is still being researched, and its dual role as a tumor suppressor and oncogene makes it a potential target for therapeutic intervention. Modulating SIRT1 activity could offer new avenues for treatment, but understanding its context-dependent effects is crucial for developing effective strategies.

Immunotherapy

Glioblastoma multiforme (GBM) has been proven to be an immunosuppressive disease that hinders the progression of tumors. Therefore, immunotherapy has emerged as a potential treatment option. Several novel approaches have been developed to enhance antigen vaccine therapies, including modified dendritic cells, peptide vaccines, and heat-shock protein vaccines. The principles of immunology help coordinate these treatments for GBM. Clinical outcomes have shown that nivolumab, along with its safety profile, is superior in treating solid tumors. The outcomes of nivolumab monotherapy treatment have been encouraging. The primary goal of treating glioblastoma multiforme is to improve life expectancy by increasing the number of patients who survive the disease and prolonging their survival [53,60-62]. Glioblastoma is known to be an exceptionally immune-suppressive disease, particularly in the tumor microenvironment. Natural immunity in the peripheral blood plays a crucial role in maintaining a functional T-cell (CD8+) response. Natural killer cells and T cells are especially important as they specifically target and kill cancer cells, monitoring their presence in the blood circulation and the patient's recovery. If a patient's immune response is compromised, neoplasms can cause a decrease in the number and function of T cells [63-66]. Researchers have been actively investigating immunotherapy for glioblastoma, which was introduced in the 1980s. Although these therapies have shown extensive side effects similar to chemotherapy, they have become a highly active field of clinical research in the past year. Cancer therapies now employ strategies that target immune checkpoint inhibitors, various antigen-specific therapeutic vaccines, and adoptive cell therapies using modified T cells to kill cancer cells [67-69]. Figure 1 highlights all the Glioblastoma-related pathways and receptors.

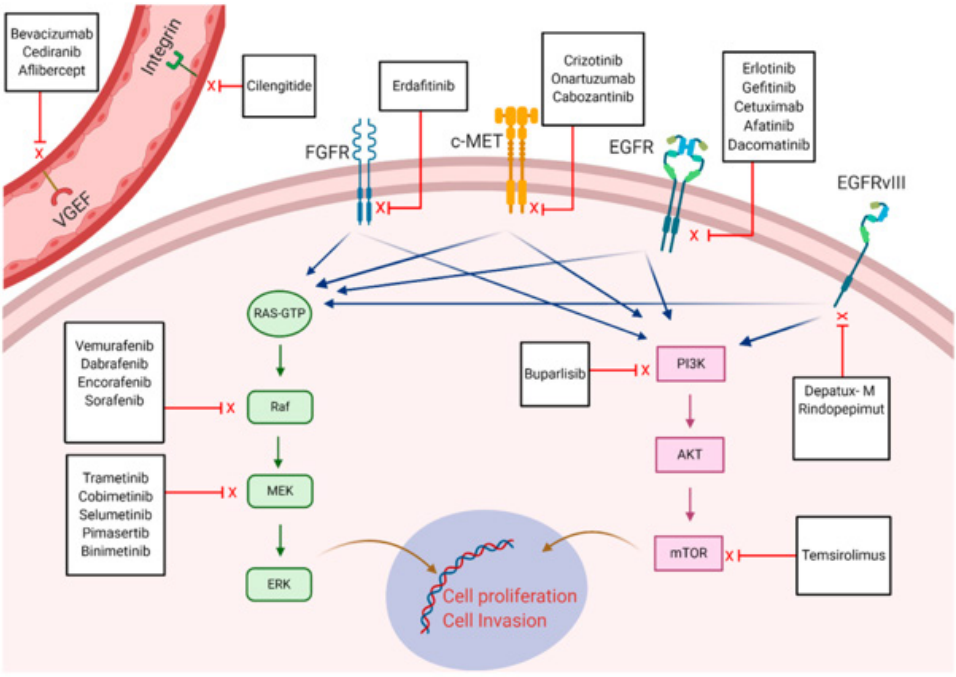

Figure 1: Glioblastoma-related pathways and receptors that are involved in angiogenesis, invasion, aggressiveness, and cell proliferation are targeted. The following list includes some of the medications that have been tested to target these particular receptors or pathways.

Challenges and Future Directions

The recent climate of clinical trials in the therapeutic management of GBM evidences that many obstacles need to be addressed to overcome the resistance of the tumor mass to the drugs. The first issue is the concentrations of drugs in blood samples, mostly too low, which evidences that the efficiency of drugs at the tumor site should be probably improved with the use of renaturalizing strategies based on bioactive nanoparticles as drug carriers, maybe to be administered subcutaneously so to bypass the blood-brain barrier. In addition to this, the cell drug resistance should be tackled by means of drugs/strategies that are able to: block the proliferative machine of GBM, enhance the death of GBM cells (in part, GBM cells may be killed by the immune system of the patients), and stop the invasion. Both the Standard of

Care temozolomide and a large proportion of trials performed so far only focus on the death of GBM and many strategies tested so far are focused on cell proliferation. There is an absolute need to test within the clinical routine trials including different therapeutic approaches to be able to propose drugs or combinations that increase the survival of patients [70-73]. On the basis of the use during the clinical routine procedures of a laboratory test named AntiCancer Assay (ATP-TCA test), which has been shown efficient to predict multi-drug resistance in glioblastoma and has been shown efficient to identify the index of apoptogenicity of cells focus drugs on the future for GBM treatment; there are two main strategies targeting the proliferative machine of the GBM mass. The first one is to decrease the GBM recruiting potential, potentiating the impossibility of the necrotic core to be recreated. A second one is to make GBM cells sensitive to apoptosis, which is currently the unique form of cell death reversible. It is also the unique form of spontaneous death of GBM cells [74,75]. The first strategy we have in our study consisted of favoring the mobilization of Glioblastoma stem-like cells out of hypoxia, considering that they are the initiating force of the GBM clone. We have shown that phenothiazines act in hypoxia to produce reoxygenation by dopaminergic signaling from TMZ-sensitive GSCs resulting in their departure from the hypoxic niches. The second anti-cancer strategy results from the present-day theory according to which GBM is an autophagic tumor and restoring a basal level of autophagy may allow GSCs and K GL cells to undergo profound autophagy, as is the case for all cells in hypoxia [76-78]. These sequential treatments reduce mainly disabling effect of hypoxia on the "good" K GL, sensitive cells of spheroids, and hypoxic stem-like cells and would destroy the highly tumorigenic stem cells. This should help in circumventing the limitations of 3D models in fundamental works on GBM and should lead to the identification of original therapeutic strategies to improve the outcome of patients [79].

Conclusion

In recent years, a multifaceted strategy to expand knowledge of glioblastoma behavior has resulted in the discovery of numerous molecular aspects of glioblastoma. It is becoming increasingly clear that there are many therapeutic approaches that are frequently used, including oncology, angiogenesis signaling pathways, and molecular therapies that can be used to target distinct proteins. A major hurdle to improving the efficacy of glioblastoma treatment is a deficiency of specific, targeted therapies and overtreatment with high-dose cytotoxic agents that fail to penetrate the BBB. The shortage of successful therapies in segment therapy of glioblastoma arises, in part, from the fact that tumor heterogeneity and resistance occur in an ongoing manner. It poses a significant risk due to the aggressive and infiltrative nature of glioblastoma cells. Several other barriers hinder the implementation of newly developed therapy at the clinical level, including acquired resistance and devastating side effects. However, recent development in animal models, organoids, and brain entry assays has the potential to represent the state of GBM. These possibilities could occur in personalized models of different courses of adjuvant treatment, which may help guide clinical trials. Thus, our growing body of information offers a variety of potential therapeutic agents that warrant clinical validation in the broader view. The future holds great promise for personalized, targeted therapies to treat an aggressive tumor such as glioblastoma. Many scientific advances have been made in traditionally challenging glioblastoma research areas. However, the broader potential for targeting therapeutic eligible components in newly diagnosed "standard" GBM must be changed in future research.

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