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REVIEW ARTICLE

Overview of Glioblastoma: Current Drugs and Novel Therapy Trends

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common type of malignant primary brain tumor. GBM, a very aggressive tumor, has a low survival rate and currently has no curative treatment. ATRX, TERT, TP53 mutations, loss of PTEN function, and EGFR and WT1 have been found to play a role in the genetic pathogenesis of GBM. It has been determined that ionizing radiation, obesity, some metals and chemicals, pesticides, TNF-α, IL-1 and IL-6 are risk factors of GBM. In GBM treatment, surgery, radiotherapy and chemotherapy are usually combined. Temozolomide, carmustine, irinotecan and bevacizumab are the most important anticancer agents used in chemotherapy for GBM therapy. Targeted molecular (precision) therapies, targeting DNA damage response pathways, targeting tumor metabolism, immunotherapies, and viral therapies are novel treatment options being studied for the treatment of GBM. In this paper, the characteristics of glioblastoma multiforme (GBM), its incidence, genetic pathogenesis, risk factors, treatment options and drugs used in chemotherapy, difficulties encountered in treatment, novel therapies for GBM and challenges and future directions are discussed.

Contents

1. Introduction

The masses that are formed by the uncontrolled proliferation and growth of cells in the brain are defined as brain tumors [1–4]. Primary brain tumors (PBTs) are tumors of brain origin, and metastases are rare because there are no lymphatic vessels within the brain [2, 4–9]. The route of metastasis is often cerebral blood circulation and cerebrospinal fluid [9].

Secondary brain tumors (SBT) are tumors that originate in a different region and then spread to the brain [1–8]. Cancer types such as lung, skin, kidney, and breast spread through the arterial circulation and cause brain tumors [4, 5, 8, 10, 11].

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The level of the patient's body functions, age, the type of surgery performed or to be performed, and the location and size of the tumor are factors that significantly affect the patient's prognosis and recovery possibilities [12].

Glioblastoma multiforme **(**GBM) is the most common type of malignant primary brain tumor, accounting for approximately 57% of all gliomas and 48% of all primary malignant central nervous system (CNS) tumors [13]. GBM is classified into two different categories: primary and secondary GBM [14]. Primary GBM is a tumor that accounts for 90% of cases, progresses without symptoms, and develops *de novo*. The mean age of incidence is 55 [14, 15]. Secondary GBM has a better prognosis than primary GBM and is seen at earlier ages. Secondary GBM occurs as a result of stage II or stage III astrocytomas [14].

GBM, which is a very aggressive tumor, was categorized as a stage IV tumor as a result of the classification made by the World Health Organization (WHO) [16].

The incidence of GBM varies by region, gender and age. For example, in the USA, incidence is 4.03 per 100000 for men and 2.4 per 100000 for women, without age range between 2013 and 2017. The total incidence is 3.23 (Figure 1) [17].

The vast majority of GBM cases occur after the age of 40. In a study, it was reported that the age at diagnosis was 65 and over in 47.9 of the cases, and the age at diagnosis was between 40-64 years in 46.3 of them [18].

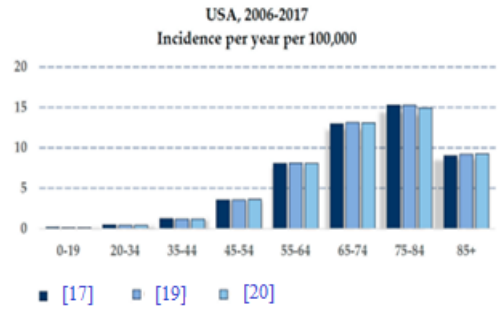

Figure 1 GBM incidence in the USA between 2006-2017 [17, 19, 20]

There is no definitive treatment for GBM. In a study conducted in the USA, the probability of survival was found to be 39.7% for 1 year, 17.2% for 2 years, and 5.5% for 5 years. There is no possibility of 10-year survival [19].

2. Genetic Pathogenesis of GBM

The structures and mutations thought to be associated with GBM include:

ATRX (Alpha thalassemia X-linked mental retardation syndrome) mutation: The ATRX gene located in Xq21.1 encodes a protein in the chromatin remodeling pathway, allowing histone H3.3 to be included in heterochromatin [21]. These mutations are seen in approximately 57% of isocitrate dehydrogenase (IDH)-mutant GBMs and more common than in IDH-wild-type GBMs [16].

TERT (Telomerase reverse transcriptase) promoter mutation: The TERT gene encodes the enzyme telomerase, which is responsible for adding the missing 3' portion of a DNA helix during replication. Mutations in the TERT gene promoter causes telomere elongation and increased telomerase activity. Telomeres are required for brain tumor formation [22, 23]. The most common TERT promoter mutations are C228T and C250T mutations located at 144 and 126 base pairs, respectively, and encode this promoter [39]. The incidence of TERT promoter mutations in IDH-wild-type GBMs is more than in IDH-mutant GBMs [16].

TP53 (Tumor protein p53) mutation: The TP53 gene is a gene located on p13.1 on human chromosome 17. TP53 mutations affect GBM progression [24]. Mutation of p53 causes invasion, cell proliferation, metastasis, and increased drug resistance; therefore, malignancy increases [25–28]. TP53 mutations are more common in IDH-mutant-type GBMs than in IDH-wild-type GBMs [16].

B-RAF V600E mutation: B-RAF is responsible for cell growth, a mutation that activates constitutive B-RAF kinase causes uncontrolled cell proliferation and tumorigenesis. Although the B-RAF V600E mutation is thought to be associated with GBM, it is not yet certain [29, 30].

GATA4 (GATA binding protein 4): GATA4 is a repressor gene transcription factor of the GATA6 family. Some studies suggest that GATA4 is associated with GBM [31, 32].

EGFR (Epidermal growth factor receptor): EGFR is a receptor activated by EGF (epidermal growth factor) and has tyrosine kinase activity. EGFR supports cell proliferation by activating the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways [33]. The EGFR gene is located at locus 7p12, and its amplification is observed in approximately 40% of GBMs [34]. EGFR amplification is more common in IDH-wild-type GBMs than in IDH-mutant-type GBMs [16].

MGMT (O ^{6}-methylguanine DNA methyltransferase): The MGMT gene is located on chromosome 10q26 and encodes a protein responsible for DNA repair by removing an alkyl group from the O^6 position of guanine. Some studies have shown that the use of MGMT inhibitors increases the effectiveness of temozolomide [35].

WT1 (Wilms tumor gene): WT1 was first identified as the gene responsible for Wilms tumors affecting children. Subsequent studies have shown that the majority of GBMs have WT1 [36–39].

PTEN (Phosphatase and tensin homolog): The PTEN gene is a suppressor gene located at 10q23. LOH (Loss of heterozygosity) or methylation mutation impairs pathways using PI3K and is observed in at least 60% of GBMs [40]. Loss of function of PTEN due to LOH and mutation is associated with a poor prognosis for GBM [41].

Meanwhile, the protective effects of female sex hormones on GBM development have been proven in the literature. In a study on the effect of female sex hormones on the incidence of glioma, it was observed that the risk of developing this cancer increased in women who had problems with menstruation delay and late menopause, and that the risk of developing cancer in women taking oral contraceptives or hormone replacement therapy was reduced [42].

3. Risk Factors of GBM

Race and ethnicity: There is limited association between ethnic groups and GBM. In a study, it was found that Caucasians have a 2.97 times higher incidence of GBM

compared to Asians and 1.97 times more than African Americans [20].

Ionizing radiation: Ionizing radiation is a risk factor for many cancers. Direct damage to genetic materials or the creation of free radicals around DNA is a condition that increases the possibility of mutation in the genetic material of cells. There are studies supporting the idea that ionizing radiation is a risk factor for brain tumors [43].

Obesity: Adipose tissue has many functions in the human body. It has been thought that it may have an effect on the formation of cancer, including GBM, since it has functions such as secreting estrogen and pro-inflammatory substances in addition to storing nutrients in the form of fat [44–46]. There are examples of studies that support and do not support this idea, but these studies are statistically more significant for women [43].

Metals: The International Agency for Research on Cancer (IARC) has identified cadmium, cadmium compounds, nickel compounds, and chromium compounds as human carcinogens and lead as a potential carcinogen, and none of these have been found to be associated with brain tumors [43]. In a study, it was concluded that occupational exposure to arsenic, mercury, and petroleum products increased the incidence of glioma, while exposure to lead, cadmium, and welding fumes did not increase the risk [47].

Nutrition, chemicals, and pesticides: Brain tissue necrosis associated with GBM invasion leads to the release of triglycerides, which may be accompanied by the release of toxins rich in phospholipids and co-stored in phospholipids in this neural tissue [48]. Some studies have shown that exposure to various chemicals will cause GBM to grow, become more aggressive, and even increase the risk of GBM formation [43].

In an *in vitro* study, long-term exposure of the U87 GBM cell line to a pesticide mixture (chlorpyrifos-ethyl, deltamethrin, metiram, and glyphosate) at low doses resulted in resistance to some chemotherapeutics (cisplatin, temozolomide, 5-fluorouracil, and others) and it has been observed that it causes an increase in the expression of ATP-binding cassette transporter (ABC) proteins [49]. In another study, it was concluded that diet, foods, or nutrition groups were not associated with gliomas [50].

Alcohol use: Alcohol can cross the blood-brain barrier (BBB) and consequently affect glial cells. Alcohol is also a risk factor in multiple cancers [51]. Especially when alcohol reaches high concentrations in the body, acetaldehyde and reactive oxygen species, which are toxic to cells, are formed as a result of its metabolism. Acetaldehyde is neurocarcinogenic in animals. In addition, alcoholic beverages contain N-nitroso compounds that cause brain tumor formation in animals [52–54]. However, contrary to what was thought in a meta-analysis, it was observed that alcohol use was not associated with the incidence of gliomas [55]. The relationship between alcohol use and the incidence of glioma was confirmed in another study [56].

Sleep and melatonin: In a study, it was concluded that sleep duration is not associated with the risk of glioma [57]. As a result of another study, it was reported that immune suppression, phase shift, decrease in melatonin levels, decrease in antioxidant levels, metabolic changes, cognitive impairment, epigenetic changes, and sleep disorders are pro-tumor mechanisms of action [58]. All these changes cause the prognosis of malignant tumors to worsen, and malignant brain tumors contribute to sleep disturbances [43].

In other studies, it has been reported that when melatonin is administered in combination with radiotherapy, it provides longer survival in patients compared to radiotherapy alone [59, 60]. In another study, it was reported that melatonin sensitized glioma cells to tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and thus increased the effect of TRAIL, and combined therapy with T-melatonin was more effective than TRAIL monotherapy [61]. In another study, it was confirmed that the mechanism of action of melatonin on gliomas is partially suppressing glioma stem cells *via* the EZH-2-NOTCH-1 signaling pathway [62].

Inflammation: Tumors are formed as a result of genetic mutations. Tumor formation can be observed even in a healthy human body. The immune system kills these tumor cells by certain mechanisms which are inflammatory [63]. However, chronic inflammation facilitates tumor formation by damaging DNA, which may cause tumors and mutations [64, 65]. In addition, chronic inflammations can prevent the immune system from fighting cancer cells by showing immunosuppressive activity, and the factors that trigger it increase the susceptibility to cancer [66]. Some of these triggering factors in GBM are tumor necrosis factor-α (TNF-α), and interleukin 1 and 6 (IL-1, IL-6) [43].

TNF-α is a soluble cytokine involved in directing the systemic inflammatory response [67]. It may exert antitumor activity on glioma cells, but may also increase tumor progression. TNF-α can facilitate angiogenesis by increasing EGFR activity, and decrease PTEN expression as a result of immune cell suppression by activation of nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) pathways. Due to these activities, TNF-α is an important factor in the progression of GBM [68–70].

IL-1 acts as an inducer of proangiogenesis and provisioning factors such as vascular endothelial growth factor (VEGF) in human astrocytes and glioma cells. Very little information is available about the role of IL-1α on GBM. IL-1β is a pro-inflammatory that has a tumorigenic effect by activating some cells to upregulate important molecules in oncogenic events [43]. The presence of IL-1β is very intense in GBMs and these tumor cells have IL-1β receptors (IL-1R) [71–73]. IL-1β binds to IL-1R, and activates NF-κB cascade and MAPK pathways [74]. IL-1β and NF-κB, increases VEGF expression, which promotes activation, angiogenesis, migration, and cancer invasion of p38 MAPK, c-Jun N-terminal kinase (JNK) pathways [75]. Therefore, IL-1β is an important factor in the GBM formation process.

Glioma is linked to chronic inflammation and IL-6 is a potent cytokine usually associated with chronic inflammation required for GBM formation [43]. In addition, IL-6 is a cytokine that plays a role in the malignant progression of gliomas and supports invasion, regeneration, and

angiogenesis [76]. The increase in IL-6 and its receptors adversely affects survival [77].

IL-6 suppresses immune surveillance by recruiting and stimulating myeloid-derived tumor suppressor cells and neutrophils, resulting in tumor survival. IL-6 is specifically found in the GBM, as stimulation of brain tumor cells by IL-6 promotes three major signal transduction pathways in gliogenesis. One of these pathways is p42/p44 MAPK. This pathway is dysregulated in approximately one-third of cancers and has a strong influence on the detection and processing of stress signals [78]. Another pathway is the PI3K/AKT pathway, which is associated with enhancement of angiogenesis, increase of invasion, promotion of metastasis, and activation of epithelial-mesenchymal transitions (EMT) [79]. The final pathway is JAK/STAT3, which is a signaling pathway that inhibits tumor recognition by immune system cells, promotes tumor cell cycle, and inhibits tumor apoptosis [80].

Electromagnetic radiation: The increase and widespread use of electronic devices such as mobile phones, computers, and microwave ovens necessitated the investigation of the effects of electromagnetic waves on the risk of CNS tumors. The mixed results obtained as a result of the studies on the effect of phone use on cancer development, the relatively new beginning of the use of smartphones, and the many confounding factors that may affect these results are not conclusive studies [43].

4. Treatment Options

Surgery, radiotherapy, and chemotherapy are generally combined for GBM treatment. However, whether or not surgical interventions will be performed or which of them will be performed depends on the patient's condition. The parameters considered in planning the treatment of GBM are tumor size, indications and risk-benefit ratio. Biopsy results and classification of tumor kind are important for the type and course of surgical interventions.

4.1. Drugs Used in Chemotheraphy

Temozolomid

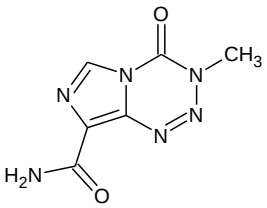

Figure 2 The chemical structure of temozolomide

Temozolomide (Figure 2) is a cytotoxic alkylating second generation imidazotetrazine prodrug that can be administered orally and intravenously, and is the methyl analogue of mitazolamide. It is used in combination with radiotherapy in the treatment of GBM, followed by maintenance monotherapy [81].

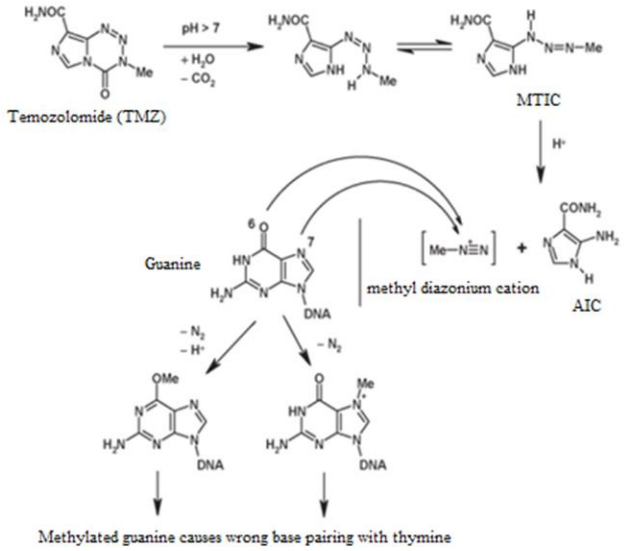

Figure 3 Mechanism of Action of Temozolomide [82]

After absorption, temozolomide is converted to its active metabolite (3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) by a spontaneous non-enzymatic conversion at physiological pH. MTIC hydrolyzes to form 5-aminoimidazole-4-carboxamide (AIC) and methyl diazonium ion which is highly reactive. The cytotoxicity of MTIC is thought to be due to alkylation of DNA at the O^6 and N^7 positions of guanine (Figure 3) [81].

Initially, it is administered orally or intravenously at 75 mg/m^2/day for 42 days with radiotherapy. Maintenance temozolomide monotherapy is started 4 weeks after the initial treatment and given orally or intravenously as 150–200 mg/m^2/day for the first five days. Then, the treatment is interrupted for 23 days. After 28 days, the second cycle is started in the same way, and total monotherapy consists of six identical cycles [83].

Resistance to temozolomide is dependent on DNA repair by the MGMT enzyme. If this repair does not occur, guanine mismatches with thymine at the O^6 position, activating the DNA mismatch repair (MMR) pathway that removes thymine and causing apoptosis. GBM cells that upregulate MGMT or downregulate MMR are resistant to [81].

It is contraindicated in cases of skin rash, hypersensitivity to dacarbazine, pregnancy, and lactation. It should be used with caution in patients with severe hepatic impairment or creatinine clearance below 36 mL/min. Alopecia, nausea, headaches, vomiting, and lymphopenia are the most common side effects. A complete blood count, liver function test, and pregnancy test in female patients are recommended prior to use [83].

Karmustine

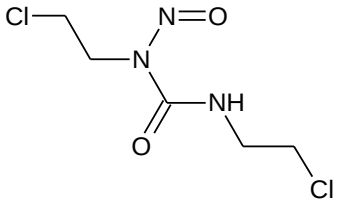

Figure 4 The chemical structure of carmustine

Carmustine (Figure 4) is a cell-cycle nonspecific nitrosourea alkylating agent used intravenously. Carmustine has a high partition coefficient, allowing it to enter the CNS in detectable concentrations [84].

Nitrosourea drugs exert their effects by inhibiting DNA replication, RNA transcription, and the functions of nucleic acids. Carmustine provides alkylation of cell proteins and nucleic acids through its 2-chloroethyl group. It causes the formation of cross-bridges between DNA-DNA and also DNA and proteins. As carmustine decomposes, isocyanates which cause substitution of the carbamoyl group on lysine residues of proteins are also formed. The 2-chloroethylisocyanate group of carmustine inhibits the repair of breaks in the DNA strand. Cross-resistance is common among carmustine and other alkylating drugs such as cyclophosphamide [84].

The recommended treatment scheme is 150-200 mg/m^2 as a single dose or divided into two days intravenously every 6 weeks [85].

It is contraindicated in pregnancy, lactation, and bone marrow depression. Common side effects include bleeding, bruising, nausea, vomiting, and respiratory problems. A complete blood count should be performed every week for 6 weeks after each dose. It is also recommended to control liver function tests, serum creatinine, and blood urea nitrogen (BUN) values [84].

Irinotecan

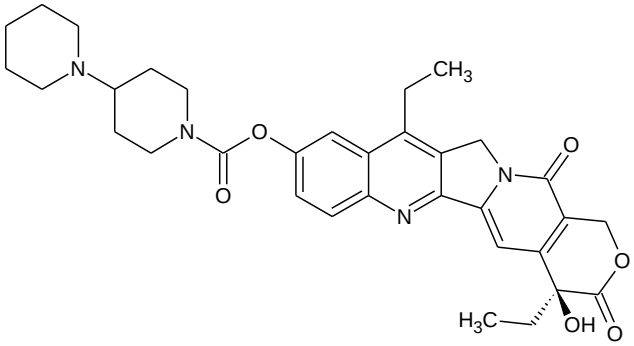

Figure 5 The chemical structure of irinotecan

Irinotecan (Figure 5) is a derivative of camptothecin (CPT), a cytotoxic alkaloid agent isolated from *Camptotheca acuminata* grown in China. Irinotecan is converted to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which is a topoisomerase inhibitor 1000 times more potent than parent drug (Figure 6) [86].

Irinotecan and SN-38 inhibit the enzyme topoisomerase I, which regulates the topology of DNA during translation, transcription, and mitosis. This enzyme induces single strand breaks during replication and RNA transcription, resulting in the release of torsional stress in the DNA helix. In addition, they prevent re-linking of the single DNA strand by binding to the topoisomerase I-DNA complex. Inhibition of replication enzymes by the ternary complex that occurs causes breaks in DNA double strands, thus inhibiting DNA replication in mammalian cells, and the cell dies as these breaks cannot be repaired [87].

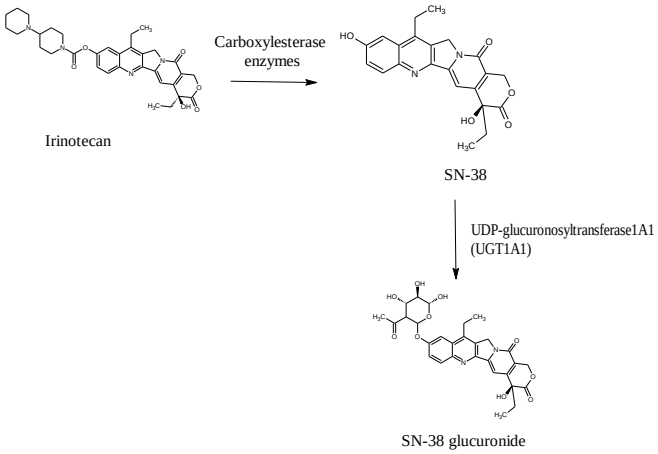

Figure 6 Mechanism of Action of Irinotecan [87, 88]

Premedication with antiemetic agents is recommended. Atropine therapy may be considered for patients experiencing cholinergic symptoms.

Regimen 1: 125 mg/m^2 is administered as a 90-minute intravenous infusion on days 1, 8, 15, and 22, followed by 2 weeks and repeated treatment.

Regimen 2: Administered as an intravenous infusion of 350 mg/ m^2 over 30-90 minutes on the first day every three weeks [89].

The use of irinotecan is contraindicated in diarrhea and bone marrow depression. Anemia, leukopenia, neutropenia, thrombocytopenia, elevated bilirubin levels and various gastrointestinal side effects such as nausea, and vomiting can be seen. Differential blood counts, liver function tests, and pregnancy tests are recommended [83].

Bevacizumab

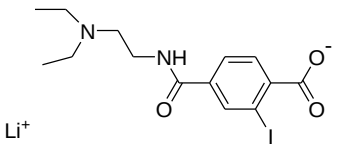

Figure 7 The chemical structure of bevacizumab

It is a recombinant humanized monoclonal antibody with VEGF inhibitory activity (Figure 7). It is indicated for the treatment of recurrent GBM. Because VEGF signaling plays an effective role in angiogenesis, bevacizumab inhibits tumor angiogenesis, depriving the tumor of blood and nutrients [83].

Transcription of the VEGF protein is induced by hypoxia-inducible factor (HIF) in hypoxic environment [90]. Circulating VEGF acts by binding to VEGF receptors (VEGFR-1 and VEGFR-2) found in endothelial cells [90, 91]. Cancer cells promote tumor angiogenesis by releasing VEGF, resulting in the formation of a disordered vascular network [92, 93]. The hypoxic microenvironment promoted by cancer cells facilitates the survival of more aggressive tumor cells and complicates the appropriate immune response [93–95]. Bevacizumab binds to VEGF and prevents VEGF from binding to its receptors [96]. This effect inhibits

the formation of new blood vessels in the tumor, reduces tumor vasculature, and reduces tumor blood flow [90, 97].

During the treatment process, the patient is recommended to have a urine test. It is given intravenously at a dose of 10 mg/kg every 2 weeks [83].

It has side effects such as fatigue, nausea, headache, and diarrhea [83].

Carboplatin

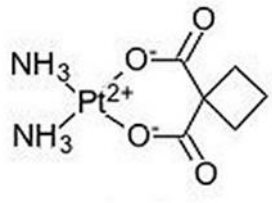

Figure 8 The chemical structure of carboplatin

Carboplatin (Figure 8) is an antineoplastic alkylating agent, a cisplatin-derived platinum compound. Studies have been conducted on its effectiveness on recurrent GBM, but sufficient data have not been obtained [98].

Temsirolimus

Temsirolimus (Figure 9) is a selective mTOR (target of rapamycin) inhibitory anticancer agent that inhibits the growth and division of tumor cells [99].

There are studies on its effectiveness in GBM treatment, but it is not yet an approved drug for GBM treatment [98].

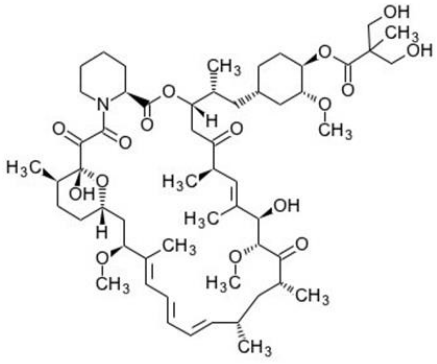

Figure 9 The chemical structure of temsirolimus

Abemacyclib

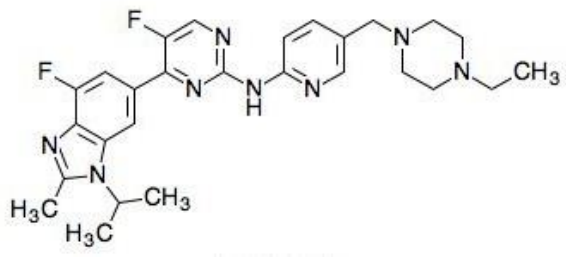

Figure 10 The chemical structure of abemaciclib

Abemacyclib (Figure 10), an inhibitor of cyclin-dependent kinase 4 (CDK4), and cyclin-dependent kinase 6 (CDK6), is an anticancer agent. [100, 101].

There are phase studies on its effectiveness [98].

Procarbazine

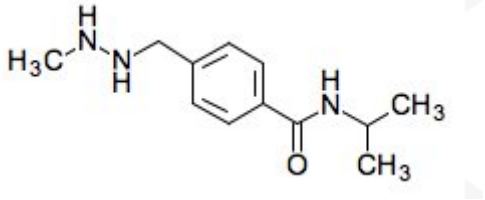

Figure 11 The chemical structure of procarbazine

Although procarbazine (Figure 11) is an antineoplastic agent indicated for stage III and IV Hodgkin's disease in combination with other agents, there are studies on its effectiveness in recurrent GBM. However, there is insufficient data [98, 102].

Etoposide

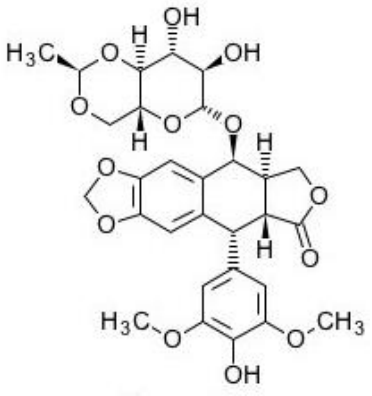

Figure 12 The chemical formula of etoposide

Etoposide (Figure 12) is a cell-cycle specific podophyllotoxin-derived drug that acts in the G2 phase of the cell cycle [103].

There are some studies on its effect on recurrent GBM, but sufficient data have not been reached [98].

Regorafenib

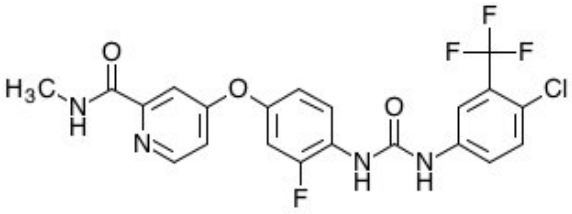

Figure 13 The chemical formula of regorafenib

A recent randomized phase II study with VEGF receptor 2 and a multikinase inhibitor, regorafenib (Figure 13), suggested that it improved survival in recurrent GBM compared to lomustine [104].

4.2. Targeted Molecular (Precision) Therapies

The advances in the molecular pathogenesis of GBM and the classification update made by the WHO in 2016 led to the idea that drug treatments targeting some mutations would be more effective, and studies were started in this field. Examples of these mutations are TERT promoter mutations, the most frequently investigated high-level EGFR amplification, and the EGFRvIII mutation. However, there

are minimal improvements in this field due to various problems such as drug scarcity that crosses the BBB, tumor heterogeneity, and difficulty in targeting some mutations [98].

4.3. Targeting DNA Damage Response Pathways

It is an emerging treatment approach, and the aim is to try to increase the effectiveness of the treatment on tumor tissue while preserving the normal tissue after chemotherapy and radiotherapy. The targeted site on the GBM is tumor-specific DNA repair weaknesses that appear to have an important stem cell compartment where DNA repair is upregulated and contributes to treatment resistance. The complex signaling and effector events that follow DNA damage are called the DNA damage response (DDR). DNA double-strand breaks (DSBs) are the main toxic lesion. They are induced by DNA-damaging agents, but single-strand breaks (SSBs) are now considered important lesions for lethality. Unrepaired SSBs are considered to delay replication forks which may indirectly join to the DSB load, especially in the status of replication stress [98].

Concomitant use of DNA-damaging agents with DDR inhibitors will rise the levels of unrepaired DSBs and SSBs in cells, resulting in significant chemosensitization and radiosensitization potential. However, combining of specific DDR inhibitors, such as polyADP-ribose polymerase (PARP) inhibitors, with DNA-damaging agents causes myelosuppression. Multiple DDR inhibitors are under testing in clinical trials for GBM therapy [98].

4.4. Targeting Tumor Metabolism

Data obtained in recent years has shown that GBM metabolism regulators can be used as prognostic, diagnostic, and therapeutic tools. The Warburg effect, an adaptation also seen in other solid tumors (independent of oxygen availability and metabolically shifted from mitochondrial oxidative phosphorylation to aerobic glycolysis), is also observed in GBM [105].

Some of the regulators in GBM are PTEN-induced kinase 1 (PINK1) and hexokinase 2 (HK2). It has been found that HK2 inhibition and PINK1 activation provided therapeutic benefit in GBM [106, 107]. Likewise, cholesterol metabolism may be an important target for GBM. There is a high dependence on cholesterol uptake in EGFR-derived tumors, making GBM cells undefended to liver X receptor agonists that decrease cholesterol uptake [105, 108].

4.5. Immunotherapies

Unlike some solid tumors, no improvement was observed in immunotherapy strategies related to GBM [109–111]. Evaluations of immunogenicity and appropriate target inhibition in the glioma microenvironment are limited. However, as more information is learned about the response of the tumor microenvironment to immunotherapy, it is possible to increase the number of patient groups responding to specific immunotherapy. GBM is an immunologically cold tumor due to the scarcity of tumor-infiltrating effector lymphocytes [111, 112].

In order to understand the mechanisms of immune resistance, the 3E hypothesis, consisting of elimination, equilibrium, and escape, has been created. For correlating the concepts of hot and cold tumors with this hypothesis, the adaptive and intrinsic resistance sizes of the tumor should also be considered. There are some factors that provide intrinsic resistance in GBM, such as scarcity of neoantigens and the release of soluble immunosuppressive mediators including transforming growth factor beta (TGF-β), IL-10, prostaglandin E2 and production of tryptophan and indolamine 2,3 dioxygenases and arginase leading to suppression of T-cell activity. Studies on these factors have been conducted [98].

In addition, strategies to increase effector immune infiltration into the microenvironment such as chimeric antigen receptor (CAR) T cells, oncolytic viruses, and various vaccines are being developed [98].

4.6. Viral Therapies

There is an interest in oncolytic viruses and gene therapy in clinical trials for GBM therapy, increasingly [113]. Oncolytic viruses are natural viral strains or viruses developed to infect and/or replicate selectively in tumor cells [114, 115]. Studies on oncolytic viruses and gene therapy to treat GBM are ongoing [98].

5. Challenges and Future Directions

Despite years of studies, there are still disadvantageous situations related to GBM treatment. Lack of data is one of the biggest problems, with only 11% of newly diagnosed GBM patients included in clinical trials [98].

Localization of the tumor in the CNS and neurological toxicities that can seriously affect the patient's quality of life are also factors to be considered during treatment. The BBB is also one of the important factor; because this tumor is located in the brain and uses the brain's defense mechanism against toxins through the BBB [116, 117]. Because of the BBB is made up of endothelial cells linked by tight junctions against a basement membrane, this barrier allows the passage of small, uncharged, and lipophilic molecules to the brain. Thus, most drugs can not cross it and reach the tumor; and this leads to the conclusion that one of the negative results of the studies to increase survival is BBB. [116, 118, 119].

Strategies to address this problem include the development of drugs with high BBB penetration, leakage of endogenous influx transporters such as low-density lipoprotein receptor-related protein 1, blocking of efflux pumps, cell mediated drug delivery, convection-enhanced delivery, focused ultrasound, and disrupting the BBB by using of microbubbles [116, 120–122].

Another important problem in GBM treatment is the high inter- and intratumoral heterogeneity. GBM, the first tumor to be characterized by the Cancer Genome Atlas, was found to show different tumor characterizations [123]. The differences among GBMs and the presence of intratumoral heterogeneity at both the molecular and functional levels complicate the tumor. Although the effect of intratumoral heterogeneity on therapeutic outcomes has not been fully

proven, preclinical study results suggest that different types of gliomas will respond differently to temozolomide and ionized radiation treatments. Additional studies are required to determine the effect of GBM heterogeneity on modern treatment methods such as molecularly targeted therapies and immunotherapies [98].

GBM is a tumor type with differential drug sensitivity among different GBM subpopulations, as well as high plasticity to generate resistance to chemotherapy. Against the efficacy of tyrosine kinase inhibitor anticancer drugs, GBM resists and survives through different mechanisms with the inclusion of dynamic reorganization of extrachromosomal DNA, chromatin modifying to a slow-cycling/drug-tolerant perminant state, depression of PTEN tumor suppressor, and reactivation in oncogenic signaling pathways. Some of the targeted molecular therapies have yielded positive results however, most studies have failed due to low BBB crossing of the drug used, unnecessary signaling pathways, molecular heterogeneity, the raised toxicity of the drug combinations, etc. [98]. There are alternative combination approaches such as those that orthogonal signaling/functional networks to increase drug responses [124, 125]. It is possible that these alternative approaches will be effective in studies for new treatment methods in GBM management [98].

Although immunotherapy is a promising method in the treatment of GBM, the negative results in large randomized studies show that getting a clinically meaningful immune therapy effect is difficult and complex. The reasons for this difficulty are limited antigenicity, impaired antigen presentation, intrinsic and treatment-induced systemic immunosuppression, and a unique immune suppressive microenvironment [112]. These reasons need to be investigated in detail in order to create effective immunotherapies [98].

6. Conclusion

Glioblastoma multiforme (GBM) is the most common type of malignant primary brain tumor and accounts for approximately 57% of all gliomas.

The location of GBM, few drugs and treatment methods approved for GBM therapy, the abundance of mutations and the complex nature of them, as understood from the genetic analysis of this tumor, as well as the fact that it is a cancer type with a very low survival rate and a lack of a definitive treatment, are the reasons why GBM is very dangerous.

Genetic studies to better define GBM and making more accurate and broad classifications of GBM have allowed to gain new perspectives on this type of cancer and increased efforts to discover new, more effective drugs and treatment methods, recently. The fact that GBM has a high diversity of mutations and high resistance to treatment methods causes improvement in new treatment methods and drug discovery to be insufficient.

It has been observed that the use of chemotherapy and radiotherapy in combination with surgical intervention in the treatment of GBM positively affects the survival of the patients. Innovative drug development studies such as targeting DNA damage response pathways, tumor metabolism, and viral therapies are promising. In addition to these new treatment methods, supportive therapies for example viral therapies and immunotherapies are also of great importance.

In conclusion, it is essential that new studies and innovative perspectives are extremely important in the treatment of GBM in light of the results of previous studies, and that studies should be continued intensively without despair.

Conflict of Interest

The authors declare that they have no conflict of interest with any person, institution, or company.

References

[1] McKinney PA. Brain tumours: incidence, survival, and aetiology. *Journal of Neurology, Neurosurgery, and Psychiatry* **2**(Suppl 2):ii12-ii17.

[2] Foundation NB. *The essential guide to brain tumors* (2007).

[3] Institute, National Cancer. *Brain tumors* (2002). Available from: http://www.cancer.gov/cancertopics/wyntk/brain,

[4] Smeltzer SC, Bare GB. *Brunner & Suddarth's textbook of medical-surgical nursing*. USA: Lippincott Williams & Wilkins (2005). 1970–1977.

[5] Armstrong TS, Gilbert MR. Metastatic brain tumors: diagnosis, treatment, and nursing interventions. *Clinical Journal of Oncology Nursing* (2000) **4**(5):217–225.

[6] Fitzsimmons B, Bohan E. *Common neurosurgical and neurological disorders* Morton PG, Fontaine D, Hudak CM, Gallo BM, editors. USA (2004). 796–838.

[7] Hill CI, Nixon CS, Ruehmeier JL, Wolf LM. Brain tumors. *Physical Therapy* (2002) **82**(5):496–502.

[8] Smith GB, Schnell S. Nursing care of patients with central nervous system disorders. In: Williams LS, Hopper PD, editors. *Understanding Medical Surgical Nursing*. USA: Philadelphia: FA. Davis Company (2003). p. 849–851.

[9] Boss BJ, Wilkerson RR. Concepts of neurologic dysfunction. In: Huether SE, editor. *Understanding Pathophysiology, McKance KL*. USA:Philadelphia: Mosby, Inc (2006). p. 491–546.

[10] Doolittle ND. State of the science in brain tumor classsification. *Seminars in Oncology Nursing* (2004) **20**(4):224–230.

[11] Soffietti R, Rudā R, Mutani R. Management of brain metastases. *Journal of Neurology* (2002) **249**(10):1357–1369.

[12] Catt S, Chalmers A, Fallowfield L. Psychosocial and supportive-care needs in high-grade glioma. *The Lancet. Oncology* (2008) **9**(9):884–891.

[13] Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro-oncology* (2018) **20**(supp_4):iv1-iv86.

[14] Tamimi AF, Juweid M. *Epidemiology and outcome of glioblastoma*. Australia:Brisbane: Codon Publications (2017). 143–153.

[15] Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clinical Cancer Research* (2013) **19**(4):764–772.

[16] Louis DN, Perry A, Reifenberger G, Deimling A, Figarella-Branger D, Cavenee WK. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathologica* (2016) **131**(6):803–820.

[17] Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. *Neuro-oncology* (2020) **22**(12 Suppl 2):iv1-iv96.

[18] Li K, Lu D, Guo Y, Wang C, Liu X, Liu Y. Trends and patterns of incidence of diffuse glioma in adults in the United States: 1973-2014. *Cancer Medicine* (2018) **7**(10):5281–5290.

[19] Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro-oncology* (2017) **19**(suppl_5):v1-v88.

[20] Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. *Neuro-oncology* (2013) **2**(Suppl 2):ii1-ii56.

[21] Schwartzentruber J, Korshunov A, Liu X-Y, Jones D, Pfaff E, Jacob K. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* (2012) **482**(7384):226–231.
[22] Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, LA, Jr, Diaz, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proceedings of the National Academy of Sciences of the United States of America* (2013) **110**(15):6021–6026.
[23] Vinagre J, Pinto V, Celestino R, Reis M, Pópulo H, Boaventura P, et al. Telomerase promoter mutations in cancer: an emerging molecular biomarker? *Virchows Archiv* (2014) **465**(2):119–133.
[24] Wang TJ, Huang MS, Hong CY, Tse V, Silverberg GD, Hsiao M. Comparisons of tumor suppressor p53, p21, and p16 gene therapy effects on glioblastoma tumorigenicity in situ. *Biochemical and Biophysical Research Communications* (2001) **287**(1):173–180.
[25] Oren M, Rotter V. Mutant p53 gain-of-function in cancer. *Cold Spring Harbor Perspectives in Biology* (2010) **2**(2):a001107.
[26] Adorno M, Cordenonsi M, Montagner M, Dupont S, Wong C, Hann B, et al. A mutant-p53/smad complex opposes p63 to empower TGFbeta-induced metastasis. *Cell* (2009) **137**(1):87–98.
[27] Schulz-Heddergott R, Moll UM. Gain-of-function (GOF) mutant p53 as actionable therapeutic target. *Cancers* (2018) **10**(6):188.
[28] Wang S-P, Wang W-L, Chang Y-L, Wu C-T, Chao Y-C, Kao S-H, et al. p53 controls cancer cell invasion by inducing the MDM2-mediated degradation of Slug. *Nature Cell Biology* (2009) **11**(6):694–704.
[29] Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, et al. Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas**.** *Pediatric Blood & Cancer* (2014) **61**(6):1101–1103.
[30] Behling F, Barrantes-Freer A, Skardelly M, Nieser M, Christians A, Stockhammer F, et al. Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. *Diagnostic Pathology* (2016) **11**(1):55.
[31] Agnihotri S, Wolf A, Picard D, Hawkins C, Guha A. GATA4 is a regulator of astrocyte cell proliferation and apoptosis in the human and murine central nervous system. *Oncogene* (2009) **28**(34):3033–3046.
[32] Agnihotri S, Wolf A, Munoz DM, Smith CJ, Gajadhar A, Restrepo A. A GATA4-regulated tumor suppressor network represses formation of malignant human astrocytomas. *The Journal of Experimental Medicine* (2011) **208**(4):689–702.
[33] Patel R, Leung HY. Targeting the EGFR-family for therapy: biological challenges and clinical perspective. *Current Pharmaceutical Design* (2012) **18**(19):2672–2679.
[34] Ekstrand AJ, Sugawa N, James CD, Collins VP. Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding portions of the N- and/or C-terminal tails. *Proceedings of the National Academy of Sciences of the United States of America* (1992) **89**(10):4309–4313.
[35] Kanzawa T, Bedwell J, Kondo Y, Kondo S, Germano IM. Inhibition of DNA repair for sensitizing resistant glioma cells to temozolomide. *Journal of Neurosurgery* (2003) **66**(6):1047–1052.
[36] Miyoshi Y, Ando A, Egawa C, Taguchi T, Tamaki Y, Tamaki H, et al. High expression of Wilms' tumor suppressor gene predicts poor prognosis in breast cancer patients**.** *Clinical Cancer Research* (2002) **8**(5):1167–1171.
[37] Inoue K, Sugiyama H, Ogawa H, Nakagawa M, Yamagami T, Miwa H, et al. WT1 as a new prognostic factor and a new marker for the detection of minimal residual disease in acute leukemia**.** *Blood* (1994) **84**(9):3071–3079.
[38] Clark AJ, Ware JL, Chen MY, Graf MR, Meter TE, Dos Santos WG. Effect of WT1 gene silencing on the tumorigenicity of human glioblastoma multiforme cells. *Journal of Neurosurgery* (2010) **112**(1):18–25.
[39] Nakahara Y, Okamoto H, Mineta T, Tabuchi K. Expression of the Wilms' tumor gene product WT1 in glioblastomas and medulloblastomas. *Brain Tumor Pathology* (2004) **21**(3):113–116.
[40] Koul D. PTEN signaling pathways in glioblastoma. *Cancer Biology & Therapy* (2008) **7**(9):1321–1325.
[41] Knobbe CB, Merlo A, Reifenberger G. Pten signalling in gliomas. *Neuro-oncology* (2002) **4**(3):196–211.
[42] Newcomb EW, Cohen H, Lee SR, Bhalla SK, Bloom J, Hayes RL, Miller DC. Survival of patients with glioblastoma multiforme is not influenced by altered expression of p16, p53, EGFR, MDM2 or Bcl-2 genes. *Brain Pathology* (1998) **8**(4):655–667.
[43] Grochans S, Cybulska AM, Simińska D, Korbecki J, Kojder K, Chlubek D, et al. Epidemiology of glioblastoma multiforme–literature review. *Cancers* (2022) **14**(10):2412.
[44] Jialal I, Devaraj S. Subcutaneous adipose tissue biology in metabolic syndrome. *Hormone Molecular Biology and Clinical Investigation* (2018) **33**(1).
[45] Nelson LR, Bulun SE. Estrogen production and action. *Journal of the American Academy of Dermatology* (2001) **45**(3 Suppl):S116-S124.
[46] Little RB, Madden MH, Thompson RC, Olson JJ, Larocca RV, Pan E, et al. Anthropometric factors in relation to risk of glioma. *Cancer Causes & Control* (2013) **24**(5):1025–1031.
[47] Parent M-E, Turner MC, Lavoué J, Richard H, Figuerola J, Kincl L, et al. Lifetime occupational exposure to metals and welding fumes, and risk of glioma: a 7-country population-based case-control study. *Environmental Health* (2017) **16**(1):90.
[48] Merritt RL, Foran CM. Influence of persistent contaminants and steroid hormones on glioblastoma cell growth. *Journal of Toxicology and Environmental Health. Part* (2007) **70**(1):19–27.
[49] Doğanlar O, Doğanlar ZB, Kurtdere AK, Chasan T, Ok ES. Chronic exposure of human glioblastoma tumors to low concentrations of a pesticide mixture induced multidrug resistance against chemotherapy agents. *Ecotoxicology and Environmental Safety* (2020) **202**:110940.
[50] Kuan AS, Green J, Kitahara CM, González AB, Key T, Reeves GK, et al. Diet and risk of glioma: combined analysis of 3 large prospective studies in the UK and USA. *Neuro-oncology* (2019) **21**(7):944–952.
[51] Galeone C, Malerba S, Rota M, Bagnardi V, Negri E, Scotti L, et al. A meta-analysis of alcohol consumption and the risk of brain tumours. *Annals of Oncology* (2013) **24**(2):514–523.
[52] Baglietto L, Giles GG, English DR, Karahalios A, Hopper JL, Severi G. Alcohol consumption and risk of glioblastoma; evidence from the Melbourne Collaborative Cohort Study. *International Journal of Cancer* (2011) **128**(8):1929–1934.
[53] Maekawa A, Mitsumori K. Spontaneous occurrence and chemical induction of neurogenic tumors in rats-influence of host factors and specificity of chemical structure. *Critical Reviews in Toxicology* (1990) **20**(4):287–310.
[54] Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. *Journal of Epidemiology and Community Health* (1996) **50**(4):442–446.
[55] Qi Z-Y, Shao C, Yang C, Wang Z, Hui G-Z. Alcohol consumption and risk of glioma: a meta-analysis of 19 observational studies. *Nutrients* (2014) **6**(2):504–516.
[56] Cote DJ, Samanic CM, Smith TR, Wang M, Smith-Warner SA, Stampfer MJ, et al. Alcohol intake and risk of glioma: results from three prospective cohort studies. *European Journal of Epidemiology* (2021) **36**(9):965–974.
[57] Samanic CM, Cote DJ, Creed JH, Stampfer MJ, Wang M, Smith-Warner SA, et al. Prospective study of sleep duration and glioma risk. *Cancer Causes & Control* (2021) **32**(9):1039–1042.
[58] Orešković D, Kaštelančić A, Raguž M, Dlaka D, Predrijevac N, Matec D. The vicious interplay between disrupted sleep and malignant brain tumors: a narrative review. *Croatian Medical Journal* (2021) **62**(4):376–386.
[59] Cutando A, López-Valverde A, Arias-Santiago S, Vicente J, Diego RG. Role of melatonin in cancer treatment. *Anticancer Research* (2012) **32**(7):2747–2753.
[60] Lissoni P, Meregalli S, Nosetto L, Barni S, Tancini G, Fossati V. Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. *Oncology* (1996) **53**(1):43–46.
[61] Martín V, García-Santos G, Rodriguez-Blanco J, Casado-Zapico S, Sanchez-Sanchez A, Antolín I, et al. Melatonin sensitizes human malignant glioma cells against TRAIL-induced cell death. *Cancer Letters* (2010) **287**(2):216–223.
[62] Zheng X, Pang B, Gu G, Gao T, Zhang R, Pang Q. Melatonin inhibits glioblastoma stem-like cells through suppression of EZH2-NOTCH1 signaling axis. *International Journal of Biological Sciences* (2017) **13**(2):245–253.
[63] Medzhitov R. Origin and physiological roles of inflammation. *Nature* (2008) **454**(7203):428–435.
[64] Meira LB, Bugni JM, Green SL, Lee C-W, Pang B, Borenshtein D, et al. DNA damage induced by chronic inflammation contributes to

colon carcinogenesis in mice. *The Journal of Clinical Investigation* (2008) **118**(7):2516–2525.
[65] Murata M. Inflammation and cancer. *Environmental Health and Preventive Medicine* (2018) **23**(1):50.
[66] Liu C-H, Chen Z, Chen K, Liao F-T, Chung C-E, Liu X, et al. Lipopolysaccharide-mediated chronic inflammation promotes tobacco carcinogen-induced lung cancer and determines the efficacy of immunotherapy**.** *Cancer Research* (2021) **81**(1):144–157.
[67] D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. *The Journal of Neuroscience* (2009) **29**(7):2089–2102.
[68] Kore RA, Abraham EC. Inflammatory cytokines, interleukin-1 beta and tumor necrosis factor-alpha, upregulated in glioblastoma multiforme, raise the levels of CRYAB in exosomes secreted by U373 glioma cells. *Biochemical and Biophysical Research Communications* (2014) **453**(3):326–331.
[69] Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. *Molecular Cancer* (2013) **12**:86.
[70] Kim S, Domon-Dell C, Kang J, Chung DH, Freund J-N, Evers BM. Down-regulation of the tumor suppressor PTEN by the tumor necrosis factor-alpha/nuclear factor-kappaB (NF-kappaB)-inducing kinase/NF-kappaB pathway is linked to a default IkappaB-alpha autoregulatory loop. *The Journal of Biological Chemistry* (2004) **279**(6):4285–4291.
[71] Lu T, Tian L, Han Y, Vogelbaum M, Stark GR. Dose-dependent cross-talk between the transforming growth factor-beta and interleukin-1 signaling pathways. *Proceedings of the National Academy of Sciences of the United States of America* (2007) **104**(11):4365–4370.
[72] Yeung YT, McDonald KL, Grewal T, Munoz L. Interleukins in glioblastoma pathophysiology: implications for therapy. *British Journal of Pharmacology* (2013) **168**(3):591–606.
[73] Sasaki A, Tamura M, Hasegawa M, Ishiuchi S, Hirato J, Nakazato Y. Expression of interleukin-1beta mRNA and protein in human gliomas assessed by RT-PCR and immunohistochemistry. *Journal of Neuropathology and Experimental Neurology* (1998) **57**(7):653–663.
[74] Griffin BD, Moynagh PN. Persistent interleukin-1beta signaling causes long term activation of NFkappaB in a promoter-specific manner in human glial cells. *The Journal of Biological Chemistry* (2006) **281**(15):10316–10326.
[75] Paugh BS, Bryan L, Paugh SW, Wilczynska KM, Alvarez SM, Singh SK, et al. Interleukin-1 regulates the expression of sphingosine kinase 1 in glioblastoma cells. *The Journal of Biological Chemistry* (2009) **284**(6):3408–3417.
[76] Shan Y, He X, Song W, Han D, Niu J, Wang J. Role of IL-6 in the invasiveness and prognosis of glioma. *International Journal of Clinical and Experimental Medicine* (2015) **8**(6):9114–9120.
[77] Tchirkov A, Khalil T, Chautard E, Mokhtari K, Véronèse L, Irthum B, et al. Interleukin-6 gene amplification and shortened survival in glioblastoma patients. *British Journal of Cancer* (2007) **96**(3):474–476.
[78] Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. *Oncogene* (2007) **26**(22):3279–3290.
[79] Crespo S, Kind M, Arcaro A. The role of the PI3K/AKT/mTOR pathway in brain tumor metastasis. *Journal of Cancer Metastasis Treatment* (2016) **2**:80–89.
[80] Nicolas CS, Amici M, Bortolotto ZA, Doherty A, Csaba Z, Fafouri A. The role of JAK-STAT signaling within the CNS. *JAKSTAT* (2013) **2**(1):e22925.
[81] Drugbank. *DB00853*. Available from: https://go.drugbank.com/drugs/DB00853.
[82] Babu NJ, Sanphui P, Nath NK, Khandavilli U, Nangia A. Temozolomide hydrochloride dihydrate. *CrystEngComm* (2013) **15**:666–671.
[83] Medscape. *Temodar Temozolomide* (2023). Available from: https://reference.medscape.com/drug/temodar-temozolomide-342229#5,
[84] Drugs.com. *Carmustine Injection Implant* (2023). Available from: https://www.drugs.com/mtm/carmustine-injection-implant.html#side-effects,
[85] Medscape. *Carmustine* (2023). Available from: https://reference.medscape.com/drug/bicnu-gliadel-carmustine-342194,
[86] Drugbank. *DB00762137* (2023). Available from: https://go.drugbank.com/drugs/DB00762137.
[87] Drugbank. *Irinotecan Reactions:1265* (2023). Available from: https://go.drugbank.com/reactions/1265.
[88] PubChem. *Glucuronide* (2023). Available from: https://pubchem.ncbi.nlm.nih.gov/compound/SN38-glucuronide#section=2D-Structure,
[89] Medscape. *Irinotecan* (2023). Available from: https://reference.medscape.com/drug/camptosar-irinotecan-342252,
[90] Kazazi-Hyseni F, Beijnen JH, Schellens J. Bevacizumab. *Oncologist* (2010) **15**(8):819–825.
[91] Karaman S, Leppänen V-M, Alitalo K. Vascular endothelial growth factor signaling in development and disease. *Development* (2018) **145**(14):dev151019.
[92] Lee SH, Jeong D, Han Y-S, Baek MJ. Pivotal role of vascular endothelial growth factor pathway in tumor angiogenesis. *Annals of Surgical Treatment and Research* (2015) **89**(1):1–8.
[93] Viallard C, Larrivée B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. *Angiogenesis* (2017) **20**(4):409–426.
[94] Rodríguez PC, Zea AH, Ochoa AC. Mechanisms of tumor evasion from the immune response. *Cancer Chemotherapy and Biological Response Modifiers* (2003) **21**:351–364.
[95] Petrova V, Annicchiarico-Petruzzelli M, Melino G, Amelio I. The hypoxic tumour microenvironment. *Oncogenesis* (2018) **7**(1):10.
[96] Brandes AA, Bartolotti M, Tosoni A, Poggi R, Franceschi E. Practical management of bevacizumab-related toxicities in glioblastoma. *Oncologist* (2015) **20**(2):166–175.
[97] *FDA Approved Drug Products: AVASTIN (bevacizumab) injection, for intravenous use*. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125085s331lbl.pdf.
[98] Wen PY, Weller M, Lee EQ, Alexander BM, Barnholtz-Sloan JS, Barthel FP, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro-oncology* (2020) **22**(8):1073–1113.
[99] Drugbank. *DB06287*. Available from: https://go.drugbank.com/drugs/DB06287.
[100] Drugbank. *DB12001*. Available from: https://go.drugbank.com/drugs/DB12001#BE0002216,
[101] Drugbank. *DB12001*. Available from: https://go.drugbank.com/drugs/DB12001,
[102] Drugbank. *DB01168*. Available from: https://go.drugbank.com/drugs/DB01168.
[103] Drugbank. *DB00773*. Available from: https://go.drugbank.com/drugs/DB00773.
[104] Lombardi G, Salvo GL, Brandes AA, Eoli M, Rudà R, Faedi M, et al. Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. *The Lancet Oncology* (2019) **20**(1):110–119.
[105] Bi J, Chowdhry S, Wu S, Zhang W, Masui K, Mischel PS. Altered cellular metabolism in gliomas - an emerging landscape of actionable co-dependency targets. *Nature Reviews* (2020) **20**(1):57–70.
[106] Agnihotri S, Mansouri S, Burrell K, Li M, Mamatjan Y, Liu J, et al. Ketoconazole and posaconazole selectively target HK2-expressing glioblastoma cells. *Clinical Cancer Research* (2019) **25**(2):844–855.
[107] Agnihotri S, Golbourn B, Huang X, Remke M, Younger S, Cairns RA, et al. PINK1 is a negative regulator of growth and the Warburg effect in glioblastoma. *Cancer Research* (2016) **76**(16):4708–4719.
[108] Villa GR, Hulce JJ, Zanca C, Bi J, Ikegami S, Cahill GL, et al. An LXR-cholesterol axis creates a metabolic co-dependency for brain cancers. *Cancer Cell* (2016) **30**(5):683–693.
[109] Medscape. *Bevacizumab* (2023). Available from: https://reference.medscape.com/drug/avastin-mvasi-bevacizumab-342257,
[110] Lim M, Xia Y, Bettegowda C, Weller M. Current state of immunotherapy for glioblastoma. *Nature Reviews. Clinical Oncology* (2018) **15**(7):422–442.
[111] Sampson JH, Gunn MD, Fecci PE, Ashley DM. Brain immunology and immunotherapy in brain tumours. *Nature Reviews* (2020) **20**(1):12–25.
[112] Jackson CM, Choi J, Lim M. Mechanisms of immunotherapy resistance: lessons from glioblastoma. *Nature Immunology* (2019) **20**(9):1100–1109.
[113] Lawler SE, Speranza M-C, Cho C-F, Chiocca EA. Oncolytic viruses in cancer treatment: a review. *JAMA Oncology* (2017) **3**(6):841–849.
[114] Kaufmann JK, Chiocca EA. Glioma virus therapies between bench and bedside. *Neuro-oncology* (2014) **16**(3):334–351.
[115] Kwiatkowska A, Nandhu MS, Behera P, Chiocca EA, Viapiano MS. Strategies in gene therapy for glioblastoma. *Cancers* (2013) **5**(4):1271–1305.

[116] Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nature Reviews* (2020) **20**(1):26–41.
[117] Sarkaria JN, Hu LS, Parney IF, Pafundi DH, Brinkmann DH, Laack NN, et al. Is the blood-brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. *Neuro-oncology* (2018) **20**(2):184–191.
[118] Heffron TP. Challenges of developing small-molecule kinase inhibitors for brain tumors and the need for emphasis on free drug levels. *Neuro-oncology* (2018) **20**(3):307–312.
[119] Vivanco I, Robins HI, Rohle D, Campos C, Grommes C, Nghiemphu PL, et al. Differential sensitivity of glioma-versus lung cancer-specific EGFR mutations to EGFR kinase inhibitors. *Cancer Discovery* (2012) **2**(5):458–471.
[120] Wen PY, Cloughesy TF, Olivero AG, Morrissey KM, Wilson TR, Lu X, et al. First-in-human phase I study to evaluate the brain-penetrant PI3K/mTOR inhibitor GDC-0084 in patients with progressive or recurrent high-grade glioma. *Clinical Cancer Research* (2020) **26**(8):1820–1828.
[121] Drappatz J, Brenner A, Wong ET, Eichler A, Schiff D, Groves MD, et al. Phase I study of GRN1005 in recurrent malignant glioma. *Clinical Cancer Research* (2013) **19**(6):1567–1576.
[122] Idbaih A, Canney M, Belin L, Desseaux C, Vignot A, Bouchoux G, et al. Safety and feasibility of repeated and transient blood-brain barrier disruption by pulsed ultrasound in patients with recurrent glioblastoma. *Clinical Cancer Research* (2019) **25**(13):3793–3801.
[123] Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell* (2016) **164**(3):550–563.
[124] Liau BB, Sievers C, Donohue LK, Gillespie SM, Flavahan WA, Miller TE, et al. Adaptive chromatin remodeling drives glioblastoma stem cell plasticity and drug tolerance. *Cell Stem Cell* (2017) **20**(2):233–246.
[125] Mai WX, Gosa L, Daniels VW, Ta L, Tsang JE, Higgins B, et al. Cytoplasmic p53 couples oncogene-driven glucose metabolism to apoptosis and is a therapeutic target in glioblastoma. *Nature Medicine* (2017) **23**(11):1342–1351.