Glioblastoma multiforme: An updated review of pathophysiology, diagnosis, and temozolomide-based therapy

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Abstract:

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, characterized by its rapid progression and poor prognosis. Malignant gliomas (Glioblastoma Multiforme) found in brain and occur more frequently than other types of primary tumors. Temozolomide, a second- generation alkylating agent is a new drug work against the glioblastoma multiforme. Alkylating agents are some traditional drugs act by producing mis- match of DNA and inhibit the replication of DNA Temozolomide, an oral alkylating agent, has emerged as a standard chemotherapy option for GBM treatment. This review aims to summarize the efficacy and safety of temozolomide in the management of GBM. Clinical trials and retrospective studies have demonstrated that the addition of temozolomide to standard radiotherapy significantly prolongs both progression-free survival (PFS) and overall survival (OS) in patients with newly diagnosed GBM. Furthermore, temozolomide is often used as maintenance therapy following chemoradiation, contributing to prolonged survival outcomes. However, temozolomide treatment is associated with several adverse effects, including nausea, vomiting, myelosuppression, and fatigue. Management of these side effects is essential to optimize patient outcomes and adherence to treatment. The efficacy of temozolomide may be influenced by various factors, including the methylation status of the O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter and the presence of other molecular biomarkers. Ongoing research is focused on identifying predictive biomarkers and developing novel treatment strategies to improve outcomes for patients with GBM. In conclusion, temozolomide plays a critical role in the

multimodal treatment approach for GBM and has demonstrated efficacy in prolonging survival, albeit with associated side effects that require careful management.

Keywords:

Glioblastoma multiforme, temozolomide, chemotherapy, radiotherapy, alkylating agent, efficacy, safety.

1. Introduction:

Glioblastoma is most common malignant tumour of central nervous system (Friedman et al., 2000). Glioblastoma is a primary type of brain tumour. It is the most dangerours subtype with 8-12 months patient's survival from time of diagnosis (Aleksandra Krajcer et al., 2003).

Surgery is the main stay of GBM treatment, and it is followed by adjuvant chemotherapy and radiation. The blood-brain barrier (BBB) hinders the delivery of therapeutic medicines to the central nervous system (CNS), and accessibility to the intended targets is the primary barrier to the creation of novel GBM medications. The blood-brain barrier (BBB) obstructs the delivery of therapeutic medicines to the central nervous system (CNS), therefore the primary barrier to the development of novel GBM medications is access to the intended targets (Manendra Singh, et al., 2021).

The two most prevalent histologies in adults are grade 4 Glioblastoma muliforme and grade 3 anaplastic astrocytoma (AA). When possible surgical resection is used to reduce the tumour's size , this is followed by radiation therapy (RT) with or without adjuvant chemotherapy. Even with this interdisciplinary approach, Glioblastoma patients still have a dismal prognosis (Wolf, A. et al., 2013).

The World Health Organisation (WHO) classification sysytem is the gold standard for Glioblastoma nomenclature and diagnosis; Glioblastoma is classified as a grade- IV cancer. Based on histological criteria for deermining the degree of malignancy, the fourh WHO classification of glioblastoma from 2016 includes four forms of this neoplasm. Have gained distinction: Astrocytic tumour (astrocytoma grade I, II [anaplastic astrocytoma], and IV [glioblastoma or GM]), Oligodendrogliomas, ependy momas, and mixed glioblastoma (Aleksandra Krajcer et al., 2003).

Temozolomide, a second- generation alkylating agent is a new drug work against the glioblastoma multiforme (J.R. Wesolowski et al., 2010) . Temozolomide is a prodrug that converts spontaneously under physiological conditions into active alkylating agent. Hepatic metabolism does not required for activation of temozolomide. In vitro, temozolomide has show schedule dependent antitumour activity against a variety of malignancies, including glioma metastatic melanoma, and other cancers (Friedman et al., 2000). Major challenge in glioblastoma treatment is to overcome the blood brain barrier in the CNS, which is the defence system of brain (Aleksandra Krajcer et al., 2023).

Temozolomide is one of the few pharmaceutical, which is able to enter the blood brain barrier and give their therapeutic effect. Phase 1 and Phase 2 clinical studies conducted by the Cancer Research Campaign, temozolomide was absorbed rapidly, exhibited 100% bioavailability wihin 1-2 hours of administration, and shows antineoplastic activity (Aleksandra Krajcer et al., 2003).

Results of these clinical studies showed that administartion of temozolomide once daily for 5 days in a 4-week cycle, it is well tolerated. These results also confirmed the ability of temozolomide to penetrate the blood brain barrier and indicated that temozolomide has potential to treat the glioblastoma. Temozolomide has approved in European Union on the basis of results of these studies for the treatment of patients with glioblastoma multiforme (Friedman et al., 2000).

2. History of glioblastoma:

Glioblastoma (GBM) is the most malignant type of glioma and the prevalent type of primary brain tumour. Prior to the most recent extensive subclassification of primary brain tumours made possible by moleculer biology and large-scale genomic studies, research on primary brain tumours was divided into two main periods: the classical period (1860-1920) and the histological period (1920-1940). The English and German medical communities referred to gliomas as “fungus medullare” and “medullary sarcomas”, respectively. This period of glioma study is commonly refferred to as the “ macroscopic ers”. Glioblastoma was originally discovered in 1863 by Dr. Rudolf Virchow, who used both macroscopic and microscopic methods to identify the tumour as having glial cell origins. Apart from creating the name “Glioma” he also initiated the “classical period’’ of glioma investigation, fusing macroscopic findings eith microscopic obsevations. A dramatic step was taken in the 1920s when two comatose patients with GBM had entire hemisphere removed by neurosurgen Dr. Walter Dandy. Even with this investigation, these patient eventually passed away from the illness, demonstarting for the first time just how invasive GBM really is. Glioblastoma was first originally identified as spongioblastoma multiforme, the tumour was termed as GBM in 1926 by neurosurgen and neurologist Dr. Percival Bailey and neurosurgen Dr. Harvey Cushing. Cushing and Bailey were crucial in initiating the glioma “histological era’’. According to bailey and cushing, several patients who had a brain glioma that was not complelety removed lived longer than anticipated. This information, together with heir discovery that no two gliomas had the same microscopic characteristic. Prompted them to conduct an extensive analysis of the composition and medical background of more than 400 confirmed gliomas. Bailey and Cushing noted that different gliomas had varying degrees of prognosis and that they were able to classify over 13 differtent forms of gliomas through their studies. Together with enormous advancements in clinical, pathological, molecular, and genetic research, these historical studies reveal the precise identify of Glioblastoma today (Wolf, A. et al., 2013).

3. Epidermiology:

The WHO classifies Glioblastoma (GBM), the most malignant diffuse glioma of the astrocytic lineage, as a grade IV glioma. GBM is the most prevalent malignant primary brain tumour, accounting for 16% of all primary brain tumours and 54% of all gliomas. GBM still has a 15- month median survival rate, making it an incurable tumor. As one ages, the incidence rises, reaching a peak beatween 75 and 84 years old and than declining after 85. Glioblastoma in children is hardly prevalent (Tali TA et al., 2003).

Site: Glioblastomas are uncommon in the cerebellum, extreamely uncommon in the spinal cord, and more frequently found in the supratentorial region (frontal, temporal, parietal, and occipital lobes).

The population-based research, and End Results did discover a variation in GBM behavior at these 2 sites . Cerebellar GBMs were smaller, less common in White individuals, and occurred in younger patients as compared to supratentorial placement . Adults seldom develop cerebellar GBM, which makes up 0.4% to 3.4% of all GBMs. The median age of patients with cerebellar GBM is 50–56 years, whereas the median age of patients with supratentorial GBM is 62–64 years; this indicates a considerable age difference between the two patient populations. Glioblastoma had the greatest frequency of frontal lobe tumors and tumors that included that overlapped two or more lobes, and then cancers in the temporal and parietal lobes. All brain subsites had higher male-to-female ratios, with the expectation of the posterior fossa; the occipital lobe had the highest ratio of these (Hanif et al., 2017).

Age: With a median diagnostic age of 64, GBM is typically diagnosed in older adults. The incidence rises with age, peaks between 75 and 84 years, and then declines after 85 years. Primary Glioblastoma typically has a higher mean diagnostic age of 55 and the median age of 64 campared mean of 40 years for secondary Glioblastoma. In children, Glioblastoma is rare. While the DNA methylation patterns of the pediatric and adults populations are comparable, there are specific clusters that are more common in younger individuals. Two of them exclusively match age-specific mutations in H3F3A that occurs often. Patients from a wider age range include another category that was enriched for DPGFRA mutations (Tamimi et al., 2017)

4. Causes:

The precise causes of glioblastoma, a very aggressive form of brain cancer, are unknown. Still, a number of variables have been linked to its development:

1. **Genetic factors**: There is a link between an increased risk of glioblastoma and mutations in specific genes. The most prominent genetic mutation, present in a considerable proportion of glioblastoma patients, is related to the **epidermal growth factor receptor** (EGFR) gene (Mason WP et al., 2005).
2. **Exposure to ionizing radiation**: Research indicates that glioblastoma risk may be elevated by ionizing radiation exposure, such as that resulting from prior radiation therapy for other

malignancies. This is especially important for people who have had radiation treatment to the head or neck

3. **Age:** About 64 is the typical age of diagnosis for glioblastoma, a disease that primarily affects older persons. But it can happen at any age.

4. **Environmental factors**: A number of environmental factors have been identified as possible glioblastoma risk factors, including exposure to specific chemicals or toxins. Yet, there is little and conflicting data associating particular environmental variables with the emergence of glioblastoma (Ostrom QT et al., 2018)

5. Risk factors:

1. **Age:** The incidence of glioblastoma rises with age, with adults 45 to 75 years old having the highest rates (Quinn T. Ostrom et al., 2014).

2. **Genetic predisposition**: An elevated risk of glioblastoma has been associated with a number of genetic disorders and familial predispositions (Malmer B et al., 2003).

3. **Ionizing radiation exposure**: A higher chance of glioblastoma development is linked to prior high doses of ionizing radiation exposure (Ron E et al., 1988).

4. **Race and ethnicity:** It has been noted that there are differences in the incidence of glioblastoma between various racial and ethnic groupings (Ron E et al., 1988).

5. **Environmental factors**: Some studies suggest associations between glioblastoma risk and certain chemical exposures, electromagnetic fields, and occupational hazards (Ron E et al., 1988).

6. Complications in glioblastoma:

Glioblastoma, a type of malignant brain tumor, presents various complications due to its aggressive nature and its location within the brain. Some of the complications associated with glioblastoma include:

1. **Neurological deficits**: Glioblastoma's infiltrative nature within the brain can result in a variety of neurological impairments. These deficiencies could include cognitive impairment, sensory abnormalities, frailty, and trouble speaking (R. Mason et al., 2005).

2. **Seizures**: When glioblastoma irritates the surrounding brain tissue, it can result in seizures (Van Breemen et al., 2009).

3. **Increased intracranial pressure (ICP):** Increased intracranial pressure brought on by glioblastoma growth can cause symptoms like headaches, nausea, and altered awareness (Chaichana et al., 2013).

4. **Cerebral edema**: As glioblastoma increases the permeability of blood vessels, it can cause swelling in the surrounding brain tissue (Stummer W et al., 2008)

5. Herniation: Glioblastoma-related increased intracranial pressure can result in herniation, a potentially fatal consequence (Bin-Alamer O et al., 2017)

6. **Venous thromboembolism (VTE)**: Patients with glioblastoma are at increased risk of developing VTE, including deep vein thrombosis and pulmonary embolism (Jeraq M et al., 2017).

7. Pathophysiology of glioblastoma:

A complex mechanism involving dysregulated signaling pathways, genetic abnormalities, and interactions with the tumor microenvironment underlies the pathophysiology of glioblastoma.:

1. **Genetic Mutations**: Numerous genetic changes that are specific to glioblastoma contribute to its etiology.

Key mutations include:

The epidermal growth factor receptor (EGFR) gene is amplified and mutated.

loss of heterozygosity (LOH) in the PTEN tumor suppressor gene on chromosome 10q.

Mutation or deficiency in the tumor suppressor genes CDKN2A and TP53. Modifications to the mTOR/AKT/phosphatidylinositol 3-kinase enzyme pathway (Brennan CW et al., 2013).

2. **EGFR Signaling Pathway Dysregulation**: Glioblastoma is characterized by aberrant activation of the EGFR pathway, which encourages tumor cell proliferation, survival, and invasion (Furnari FB et al., 2007).

3. **Angiogenesis:** VEGF and other proteins, such as hypoxia-inducible factors (HIFs) are responsible for the strong angiogenesis seen in glioblastomas. This mechanism promotes the growth of tumors and makes it easier for a dense vascular network to emerge (Plate KH et al., 1993).

4. **Tumor Microenvironment Interactions**: Tumor growth, invasion, and response to therapy are all influenced by the interactions between glioblastoma cells and different elements of the tumor microenvironment, such as immune cells, stromal cells, and extracellular matrix components. (Quail DF et al., 2013).

5. **Invasion and Migration**: Because glioblastoma cells can travel along white matter routes and alter the extracellular matrix, they are more likely to infiltrate neighboring brain tissue (Osswald M et al., 2015).

8. Diagnosis of glioblastoma:

Glioblastoma diagnosis is made up of multiple processes, such as histological analysis, neuroimaging, and clinical evaluation.

1. **Clinical Assessment:** Symptoms include headaches, seizures, altered cognition, and localized neurological impairments are frequently seen in patients. To evaluate the symptoms and indicators of intracranial disease, a comprehensive medical history and neurological examination are performed.

2. **Neuroimaging:** The main imaging technique for glioblastoma and other brain cancers is magnetic resonance imaging (MRI). MRI offers fine-grained pictures of the structure of the brain and enables the identification of aberrant tissue traits—like necrosis and contrast enhancement—that are linked to glioblastoma (Ellingson BM et al., 2017)**.**

3. **Histopathological Examination:** A sample of the tumor is taken for histological analysis through tissue biopsy or surgical resection. Characteristics of glioblastoma include necrosis, microvascular proliferation, nuclear atypia, and cellular pleomorphism (Louis DN et al., 2016).

4. **Molecular and Genetic Analysis**: Glioblastoma molecular profiling is becoming more crucial for treatment planning and prognosis. Testing for genetic changes such EGFR amplification, MGMT promoter methylation, and IDH mutation status may be necessary for this (Eckel-Passow JE et al., 2015).

5. **Clinical Staging:** The degree of surgical resection, the existence of a residual tumor, and the involvement of expressive brain regions are among the characteristics that determine the stage of glioblastoma. This stage aids in guiding prognostication and therapy choices (Stupp R et al., 2009).

9. Treatment of glioblastoma:

Usually, glioblastoma is treated with a mix of radiation therapy, chemotherapy, and surgery.

1. **Surgery:** The goal of surgical resection is to remove the tumor as much as possible without compromising brain function. However, because glioblastoma is infiltrative, full resection is frequently difficult (Stupp R et al., 2005).

2. **Radiation Therapy:** External beam radiation therapy (EBRT) is usually used to treat microscopic illness and remaining tumor cells after surgery. Delivered over several weeks, fractionated radiation therapy is the typical protocol (Stupp R et al., 2009).

3. **Chemotherapy:** For the treatment of glioblastoma, the main chemotherapeutic medicine is temozolomide, an oral alkylating agent. Usually, it is used in conjunction with radiation therapy and carried out as adjuvant therapy thereafter. (Stupp R et al., 2005).

4. **Novel Therapies:** Clinical studies are being conducted to test a variety of potential therapeutics for glioblastoma, including immunotherapy, gene therapy, and targeted medicines. These treatments seek to improve the immune system's ability to combat the tumor or target particular biological pathways (Weller M et al., 2017).

5. **Supportive Care:** Glioblastoma patients' quality of life is greatly enhanced by supportive care measures such corticosteroids for symptom management, anti-epileptic medications for seizure control, and physical therapy for rehabilitation (Stupp R et al., 2005).

10. Use of temozolomide in treatment of glioblastoma:

Temozolomide (TMZ) is a chemotherapy drug commonly used in the treatment of glioblastoma.

1. **Concurrent Chemoradiotherapy:** Temozolomide is often administered concurrently with radiation therapy (RT) following surgical resection of glioblastoma. This regimen, known as chemoradiotherapy, has been shown to improve overall survival compared to radiation therapy alone (Stupp R et al., 2005).

2. **Adjuvant Chemotherapy:** After completing chemoradiotherapy, patients typically receive adjuvant temozolomide for several cycles (Stupp R et al., 2009)

3. **Dosing and Schedule**: Temozolomide is typically administered orally once daily during both the concurrent chemoradiotherapy phase and the adjuvant chemotherapy phase. The dosing and schedule may vary based on individual patient factors and institutional protocols (Hegi ME et al., 2005).

4. **MGMT Promoter Methylation**: Methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter is a predictive biomarker for temozolomide response in glioblastoma. Patients with MGMT promoter methylation tend to have better outcomes with temozolomide therapy (Hegi ME et al., 2005).

5. **Management of Side Effects:** Temozolomide is generally well-tolerated, but common side effects may include myelosuppression (decreased blood cell counts), nausea, vomiting, and fatigue. Supportive care measures and dose adjustments may be necessary to manage side effects effectively (Stupp R et al., 2005).

Introduction of Temozolomide:

The FDA has approved temozolomide, also known as Temodar, as an oral alkylating drug for the first-line treatment of recurrent anaplastic astrocytoma and glioblastoma multiforme. Among the earliest medications are alkylating agents, which the chemotherapeutic arsenal and were first created as chemical weapons in the first half of the 1900s. Only after World War II were their anti-neoplastic properties examined in greater detail. Conventional alkylating chemicals work by creating cross-links in DNA, which prevents DNA replication and cellular growth. Methylation of DNA is the mechanism of action

for other medications that act in a similar way, like temozolomide, which likewise inhibits DNA and cellular replication. These substances all have a non-specific effect on both healthy and malignant cells. But since cancer cells proliferate more quickly than healthy tissue, there should be more sensitive to these effects (J.R. Wesolowski et al., 2010).

Temozolomide is a second-generation alkylating chemotherapeutic drug that is derived from imidazoles. It was created in the 1980s as a component of a sensible drug development program. Prodrug temozolomide claims that, is transformed into the active metabolite 5-(3-methyl)-1-triazen-1-yl-imidazole-4-carboximide (MTIC) by spontaneous hydrolysis, in contrast to dacarbazine. Temozolomide exhibits a schedule-dependent anticancer efficacy, is effectively absorbed, and crosses the blood–brain barrier. A reactive DNA-methylating agent with an affinity for the middle guanine residue of GGG DNA sequences is formed during conversion of TMZ to MTIC. Thirteen It is thought that the production of O6-methylguanine starts a series of DNA mismatch-repair processes that eventually result in apoptosis. Due to the irreversible inactivation of MGMT caused by this series of events, mismatch repair activity must be restored by increased de novo protein synthesis (M Mrugala et al.,2008).

Temozolomide works by methylating DNA, particularly at the O^6 and N^7 positions of guanine. This methylation leads to DNA damage and triggers cell death, particularly in rapidly dividing cells like cancer cells. Temozolomide is typically administered orally in capsule form. It's often used as part of a standard treatment regimen for GBM, which includes surgical resection of the tumor followed by concurrent chemoradiation therapy with temozolomide and radiation therapy. After this initial phase, patients may continue with adjuvant temozolomide treatment. The presence of the DNA repair enzyme MGMT in GBM tumors can influence the response to temozolomide. Tumors with low MGMT expression are more sensitive to the drug, while those with high MGMT expression may be more resistant. Testing for MGMT status can help guide treatment decisions (Stupp R et al., 2005).

History of Temozolomiode:

A lady create mental confusion and a right temporoparieal brain mass was found in her in 2000. She had undergo breast cancer treatment a few year ago. She was developed immoderate myelo-suppression during first cycle and further the chemotherapy was stopped. Disease developing was explore six month after initial diagnosis, and the mass was again drawn (Vanita et al., 2006).

Robert Stone, A research student at Aston University in 1980 sponsored by DISCOVERY AND CURRENT DEVELOPMENT 37 May and Baker Ltd, synthesized an example of a new ring- system imidazo [5, I-c and 1,2,3,5-tetrazine]. In 1983, entered lead compound mitozolomide with high hopes, phase 1 trial completed in 1985. Unfortunately, its curative activity not withstanding in many rodent tumour models (mitozolomide demonstrated only limited clinical activity and elicicted unexpected and severe myelosuppression). On this stage, lacking an industrial sponsor (Chang L et al., 2014). These results prevents the further clinical development of mitozolomide (Friedman et al., 2000).

Temozolomide, is a derivative of 3-methyl of mitozolomide, and less toxic than mitozolomide and exhibited compareable anitumour activity against various tumours. Temozolomide is a strong molecule, stable at acid pH and allow it to be absorb oral administration. Additionally, temozolomide is a strong molecule, stable at acid pH allow to absorb after oral administration (Malcolm FG et al., 1987).

Mechanism of action of Temozolomide on Glioblastoma:

An oral alkylating medication called temozolomide is used to treat glioblastoma multiforme (GBM), a kind of brain cancer. DNA adducts are formed as part of its mechanism of action, which eventually causes tumor cells to undergo programmed cell death, or apoptosis.

Alkylation: Temozolomide undergoes spontaneous chemical conversion at physiological pH to the active compound, methyl triazenoimidazole carboxamide (MTIC). MTIC then undergoes further decomposition to methyl diazonium ions, which alkylate DNA at the O6 and N7 positions of guanine and the N3 position of adenine.

↓

DNA damage: Alkylation of DNA by temozolomide leads to the formation of DNA adducts, particularly at the O6-guanine position. This interferes with DNA replication and transcription processes.

Activation of DNA repair mechanisms: Cells ↓ attempt to repair the DNA damage induced by temozolomide through various DNA repair mechanisms. However, the repair of O6-methylguanine lesions, in particular, is inefficient.

↓

Induction of apoptosis: Accumulation of unrepaired DNA damage, especially O6-methylguanine lesions, triggers the activation of apoptotic pathways, leading to programmed cell death in tumor cells (Stupp R et al., 2005).

Uses of Temozolomide:

Temozolomide is primarily used in the treatment of malignant brain tumors, particularly glioblastoma multiforme (GBM), which is the most aggressive form of brain cancer. It is also utilized in the management of other types of brain tumors, including anaplastic astrocytoma and metastatic melanoma to the brain. Additionally, temozolomide has been investigated in clinical trials for its potential efficacy in treating other types of cancers, such as metastatic colorectal cancer and metastatic breast cancer.

summary of the uses of temozolomide:

Glioblastoma Multiforme (GBM): Temozolomide is a standard component of the treatment regimen for newly diagnosed and recurrent GBM. It is typically administered concomitantly with radiotherapy followed by adjuvant treatment.

Anaplastic Astrocytoma: Temozolomide is also used in the treatment of anaplastic astrocytoma, a type of malignant brain tumor that is less aggressive than GBM but still requires intensive therapy.

Metastatic Melanoma to the Brain: Temozolomide is employed in the management of metastatic melanoma that has spread to the brain, either as a single agent or in combination with other treatment modalities.

Clinical Trials: Temozolomide has been investigated in clinical trials for its potential efficacy in treating other types of cancers, including metastatic colorectal cancer, metastatic breast cancer, and various other solid tumors (Osswald M. et al., 2015).

Side effects of Temozolomide:

Temozolomide, like many chemotherapy drugs, can cause a range of side effects. Here are some common side effects associated with temozolomide treatment in glioblastoma patients:

1. **Nausea and Vomiting**: Nausea and vomiting are common side effects of temozolomide treatment. They can often be managed with anti-nausea medications (Monika E et al., 2008).
2. **Fatigue**: Temozolomide treatment can lead to fatigue, which may impact the patient's quality of life and daily activities (Stupp et al., 2009).
3. **Myelosuppression**: Temozolomide can suppress the bone marrow's ability to produce blood cells, leading to low blood cell counts (neutropenia, thrombocytopenia, anemia) (Perry et al., 2017).
4. **Increased Risk of Infections**: Due to myelosuppression, patients undergoing temozolomide treatment may be at increased risk of infections (Gilbert et al., 2014).
5. **Headache:** Some patients may experience headaches as a side effect of temozolomide treatment (Wick et al., 2012).
6. **Hair Loss (Alopecia):** Some patients may experience hair loss or thinning during temozolomide treatment (Wick et al., 2012).

Contraindications of Temozolomide:

Temozolomide has several contraindications, meaning situations in which it should not be used due to potential risks. Here are some contraindications associated with temozolomide:

1. **Hypersensitivity:** Patients who have a known hypersensitivity to temozolomide or any of its components should not receive the drug (Lietzan et al., 2018).
2. **Severe Myelosuppression:** Patients with pre-existing severe myelosuppression, such as bone marrow failure or significant cytopenias, should not receive temozolomide due to the potential for exacerbation of myelosuppression.
3. **Pregnancy:** Temozolomide can cause fetal harm when administered to pregnant women. Therefore, it is contraindicated during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with temozolomide (Stupp R et al., 2005).
4. **Breastfeeding:** Temozolomide is excreted in human milk, and breastfeeding is contraindicated during treatment with temozolomide (Lietzan et al., 2018).
5. **Severe Hepatic Impairment:** Temozolomide should be used with caution in patients with severe hepatic impairment, as there is limited information on its use in this population. However, it is not specifically contraindicated (Lietzan et al., 2018).

11. Conclusion:

Glioblastoma multiforme (GBM) is a very aggressive and deadly type of brain tumor that grows rapidly and has poor treatment outcomes. Even with advances in surgery, radiotherapy, and chemotherapy, controlling the disease remains difficult. This is mainly due to its invasive growth, high molecular diversity, and the blood–brain barrier, which limits the amount of drug reaching the tumor, leading to poor patient prognosis.

Temozolomide is an important drug in the standard treatment of GBM because it can be taken orally, effectively crosses the blood–brain barrier, and improves survival when used with radiotherapy. The effectiveness of temozolomide depends on molecular factors, especially MGMT promoter methylation, which helps predict patient response to treatment. Although the drug is generally well tolerated, side effects such as bone marrow suppression and gastrointestinal problems may occur, requiring regular patient monitoring. Overall, temozolomide remains a key therapy for GBM, while ongoing research aims to reduce resistance and improve treatment outcomes.

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