Temozolomide for glioblastoma

- Effect of Acoustic Pressure on Temozolomide-Loaded Oleic Acid-Based Liposomes and Its Safety to Brain Tissue
- Second-line temozolomide in first recurrent MGMT-methylated glioblastoma after lomustine/temozolomide: Efficacy and safety
- Radiation Therapy for WHO Grade 4 Adult-Type Diffuse Glioma: An ASTRO Clinical Practice Guideline
- Piperine Targets MAOB and Enhances Temozolomide-induced Cytotoxicity in Glioblastoma Cell Lines
- Effects of Azelastine on Glioblastoma Cells
- Correction: SH3GLB1-related autophagy mediates mitochondrial metabolism to acquire resistance against temozolomide in glioblastoma
- Integrated Workflow for Drug Repurposing in Glioblastoma: Computational Prediction and Preclinical Validation of Therapeutic Candidates
- IDH1 Mutation Impacts DNA Repair Through ALKBH2 Rendering Glioblastoma Cells Sensitive to Artesunate

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Temozolomide (TMZ) is a cornerstone chemotherapeutic agent for the treatment of glioblastoma (GBM), a highly aggressive brain tumor. Its role is well-established in the current standard of care, often referred to as the Stupp protocol.

Mechanism of Action

TMZ is an oral alkylating agent that works by methylating DNA at the O6, N7, and N3 positions of guanine residues. This results in DNA damage, leading to apoptosis or autophagy of rapidly dividing cancer cells. The effectiveness of TMZ depends on the DNA repair capacity of the tumor. Tumors with silenced MGMT (O6-methylguanine-DNA methyltransferase) promoter via methylation are less capable of repairing TMZ-induced DNA damage and respond better to the treatment.

Standard Treatment Protocol

Concurrent Phase:

TMZ is administered orally at a dose of 75 mg/m² daily during radiation therapy (60 Gy in 30 fractions over 6 weeks). Adjuvant Phase:

After a 4-week break, TMZ is given at a higher dose (150–200 mg/m²) for 5 days every 28-day cycle, typically for 6–12 cycles.

Efficacy

TMZ significantly improves overall survival (OS) and progression-free survival (PFS). Median survival is extended from approximately 12 months (radiotherapy alone) to 14–16 months with the addition of TMZ. Five-year survival rates increase from 2% to approximately 9–10% for patients receiving TMZ.

Predictive Biomarkers

MGMT Promoter Methylation Status: A critical predictor of TMZ efficacy. MGMT-methylated tumors show better responses and prolonged survival compared to MGMT-unmethylated tumors. IDH1/IDH2 Mutation: Although rare in primary GBM, these mutations are associated with better prognosis and may influence TMZ sensitivity.

Side Effects

Common: Fatigue, nausea, vomiting, and anorexia. Myelosuppression, particularly thrombocytopenia and neutropenia, requiring monitoring. Long-Term: Rarely, secondary malignancies due to TMZ's alkylating properties.

Challenges and Considerations

Resistance: Tumor heterogeneity and adaptive resistance mechanisms, particularly in MGMT-unmethylated GBM, limit TMZ's efficacy. Combination Therapies: Research is ongoing to combine TMZ with targeted therapies, immunotherapies, or radiosensitizers to improve outcomes. Emerging Research Novel dosing schedules (e.g., metronomic TMZ) and personalized approaches based on molecular profiling are under investigation. Combination with checkpoint inhibitors, such as PD-1/PD-L1 inhibitors, holds promise but requires further validation in clinical trials.

Concurrent treatment with temozolomide and radiotherapy followed by maintenance temozolomide is the standard of care for patients with newly diagnosed glioblastoma.

O6 methylguanine DNA methyltransferase (MGMT), which is frequently expressed in cancer stem cells of glioblastoma, has been implicated in their resistance to temozolomide, the first-line chemotherapeutic agent against newly diagnosed glioblastoma.

JNK contributes to temozolomide resistance of stem-like glioblastoma cells via regulation of MGMT expression [1].

Temozolomide induced autophagic, but not apoptotic processes, in U251 cells and thus reduced their viability and migration [2].

Steroids are very commonly administered concurrently with temozolomide and radiotherapy after the initial surgical resection of glioblastoma (Glioblastoma) to control neurological morbidity. Although the potent anti-inflammatory effect of steroids is well documented to ameliorate vasogenic edema in these tumors, the deleterious effects of steroids on the efficacy of alkylating agents or radiotherapy have been a matter of debate [3] [4] [5] [6].

Neoadjuvant Temozolomide for Glioblastoma

- Cytomegalovirus Ventriculoencephaltis Post-Temozolomide Use For Glioblastoma Multiforme
- Anti-PD-1 and anti-PD-L1 antibodies for glioma
- Postoperative NEOadjuvant TEMozolomide followed by chemoradiotherapy versus upfront chemoradiotherapy for glioblastoma multiforme (NEOTEM) trial: Interim results
- Using a pre-radiation window to identify potentially active cytotoxic agents in adults with newly diagnosed glioblastoma
- Response to correspondence on an exploratory prospective phase II study of preoperative neoadjuvant bevacizumab and temozolomide for newly diagnosed glioblastoma
- Neoadjuvant combination treatment with checkpoint inhibitors, chemotherapy, and BRAF/MEK inhibitors for BRAF(V600E) glioblastoma results in sustained response: A case report
- Preoperative neoadjuvant bevacizumab and temozolomide for newly diagnosed and resectable glioblastoma
- State of the neoadjuvant therapy for glioblastoma multiforme-Where do we stand?

Neoadjuvant therapy involves administering treatment before the primary intervention, typically surgery, to shrink tumors, reduce disease burden, or improve resectability. In glioblastoma (GBM), one of the most aggressive and lethal brain tumors, temozolomide (TMZ) has been explored as a neoadjuvant agent.

Rationale for Neoadjuvant Temozolomide Tumor Downstaging: Preoperative TMZ can reduce tumor size, making surgical resection more effective. Microenvironment Alteration: Early intervention may modify the tumor microenvironment, potentially impacting invasiveness and resistance mechanisms. Enhanced Drug Delivery: By initiating therapy before surgical disruption of the blood-brain barrier (BBB), neoadjuvant TMZ ensures consistent drug delivery. Mechanism of Action Temozolomide is an alkylating agent that crosses the BBB and induces cytotoxicity by methylating DNA at the O6, N7, and N3 positions of guanine. The most critical site, O6-methylguanine, leads to mismatches during replication, triggering apoptosis.

Clinical Evidence The use of neoadjuvant TMZ in GBM is still under investigation. Studies have reported:

Improved Resection Outcomes: Some trials suggest better gross total resection rates due to tumor shrinkage. Mixed Survival Benefits: Overall survival and progression-free survival data are variable, depending on the timing, dosage, and patient selection. MGMT Promoter Methylation: The efficacy of TMZ is strongly correlated with methylation of the MGMT promoter, which silences the DNA repair enzyme O6-methylguanine-DNA methyltransferase. Limitations Heterogeneity: GBM's molecular and genetic heterogeneity affects the response to TMZ. Resistance: Intrinsic or acquired resistance mechanisms, including unmethylated MGMT promoter and DNA mismatch repair proficiency, can limit efficacy. Toxicity: Neoadjuvant TMZ may induce early hematological toxicity, complicating surgical planning. Future Directions Biomarker-Based Approaches: Identifying biomarkers such as MGMT status, IDH mutations, and other molecular signatures can optimize patient selection. Combination Therapies: Combining neoadjuvant TMZ with immunotherapy, targeted therapies, or radiation might enhance outcomes. Clinical Trials: Ongoing randomized trials are needed to establish standardized protocols and assess the balance between benefits and risks. In summary, while neoadjuvant TMZ for GBM shows promise, its role is not yet definitive. Personalization of treatment based on molecular

profiling and integration into multimodal strategies are crucial for optimizing patient outcomes.

It has been suggested that neoadjuvant temozolomide may provide sufficient tumor shrinkage to facilitate aggressive surgical debulking.

A Phase 2 randomized controlled trial assessed the safety and efficacy of neoadjuvant TMZ (nTMZ) before and during chemoradiotherapy in newly diagnosed glioblastoma patients.

Newly diagnosed GBM patients who underwent maximal safe resection were randomized into 2 groups. One received nTMZ before standard chemoradiotherapy and adjuvant TMZ (intervention). The other received standard chemoradiotherapy followed by adjuvant TMZ (control). Primary endpoints were progression-free survival (PFS) at 6 and 12 months. Secondary endpoints included overall survival, radiological and clinical responses, and adverse events.

Of 35 patients, 16 were in the intervention group and 19 in the control group. Median PFS was 9 months (95% CI: 3.93-14.06) versus 3 months (95% confidence interval [CI]: 1.98-4.01) in the control and intervention groups (P = .737), with a high progression rate (73.4%) during nTMZ treatment. The 6-month PFS rates were 58% versus 25% (P = .042), and 12-month PFS rates were 26% versus 25% (P = .390) in the control and intervention groups, respectively. Patients with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) and those with good performance status (PS) had significantly worse PFS with nTMZ. However, those who underwent larger extent of resection exhibited significantly better PFS with nTMZ. Adverse events were similar between groups.

Neoadjuvant TMZ before standard of care (SOC) chemoradiotherapy did not improve outcomes for newly diagnosed GBM patients and is unsuitable for those with unmethylated MGMT and good performance status (PS). However, It may benefit patients with near or gross total resection. Further research is needed to refine glioblastoma treatment strategies [7].

This study provides valuable insights into the limited efficacy of nTMZ as a neoadjuvant therapy in newly diagnosed GBM patients. While it fails to demonstrate overall benefit, the findings underscore the importance of tailoring treatments to individual patient characteristics. Further research is needed to elucidate the role of neoadjuvant strategies in GBM management, emphasizing personalized and biomarker-driven approaches.

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