The Clinical Frontier of Combining Traditional and New Drugs: Temozolomide Co-Therapy of Glioma

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Abstract: Glioma is the most common primary central nervous system tumor. Median survival rates are extremely low even with aggressive treatment using surgery, radiation, and chemotherapy. Temozolomide (TMZ), a triazene analog of dacarbazine, has antitumor activity and a good safety profile in malignant gliomas. However, there is an inevitable presence of resistance to TMZ for the treatment of glioma due to the enhancement of DNA damage repair proteins within the tumor. In contrast, the combination of TMZ and other drugs in adjuvant and TMZ immunotherapy can effectively reduce drug resistance. This literature provides an updated overview of the contribution and progress of the most recent cutting-edge new drug development to the adjuvant therapy of TMZ based on the mechanism of action in glioma and a summary of the results of clinical trials of TMZ in combination treatment. Finally, we conclude the article by exploring the TMZ immunotherapy as a new experimental therapy, providing an outlook on the new frontier of future treatment of glioma.

1. Introduction

Gliomas account for over 80% of malignant brain tumors and have very high mortality and morbidity rate [1]. Glioblastoma (GBM) is the most malignant form and is known for its treatment resistance [2]. Current treatment options at diagnosis are multimodal and include surgical resection, radiation, and chemotherapy [3]. Traditionally, they are classified according to tissue type and malignancy grade. The most common types of histologic gliomas in adults include astrocytomas, oligodendrogliomas, and oligodendrogliomas [4]. Age is significantly associated with survival after diagnosis for all gliomas, but most significantly for GBM.

Temozolomide (TMZ), a lipophilic, monofunctional alkalinizing agent and well-tolerated second-generation alkalinizing agent [5], is the main compound among the new chemotherapeutic agents entering the cerebrospinal fluid, with mild nausea, vomiting, and dose limitation as major toxicities. No hepatic metabolic activation is required. TMZ has shown schedule-dependent antitumor activity in vitro against highly anti-malignant tumors, including high-grade gliomas. TMZ demonstrated reproducible linear pharmacokinetics, rapid and reversible non-cumulative minimal myelosuppression, and activity against a wide range of solid tumors in children and adults [6]. TMZ was recently approved in the United States for the treatment of adult patients with refractory allergic astrocytoma and the European Union for the treatment of GBM multiforme that has progressed or recurred after standard therapy [6]. Radiotherapy and chemotherapy with the DNA alkylating drug TMZ are the current standard of care for glioma. Many cancers, however, are resistant to TMZ-induced DNA damage due to the increased expression of DNA damage repair proteins, and survival rates remain low [7].

2. Methods

Building on Friedman et al.'s clinical study of TMZ and malignant glioma in 2000, we searched MEDLINE for [Glioma] and [Temozolomide] to update relevant articles published from 2000 to 2021. We combined the most influential (ranked by impact factor) reviews on glioma and TMZ in the last two decades with the most recent mechanistic studies on adjuvant resistance to new TMZ drugs and clinical trial data. In addition, we used several cancer clinical studies from clinical trials and online sources, incorporating case-control and cohort studies as well as selected laboratory outcome reports. This review aims to investigate the mechanism of action of TMZ as a traditional conservative drug for glioma therapy due to its inherent susceptibility to drug resistance. Based on the mechanism of action of TMZ in glioma, we provide an exhaustive discussion examining the contribution and progress of new drug development in recent years for the adjuvant treatment of glioma with TMZ and highlighting promising new research areas for TMZ combination therapy. This article is not an exhaustive review of all relevant literature [8].

3. The mechanism of TMZ in therapy

At physiologic pH, TMZ is transformed to the short-lived active molecule monomethyl triazine imidazole carboxamide (MTIC), which is cytotoxic. MTIC's cytotoxicity is primarily due to DNA methylation at the O6 and N7 sites of guanine, which inhibits DNA replication. At all sites, TMZ is converted to MITC. TMZ is taken orally and has a strong effect on the central nervous system. The critical mechanism responsible for TMZ's cytotoxicity to malignant cells is DNA methylation. The action of water in the highly charged ion at the position of TMZ causes the spontaneous conversion of TMZ to the active methylating agent MTIC. This activity releases CO_2 and creates MTIC by opening the ring (Figure 1). More research is needed to determine the relevance of these targets in TMZ's molecular mechanism of action [6].

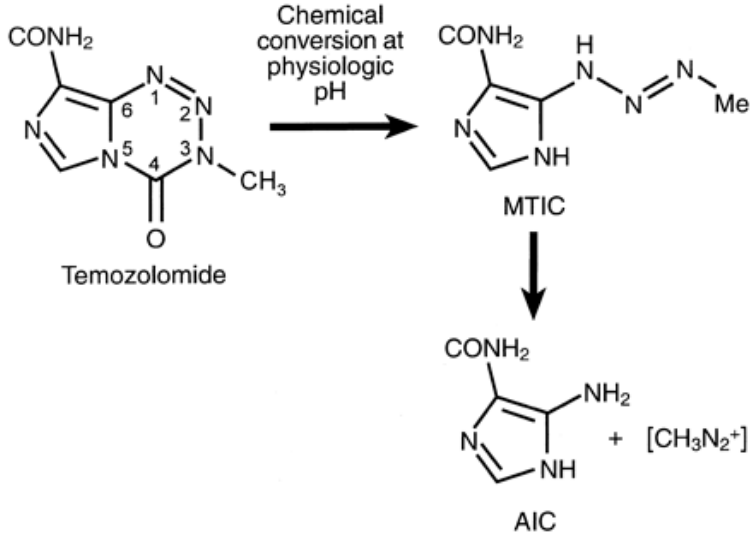

Figure 1. Metabolic pathway of TMZ [6]. TMZ spontaneously transforms into active methylating agent MTIC, releases CO2, and further transforms into AIC.

3.1 Pathway mechanism: Drug-assisted treatment of TMZ resistance

GBM is the most aggressive type of glioma. TMZ is currently the first choice for postoperative chemotherapy for GBM. However, the existence of inherent and acquired drug resistance hinders the success of chemotherapy [9]. In order to understand the mechanism of TMZ resistance in gliomas, some researchers have studied changes in cell signaling pathways by conducting transcriptional analysis of TMZ-treated glioma cells. The results indicate that activation of the Wnt/β-catenin pathway involves an ATM/ CHK2-independent PI3K/Akt/GSK-3 cascade in TMZ-treated cells, as well as other mechanism-based glioma chemotherapy to TMZ [9].

3.2 Preclinical Development Research

Many studies have now demonstrated that the combination of TMZ with other chemotherapies did not lead to improved outcomes. To improve treatment, Kim et al. coupled TMZ with additional alkalizing drugs (nimustine or carmustine and lomustine) [10]. However, the experiments were halted due to the high rate of toxicity. The use of TMZ in conjunction with small molecule inhibitors has also been unsatisfactory. Furthermore, when added to radiation therapy-TMZ for newly diagnosed GBM, bevacizumab, which suppresses vascular endothelial development, showed no benefit. The combo therapy, as well as several TMZ dose versions, have yielded inconsistent results. The most logical next step for TMZ is dose intensification.

Sequential dose intensification of TMZ in patients with recurrent GBM was shown to be safe in phase II clinical trials. Following studies found that using TMZ with concurrent radiation therapy for nine cycles or longer enhanced progression-free and overall survival without increasing toxicity in newly diagnosed GBM patients. In patients with newly diagnosed GBM, phase III clinical studies found no enhanced efficacy with dose-dense TMZ compared to conventional dosages, independent of methylation status. In patients with GBM, a lower, more consistent dose as also investigated. This dosing regimen was created for senior people who may be unable to handle conventional TMZ dosage. Some researchers believe that the metered dose prevents anti-TMZ cancer cells from forming and improves cancer vascular targeting. Furthermore, animal investigations have revealed that a metered TMZ treatment lowers immunosuppressive teres. In patients with GBM, only limited phase I and II studies using metered TMZ with safety precautions have been done.

4. Drug inhibitors sensitizes glioma to TMZ

4.1 Traditional medicines

4.1.1 Bortezomib

The sensitization or resistance of glioma to TMZ can be affected by other drugs, which are related to multiple proteins, enzymes, and signaling pathways. Tang et al. studied its anti-glioma activity and underlying mechanism on glioma, and found that bortezomib significantly inhibited elliptical growth, colony formation, and stem cell-like cell proliferation in U251 and U87 cells. In addition, when TMZ was administrated in combination with bortezomib, bortezomib synergized with TMZ in vitro and sensitized glioma cells to TMZ in vitro and in vivo. The chemotherapeutic efficacy of TMZ was enhanced by bortezomib by a mechanism that may be related to downregulation of the FOXM1-Survivin axis. Bortezomib, either alone or in combination with TMZ, may be a viable therapeutic agent for malignant gliomas [12].

4.1.2 Connexin 43 Inhibition

Studies demonstrated connexins is vital in the microenvironment of malignant glioma, and the gap junction protein connexin 43 (Cx43) is one of the reasons for the resistance to TMZ of malignant glioma. Apart from its critical regulatory and developmental activities in a variety of tissues, Cx43 is a driving factor of tumor invasion, a marker of tumor growth, and an inducer of TMZ resistance in GBM cells. Results showed inhibition of Cx43's half-channel activity with c-terminal peptide aCT1 restored TMZ sensitivity of TMZ-resistant/CX43-high GBM cells (including glioma stem cells (GSCs)) and reduced LN229/GSC tumor development in TMZ-treated mouse. Cx43 has been identified as a potential therapeutic target to reduce GBM aggressiveness, proliferation, and mortality, limit tumor recurrence after primary tumor resection, and overcome congenital or acquired TMZ resistance [13].

4.1.3 Coumarins

J. Sumorek-Wiadro et al. investigated the prospect of employing simple coumarins in conjunction with TMZ to treat glioma cells undergoing programmed death for the first time. They investigated the efficacy of osthole, umbelliferone, esculin, and 4-hydroxycoumarin, both alone and in combination

with TMZ, in programmed cell death of anaplastic astrocytoma (AA) and GBM cells, and discovered that osthole inhibited the GBM and AA cells' migratory phenotype. Co-incubation with TMZ had little effect on the pro-apoptotic potential of natural compounds, but did inhibit autophagy in T98G cells. Glioma cell death was associated with activation of caspase 3, suppression of Bcl-2 expression, and the existence of a Bcl-2/Beclin 1 complex. Inhibiting Bcl-2 expression induced apoptosis but not autophagy in the MOGGCCM and T98G lines. Additionally, inhibiting Bcl-2 expression increased the sensitivity of astrocytoma cells to combined osthole and TMZ treatment, but not of GBM cells, which was associated with a decrease in Beclin 1 and an increase in caspase 3 expression [14].

4.2 Nanoparticles

Nanoparticles can be utilized to enhance TMZ sensitivity in glioma. The crosstalk activation of EGFR and MET signaling pathways are factors of TMZ resistance, leading to a poor prognosis for patients with GBM. Meng, et al. developed BIP-MPC-NP, a dual functionalized brain-targeting nanoinhibitor (Figure 2), to alleviate the activation of EGFR and MET simultaneously [7].

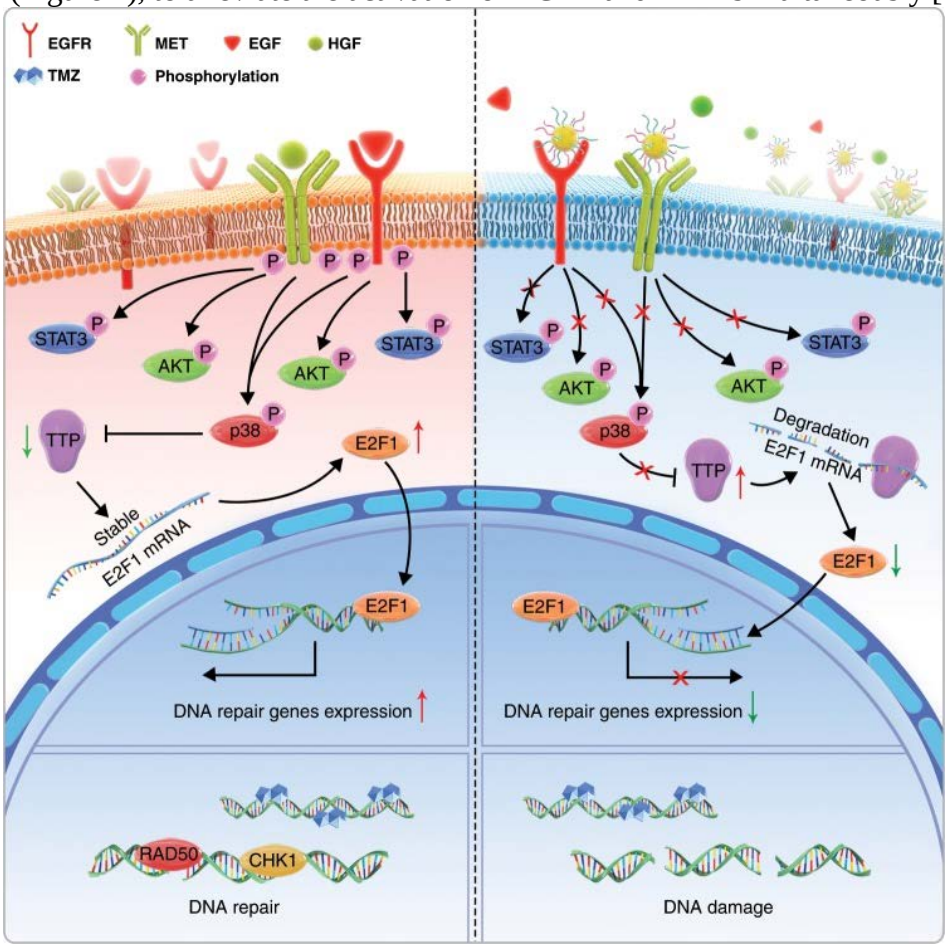

Figure 2. The mechanistic scheme of a dual functionalized BIP-MPC-NP in temozolomide-resistant glioma [7]. The mechanistic scheme of BIP-MPC-NP attenuating DNA damage repair to enhance TMZ sensitivity by simultaneously mitigating EGFR and MET activation in TMZ-resistant gliomas.

Another example is the TMZ-A2PEC/siPLK, an endothelin-2 (A2) modified polymer micelle (A2PEC) embedded in TMZ and plK1-targeting small interfering RNA (siRNA) (siPLK1) to attenuate TMZ resistance in gliomas, Targeted therapy based on polo-like kinase 1 (PLK1) leads to G2/M blockade and enhances the sensitivity of glioma to TMZ. In vitro studies showed that TMZ-A2PEC/siPLK successfully increased the absorption of TMZ and siPLK1 cells, induced a large number of apoptosis and cytotoxicity of glioma cells, while in vivo studies showed that the development of glioma was prevented, and the survival time was significantly prolonged [15].

4.3 Cyclic RNA and TMZ resistance in glioma cells

The development of chemoresistance remains a major obstacle in the management of glioma. NRCAs are associated with the development and progression of cancer [16].In addition, circRNAs operate as critical regulators in cancer biology through the ceRNAsby networks sequestering their target miRNAs. Several circRNAs, have been implicated in glioma growth and progression by functioning as a molecular sponge for particular miRNA.

- The study by Ding et al. illustrates that in the sera of TMZ-resistant patients, exonic CircNFIX is upregulated, which indicates a bad prognosis. Exon CircNFIX from TMZ-resistant cells makes recipient-sensitive cells resistant to TMZ by increasing cell motility and invasion and blocking apoptosis in response to TMZ treatment. circNFIX binds to miR-132 and interacts with it directly. In immune glioma cells, circNFIX lowers resistant glioma by increasing miR-132 TMZ sensitivity. Furthermore, exosomal CircNFIX stimulates tumor development, and its removal in glioma cells improves TMZ sensitivity in vivo [17].
- In another research, Ding et al. demonstrated that In TMZ-resistant glioma cells, serum samples, and glioma tissue, circ 0005198 was significantly regulated. In the TMZ-resistant glioma cells, silencing circ 0005198 reduced TMZ resistance, limited proliferation, and promoted apoptosis. The impact of circ 0005198 on TMZ-resistant glioma cell advancement was attributable to inhibition of miR-198 activity and indicated that circ 0005198 on TMZ-resistant glioma cell progression was due to inhibition of miR-198 activity [18].
- Earlier miRNA expression profiles obtained from short RNA sequencing on human GBM patient samples revealed MiR-138 to be one of the most substantially down-regulated miRNAs in GBM. GBM cells were more sensitive to TMZ treatment when miR-138 was overexpressed ectopically, and apoptosis was increased. MiR-138 boosted apoptosis generated by xanthophores during TMZ treatment by directly blocking the synthesis of the pro protein survivin, according to Ji-Young Yoo et al. This study provides strong experimental data for the therapeutic effectiveness of miR-138 reintroduction in GBM cancers that have been resistant to conventional therapy [19]. MiR-155-3p regulates Six1 expression and promotes GBM development and TMZ resistance, suggesting that it might be used be a new therapy target for glioma [20].
- By targeting FBXL7 with strong TMZ sensitivity, miR-152-5p suppresses glioma growth. The suppression of FBXL7 or overexpression of miR-152-5p inhibited invasion of glioma cells, proliferation, migration, and TMZ-induced cytotoxicity, according to Kong et al. Furthermore, miR-152-5p expression was dramatically decreased in glioma cells, and its action was mediated via FBXL7 targeting. Overexpression of miR-152-5p and reduction of FBXL7 boosted TMZ-mediated antitumor effects and slowed tumor development in a glioma xenograft model. Thus, miR-152-5p decreased glioma and associated tumor growth, targeted FBXL7, improved TMZ-induced glioma cytotoxicity, and helped us learn more about glioma FBXL7 activity [21].
- The miR-181 family has been identified to have a significant function in modulating glioma cellular processes. Zhang et al. discovered that combining miR-181b-5p with TMZ reduced U87MG cell invasion, migration, and proliferation while enhancing apoptosis and S-phase arrest more effectively than using either miR 181b-5p or TMZ alone. The apoptosis-related molecule Bax is upregulated, whereas recycling-related proteins are downregulated. The similar trend was followed by CyclinD1 and CDK4. MiR-181b-5p improved the tumor suppressive activity of TMZ in vivo trials. In conclusion, their findings suggest that expression of miR-181b-5p directly targets Bcl-2 and may play a role in glioma cell sensitivity to TMZ [22].
- According to growing data, the discordant regulation of miRNA/mRNA-mediated oncogenic signaling pathway networks is highly linked to gliomagenesis and development. RPN2 levels in glioma specimens were shown to be much greater than in control subjects, and its overexpression was linked to a bad WHO grade and prognosis. According to Sun et al., RPN2 knockdown decreased tumor growth and invasion, increased apoptosis, and improved TMZ sensitivity in vivo. They also discovered that RPN2 is a direct miR-181c functional target. RPN2 partly

restored the miR-181c-induced suppression of -catenin/Tcf-4 activity, revealing a biological basis for TMZ sensitivity mediated by miR-181c [23].

5. Clinical treatment of glioma with TMZ combination

Even with therapy, the prognosis for most GBM patients is still bleak, with a 2-year survival rate of about 27%. As a result, more effective GBM therapies are urgently needed. Herrlinger et al. evaluated the effect of lomustine TMZ treatment in a randomized phase III study in an open-label, randomized design. In 129 patients, they discovered that median overall survival increased from 31±4 months with TMZ to 48±1 months with lomustine TMZ. In the TMZ group, 32 of 63 patients (51%) had grade 3 or higher adverse events, whereas, in the lomustine-TMZ group, 39 of 66 patients (59%) experienced grade 3 or higher adverse events. There were no fatalities as a result of the therapy. Their findings imply that lomustine-TMZ chemotherapy may increase survival in newly diagnosed GBM patients compared to the usual treatment with methylation methylguanine methyltransferase (MGMT) boosters [24].

In vitro and in vivo, O6-benzylamine is an AGT ligand that inhibits AGT activity while increasing TMZ cytotoxicity. Jennifer et al. provide the results of a two-stage clinical study in individuals with malignant glioma that has recurred or progressed. They observed that a 120 mg/m2 IV bolus administered over 1 hour followed by a 30 mg/m2/d continuous infusion for 48 hours substantially reduced tumor AGT activity [25]. Retinoids and alkylators, either alone or in combination, have been shown to have acted in gliomas in preclinical and clinical studies. In phase II clinical studies, TMZ and 13-cis-retinoic acid (RA), two orally given medicines with separate mechanisms of action, showed effectiveness in recurring malignant gliomas without overlapping toxicity. Kurt A et al. discovered that TMZ and CRA were active, assuming a 20% increase over the prior database [26].

The treatment paradigm is generally maximally safe surgical resection followed by adjuvant chemotherapy. A study confirmed that postoperative radiation therapy with both concurrent and adjuvant TMZ improved survival in GBM patients when compared to adjuvant radiation therapy, and subsequent studies have shown that survival rates with TMZ were improved even with adjuvant hypoxic radiation therapy in elderly patients. Adjuvant prostaglandin, lomustine (CCNU), and vincristine (PCV) chemotherapy regimens have been shown to be beneficial in allergic oligodendroglioma studies [11].

6. The immunomodulatory effects of TMZ

TMZ is widely used with GBM. However, resistance to existing therapies TMZ remains to be improved- and immunotherapy is being extensively investigated in GBM patients. Despite the strong interest in developing new therapies for GBM, most clinical trials have failed to deliver survival benefits to patients [5].

Chemotherapy has a significant effect on host immunity. The effect of chemotherapy depends on the mechanism of action of the drug, the dose and the immune environment of the host. As immunotherapy options for GBM patients expand and are studied, the role of TMZ as an immunotherapy combination strategy will become increasingly important.

TMZ has been shown to cause lymphoid cortical proliferation, increase the proportion of regulatory T cells (Tregs), and possibly enhance dendritic cell function. Human studies have shown that TMZ can be successfully used for cellular immunotherapy. In addition, TMZ enhances the proliferation and function of antigen-specific T cells due to the built-in recovery period after the reduction of lymphocytes.

TMZ has an immunomodulatory effect as an immunomodulator. TMZ can affect the immune function of patients with brain tumors through two effects on tumor cells and a direct effect on immune cells. TMZ-induced tumor cell death allows the release of tumor antigens presented by dendritic cells (DCs). TMZ treatment leads to the cytoplasmic accumulation of antigen peptides in tumor cells, thereby better identifying immune cells. The effects of TMZ on host immunity include the decrease of

lymphocytes. The recovery of dormant lymphocytes after tmz-induced lymphopenia is the window period for the rapid expansion of antigen-specific T cells. TMZ may deplete or expand Tregs, which is immunosuppressive depending on the dosing regimen [5]. As shown in fig 3.

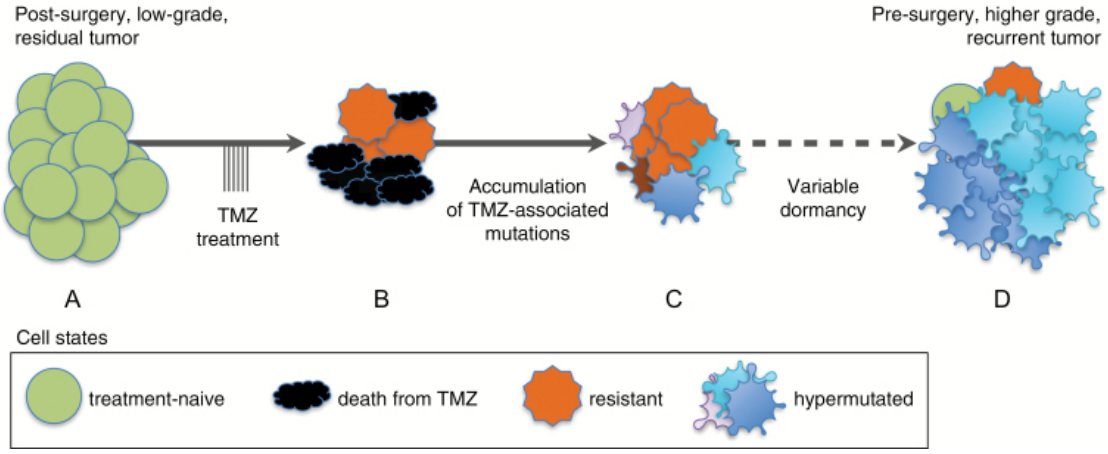

Figure 3. Model of TMZ-associated malignant transformation [5]. An initial low-grade glioma (A) is resected and residual disease is treated with TMZ, causing tumor cell death (B). If DNA repair capacity is low and TMZ-associated mutations occur within key amino acids of MMR genes, the loss of MMR function may render cells resistant to TMZ. Resistant cells can acquire high numbers of de novo TMZ-associated mutations, including thousands in coding regions, resulting in hypermutation (C). After widely varying periods of dormancy, clonal expansions of hypermutated cells drive formation of higher-grade tumor recurrences. Multiple unique hypermutated tumor clones may expand concurrently, as depicted by the different colored groups of hypermutated cells (D).

The central nervous system has long been considered a privileged immune organ due to the presence of the blood-brain barrier. However, immunotherapy is a new approach to treating patients with glioma and has shown promising results in several clinical trials, especially in adult populations. Immunization, with or without dendritic cells, blocking immune checkpoints, over when T-cell transfer is the most studied mode of immunotherapy for diffuse glioma. The most likely future is a combination therapy combining conventional treatment (surgery, radiotherapy) and immunotherapy [27].

7. Conclusion

At present, high-grade glioma is still incurable due to high morbidity and mortality. TMZ adds methyl groups to the DNA, causing cell damage and ultimately apoptosis. However, over 50% of GBM patients became resistant to TMZ due to the MGMT DNA repair system, which transfers methyl groups from guanine to repair damaged DNA and counteract the cytotoxic effects of TMZ tumor cells. In addition, even patients with initial responses to TMZ cannot be treated because resistance is acquired. It has been shown that glioma sensitization or resistance to TMZ may be influenced by other drugs, peptides, compounds, and siRNA associated with multiple proteins, signaling pathways, and gene expression. Inhibition of specific proteins and suppression of expression of certain genes may lead to enhanced sensitivity of gliomas to TMZ. Circa-based therapies are promising, and studies have shown a potential of using circulating RNA and TMZ binding as a potential prognostic/diagnostic marker and a possible target for glioma therapy.

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