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REVIEW ARTICLE

Temozolomide resistance in glioblastoma multiforme

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Abstract Temozolomide (TMZ) is an oral alkylating agent used to treat glioblastoma multiforme (GBM) and astrocytomas. However, at least 50% of TMZ treated patients do not respond to TMZ. This is due primarily to the over-expression of O^6-methylguanine methyltransferase (MGMT) and/or lack of a DNA repair pathway in GBM cells. Multiple GBM cell lines are known to contain TMZ resistant cells and several acquired TMZ resistant GBM cell lines have been developed for use in experiments designed to define the mechanism of TMZ resistance and the testing of potential therapeutics. However, the characteristics of intrinsic and adaptive TMZ resistant GBM cells have not been systemically compared. This article reviews the characteristics and mechanisms of TMZ resistance in natural and adapted TMZ resistant GBM cell lines. It also summarizes potential treatment options for TMZ resistant GBMs.

Abbreviations: AGT (also known as MGMT), O^6-methylguanine-DNA alkyltransferase; APE1, apurinic/apyrimidine endonuclease/redox factor-1; APNG, Alkylpurine-DNA-*N*-glycosylase; AP-1, activator protein 1; BBB, blood-brain-barrier; BCRP1, breast cancer resistance protein 1; BER, base excision repair; BG, benzylguanine; C8orf4, Chromosome 8 open reading frame 4; EGFR, epidermal growth factor receptor; ERK1/2, Extracellular Signal Regulated Kinases 1 and 2; FDA, Food and Drug Administration; GBM, glioblastoma multiforme or glioblastoma; HDAC, histone deacetylase; IFN-β, Interferon-β; JNK, Jun N-terminal kinase; KDM, Histone lysine demethylase; LC_{50}, 50% cell death concentration; LIF, Leukemia inhibitory factor; MGMT, O^6-methylguanine methyltransferase; MSH6, mutS homolog 6; NHA, normal human astrocytes; MMR, DNA mismatch repair; MTIC, 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide; mTOR, mammalian target of rapamycin; NAMPT, nicotinamide phosphoribosyl transferase; NF-κB, nuclear factor-Kappa B; PARP, poly ADP ribose polymerase; SAHA, N-hydroxy-N′-phenyl-octanediamide; STAT3, Signal Transducer and Activator of Transcription 3; TMZ, Temozolomide; TNFAIP3, Tumor necrosis factor-α-induced protein 3; VPA, Valproic acid.

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What is Temozolomide?

Temozolomide (TMZ) is an imidazotetrazine derivative of the alkylating agent dacarbazine and a prodrug of the anti-cancer drug Temodar.[1] The chemical name of TMZ is 3-methyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide (Fig. 1). TMZ is stable at a pH less than 5 but at a pH greater than 7 it is rapidly hydrolyzed to 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC).[2] The lipophilic nature of TMZ permits it to penetrate the blood-brain-barrier (BBB) allowing it to be administered orally.

Use of Temozolomide (sold as Temodar) to treat brain tumors

TMZ is active against human cancers such as melanomas and astrocytomas.[3–6] It was approved by the US Food and Drug Administration (FDA) for use in the treatment of refractory anaplastic astrocytoma in adults in 1999 and newly diagnosed adult glioblastoma (GBM) patients in 2005. The antitumor effect of TMZ is schedule-dependent with multiple administrations being more effective than a single treatment. In a Phase I clinical trial, the recommended dose of TMZ was 750—1000 mg/m^2 given orally for 5 days per week for 4 weeks.[7] Temodar capsules containing 5—250 mg of TMZ are available for its oral administration to patients and in vials containing 100 mg for those being given TMZ intravenously.

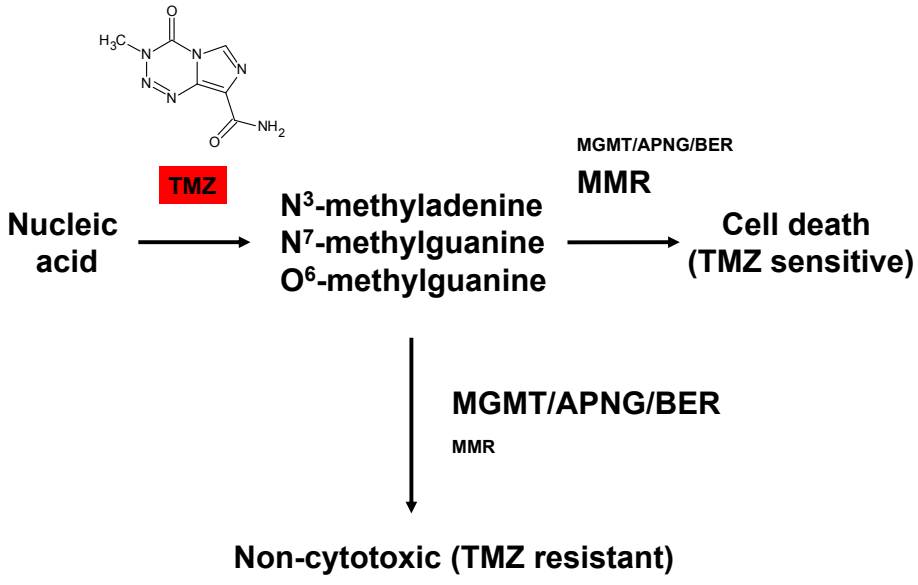
Concomitant therapy using both Temodar and radiation improved overall survival of newly diagnosed adult GBM patients relative to those treated with radiation alone (12.1 → 14.6 months median survival).[8] Newly diagnosed GBM patients tend to be given 75 mg/m^2/day of Temodar for 6 weeks concomitantly with focal radiotherapy (60 Gy) followed by 6 cycles of in which they are given 150 mg/m^2 once daily for 5 days in a row followed by 23 days of no treatment prior to the next cycle. Patients given Temodar iv are injected over a 90 min time period with the same amount that is administered orally.

Mechanism of action of Temozolomide

TMZ is a DNA alkylating agent known to induce cell cycle arrest at G2/M and to eventually lead to apoptosis.[9] At physiologic pH it is converted to the short-lived active compound, MTIC. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) and to methylhydrazine. The cytotoxicity of TMZ is mediated by its addition of methyl groups at N^7 and O^6 sites on guanines and the O^3 site on adenines in genomic DNA (Fig. 1). Alkylation of the O^6 site on guanine leads to the insertion of a thymine instead of a cytosine opposite the methylguanine during subsequent DNA replication, and this can result in cell death.

Temozolomide resistance in natural TMZ resistant GBM cell lines

To identify TMZ resistant GBM cell lines, we conducted literature searches in PubMed/MEDLINE using the terms Temozolomide/TMZ resistant glioblastoma/GBM and acquired Temozolomide/TMZ resistant glioblastoma/GBM.



Alkylpurine-DNA-*N*-glycosylase (APNG), Base excision repair (BER), DNA mismatch repair (MMR), O^6-methylguanine-DNA methyltransferase (MGMT)

Fig. 1 Mechanism of Temozolomide and Temozolomide resistance. Temozolomide (TMZ) modifies DNA or RNA at N^7 and O^6 sites on guanine and the N^3 on adenine by the addition of methyl groups. The methylated sites can remain mutated, be fixed by DNA mismatch repair (MMR), be removed by base excision repair (BER) by the action of a DNA glycosylase such as, alkylpurine-DNA-N-glycosylase (APNG), or deakylated by the action of a demethylating enzyme such as O^6-methylguanine methyltransferase (MGMT). Cells are TMZ sensitive when MMR is expressed and active. When MGMT, APNG, and BER proteins are expressed, GBM cells are resistant to TMZ.