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Review

The role of temozolomide in the treatment of aggressive pituitary tumors

James K. Liu [a,b,c,*], Jimmy Patel [b], Jean Anderson Eloy [a,b,c]

[a] Center for Skull Base and Pituitary Surgery, Neurological Institute of New Jersey, Department of Neurological Surgery, Rutgers University, New Jersey Medical School, Suite 8100, 90 Bergen Street, Newark, NJ 07103, USA
[b] Department of Neurological Surgery, Rutgers University, New Jersey Medical School, Newark, NJ, USA
[c] Department of Otolaryngology-Head and Neck Surgery, Rutgers University, New Jersey Medical School, Newark, NJ, USA

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ABSTRACT

Pituitary tumors are amongst the most common intracranial neoplasms and are generally benign. However, some pituitary tumors exhibit clinically aggressive behavior that is characterized by tumor recurrence and continued progression despite repeated treatments with conventional surgical, radiation and medical therapies. More recently, temozolomide, a second generation oral alkylating agent, has shown therapeutic promise for aggressive pituitary adenomas and carcinomas with favorable clinical and radiographic responses. Temozolomide causes DNA damage by methylation of the O^6 position of guanine, which results in potent cytotoxic DNA adducts and consequently, tumor cell apoptosis. The degree of MGMT expression appears to be inversely related to therapeutic responsiveness to temozolomide with a significant number of temozolomide-sensitive pituitary tumors exhibiting low MGMT expression. The presence of high MGMT expression appears to mitigate the effectiveness of temozolomide and this has been used as a marker in several studies to predict the efficacy of temozolomide. Recent evidence also suggests that mutations in mismatch repair proteins such as MSH6 could render pituitary tumors resistant to temozolomide. In this article, the authors review the development of temozolomide, its biochemistry and interaction with O^6-methylguanine-DNA methyltransferase (MGMT), its role in adjuvant treatment of aggressive pituitary neoplasms, and future works that could influence the efficacy of temozolomide therapy.

1. Introduction

Pituitary adenomas are the second most common intracranial neoplasms behind gliomas, representing about 10–15% of all intracranial tumors [1]. Although the majority of pituitary tumors are benign, a subset of these tumors can exhibit more aggressive clinical behavior with high rates of recurrences and resistance to conventional treatments [1–6]. These aggressive pituitary adenomas can sometimes be characterized by markers of high cell proliferation such as a Ki-67 index ⩾3%, mitotic activity >2 per 10 high power field, and p53 expression on immunohistochemistry [1,6]. In general, aggressive adenomas can exhibit invasiveness (invasion into cavernous sinus, dura, bone), large tumor size (macro or giant adenomas) and high rates of recurrence. Pituitary carcinomas, characterized by craniospinal dissemination or systemic metastases are very rare and represent only 0.2% of all pituitary tumors [6,7]. Surgical treatment via transsphenoidal resection with adjuvant radiation therapy, pharmacological therapy or a combination of both may be needed for overall tumor control. Despite this, aggressive pituitary adenomas and carcinomas can be difficult to manage due to high rates of recurrence after incomplete removal, as well as the locally invasive and rapidly growing nature of these tumors.

More recently, the use of temozolomide appears to have potential benefits in the treatment of aggressive pituitary adenomas and carcinomas with favorable results [2,4,8–13]. Temozolomide has been used successfully in aggressive prolactinomas, adrenocorticotrophic hormone (ACTH) producing tumors, Nelson's syndrome and nonfunctional adenomas that exhibit continued growth despite surgery, radiotherapy and medical therapy. As a second generation alkylating agent, temozolomide exerts its antitumor cytotoxic effects by methylating DNA at the O^6 position of guanine resulting in mispairing with thymine during the next cycle of DNA replication which then leads to apoptosis. In this paper, the authors

* Corresponding author. Tel.: +1 973 972 2906.
E-mail address: james.liu.md@rutgers.edu (J.K. Liu).

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review the role of temozolomide in the treatment of aggressive pituitary tumors and discuss the indications, mechanisms of action and review the published results in the literature.

2. Temozolomide and mechanisms of action

Temozolomide (International Union of Pure and Applied Chemistry name 3-methyl-4-oxoimidazo [5,1-d][1,2,3,5]tetrazine-8-carboxamide) is an analogue of the antineoplastic drug mitozolomide (Fig. 1) and was introduced as an alternative to dacarbazine (DTIC; Bayer Healthcare, Leverkusen, Germany) [14]. Mitozolomide was an imidazotetrazine derivative that showed potent antitumor capabilities in preclinical studies, including murine models and human tumor xenografts, but did not make it past Phase II trials due to toxicity concerns [15–17]. Structurally the difference between temozolomide and mitozolomide is the substitution of the chloroethyl group of mitozolomide with a methyl group. The synthesis of temozolomide was first presented by Stevens et al. in 1987 in an attempt to elucidate structure activity relationships of mitozolomide [14,18]. Additionally, it was observed that temozolomide showed antitumor activity against the TLX5 lymphoma cell line transplanted into CBA/CA mice, a tumor to which mitozolomide showed very potent antitumor capabilities [14,16].

Temozolomide is orally administered and readily crosses the blood–brain barrier. Under physiological conditions, temozolomide is rapidly hydrolyzed and converted into 5-(3-methyltriazeno) imidazole-4-carboxamide (MTIC), the active agent [19]. MTIC is subsequently hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which, when bound as a ribonucleotide, is an intermediate in the generation of inosine monophosphate and hence an intermediate compound of purine biosynthesis. AIC is additionally converted to a methyldiazonium cation which is capable of alkylating DNA, again at the O^6 and N^7 positions on guanine and N^3 position on adenine [20,21]. Alkylation at the O^6 position of guanine leads to mispairing with thymine and continual mispairing leads to double stranded breaks and apoptosis of the affected cell.

Temozolomide was initially administered intravenously at doses ranging from 50–200 mg/m^2 [22]. Currently temozolomide is given by oral administration after which the drug is rapidly absorbed [23]. The current standard of treatment is 150–200 mg/m^2 for 5 days in a 28 day cycle. Temozolomide demonstrates linear pharmacokinetics with increasing dose in the therapeutic range and a half life of 1.8 h [20,22,23]. It is found in the cerebrospinal fluid and readily crosses the blood–brain barrier, however, concentrations in the cerebrospinal fluid are not indicative of drug delivery to tumors and this interaction is currently not known [20]. Because temozolomide is not cell cycle specific and can therefore exhibit its effects in all phases of tumor cell growth, it is an ideal drug for treating slower growing neoplasms such as pituitary tumors [11,13].

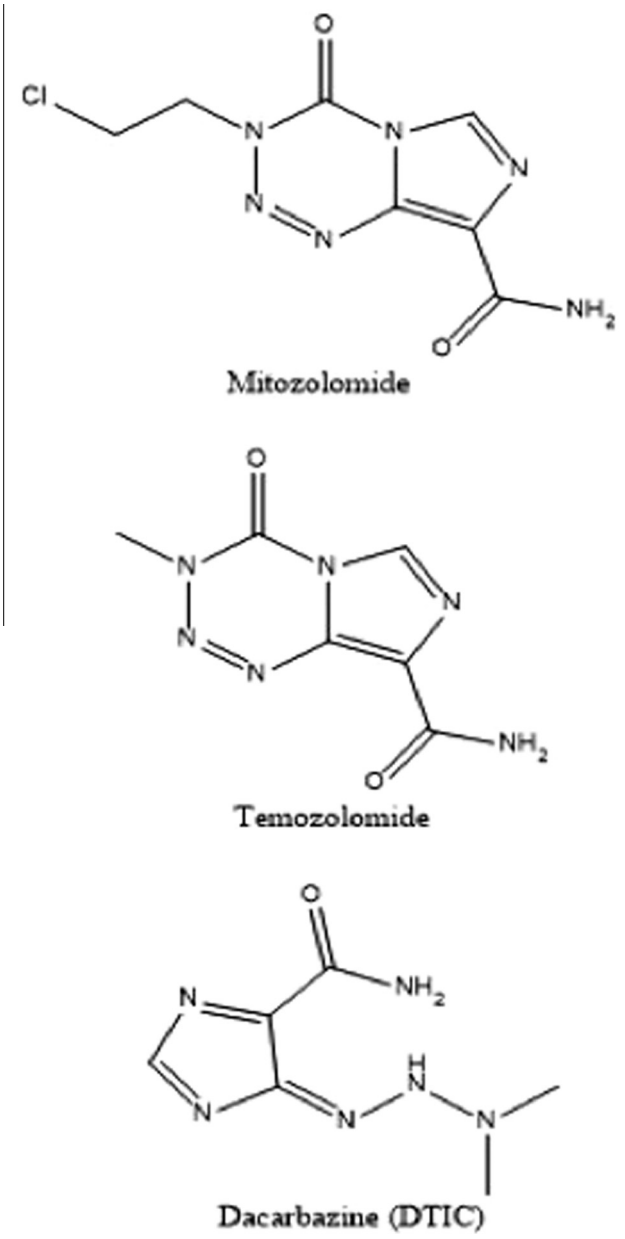

Fig. 1. Temozolomide (International Union of Pure and Applied Chemistry name 3-methyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide) is an analogue of the antineoplastic drug mitozolomide and was introduced as an alternative to dacarbazine (DTIC; Bayer Healthcare, Leverkusen, Germany). Structurally, the difference between temozolomide and mitozolomide is the substitution of the chloroethyl group of mitozolomide with a methyl group.

3. MGMT expression and implications for temozolomide sensitivity

The DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) is a human protein encoded by chromosome 10q26 that is crucial for the stability of DNA. MGMT repairs the methylated DNA adducts induced by temozolomide, thus, counteracting its antineoplastic effects by reversing the alkylation at the O^6 position of guanine and transferring the alkyl group to the cysteine-145 residue in its active site. Hence, high tumor expression of MGMT can cause resistance to alkylating agents such as temozolomide [20,21,24–26]. Kovacs et al. [27] and McCormack et al. [28] reported the inverse relationship between MGMT expression and temozolomide response in aggressive pituitary adenomas and carcinomas. Both studies demonstrated low MGMT expression in tumors that responded to temozolomide and high MGMT expression in temozolomide resistant tumors. Therefore, assessment of MGMT expression can be useful for predicting the efficacy and therapeutic responsiveness of temozolomide treatment in aggressive pituitary adenomas and carcinomas [12,13,29]. This relationship has also been observed in temozolomide treatment of high grade gliomas [20,30,31].

Furthermore, it has been shown that the MGMT promoter could be methylated and the relationship between MGMT promoter methylation and temozolomide sensitivity has been studied [32–36]. In 2010, van Nifterik et al. presented a comprehensive study of the relationship of MGMT, MGMT promoter, and temozolomide