Derleme / Review

The role of temozolomide in the treatment of aggressive pituitary adenomas and pituitary carcinomas

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ABSTRACT:

The role of temozolomide in the treatment of aggressive pituitary adenomas and pituitary carcinomas

Except for aggressive prolactinomas, which are could be treated with dopamin agonists, surgery is the first-line treatment option for most aggressive pituitary adenomas, but usually, due to their size, invasion of surrounding tissues, and high frequency of regrowth, they are difficult to treat with standard treatment paradigms, including surgery and radiotherapy. Pituitary carcinomas are rare tumours, and are defined by aggressive adenomas with brain and/or systemic metastasis. These carcinomas are highly aggressive, resistant to surgery, radiotherapy and systemic chemotherapy, and are associated with poor survival. Recently, temozolomide, an alkylating imidazoltetrazine derivative, chemically related to dacarbazine, have been used successfully in the management of aggressive pituitary adenomas and pituitary carcinomas, resistant to conventional treatments. O-6 methylguanine DNA methyltransferase, a DNA repair enzyme, have been demonstrated to be associated with sensitivity to temozolomide. Temozolomide is considered to be a novel drug in the treatment of aggressive pituitary adenomas and pituitary carcinomas, with few side effects, however it may cause serious side effects and proper follow-up of patients is essential.

Key words: Aggressive pituitary adenoma, pituitary carcinoma, temozolomide, MGMT

ÖZET:

Agresif hipofiz adenomları ve hipofiz karsinomların tedavisinde Temozolomide'in rolü

Dopamin agonistleriyle tedavi edilebilen agresif prolaktinomalar dışındaki agresif hipofiz adenomlarında ilk tedavi seçeneği cerrahidir. Fakat sıklıkla bu tümörlerin çaplarının büyük olması, çevre dokulara invazyon yapması ve nüks oranlarının yüksek olması nedeniyle cerrahi ve radyoterapi gibi standart tedaviler yetersiz kalmaktadır. Hipofiz karsinomları ise nadir görülen tümörler olup agresif hipofiz adenomlarının kraniyospinal veya sistemik metastaz yapmaları şeklinde tanımlanır. Bu karsinomlar oldukça invaziv olup cerrahi, radyoterapi ve kemoterapiye dirençlidirler ve prognozları kötüdür. Son zamanlarda, kimyasal olarak dakarbazin ile ilişkili, imidazoltetrazin derivesi alkilleyici bir ajan olan temozolomid agresif hipofiz adenomları ve hipofiz karsinomlarının tedavisinde başarıyla kullanılmıştır. O-6 metilguanin DNA metiltransferaz bir DNA tamir enzimi olup temozolomid tedavisine yanıtta rolü olduğu gösterilmiştir. Temezolomid tedavisinin genellikle hafif derecede yan etkileri olmakla birlikte bazen ciddi yan etkilere neden olabileceğinden yakın takip gerekmektedir. Temozolomid, konvansiyonel tedavilere yanıtsız ve O-6 metilguanin DNA metiltransferaz düzeyi düşük olan agresif hipofiz adenom ve hipofiz karsinomlarında alternatif bir tedavi ajanı olarak düşünülebilir.

Anahtar kelimeler: Aggressive hipofiz adenomu, hipofiz karsinomu, temozolomide, MGMT

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INTRODUCTION

Pituitary adenomas are benign tumours usually with slow growth, comprising 10-15% of all primary brain tumours (1). Approximately 10-20% of normal population may have such tumours according to autopsy series and pituitary magnetic resonance imaging (MRI), most of them are clinically insignificant and smaller than 5mm in diameter (2). A recent population based cross sectional study performed in Belgium showed a prevalence of 94/100,000 cases and non-functional anterior pituitary adenomas constitute approximately one third of them (3). The majority of pituitary tumors are noninvasive benign

tumors and remain within the sellar region, but their behaviour vary considerably and ranges from slow intrasellar enlargement through marked invasion. Patients with pituitary adenomas can be treated by surgery, radiotherapy and certain drugs, but except for invasive prolactinomas which could be treated with dopamin agonists (DA), aggressive adenomas frequently demonstrate regrowth and repeated treatment modalities are needed to be applied (4). Pituitary carcinomas are extremely rare, generally arise from corticotroph adenomas or prolactinomas and do not respond well to radiotherapy and systemic chemotherapy, and are associated with poor survival (5). Consequently, most patients die within 1 year of the diagnosis (5). When conventional treatment modalities fail to control tumor progression in invasive pituitary adenomas and pituitary carcinomas, experimental treatments may need to be considered. Temozolomide (TMZ) is an alkylating agent and deplets O-6 methylguanine DNA methyltransferase (MGMT), a DNA repair enzyme and possesses an antitumour effect against different forms of tumours (35). TMZ have been reported to be effective against various forms of pituitary adenomas and pituitary carcinomas resistant to standard therapies (6-13).

Aggressive Adenomas

Altough there is no consensus on the definition of aggressive pituitary adenoma, they are defined as adenomas with massive invasion of surrounding structures, rapid growth and giant size. They are generally recurring after treatment and are unresponsive to therrapy. 45-55% of all pituitary tumors can become invasive and infiltrate surrounding structures including dura mater, bone, skull base, cavernous sinus and optic chiasma, this invasiveness is not indicative of malignancy, but may put the patient at higher risk for carcinoma (14).

The estimation of the Ki-67 antigen using MIB-1 antibody correlates best with invasiveness and prognosis (15,16). The majority of aggresive adenomas have Ki-67 labeling index (LI) less than 10%, and a Ki-67 LI of less than 3% demonstrates 97% specificity in differentiating aggressive from nonaggressive pituitary adenomas, whereas a Ki-67 LI higher than 10% should raise the suspicion of malignant potential of the pituitary adenoma (16). The immunuhistochemical positiveness for p53 is also an indicative of prognosis and predictive of malignant potential, and the combination of p53 with Ki-67 LI is superior than Ki-67 LI and p53 alone in prediction of malignant potential (14).

The most clinically useful classification of invasiveness is demonstrating sphenoid and cavernous sinus invasion by MRI based on Hardy's classification. According to this classification aggresive adenomas are divided into five types: A) tumor bulging into the chiasmatic cistern; B) tumor reaching the anterior third ventricle; C) huge suprasellar extension filling the entire third ventricle; D) parasellar extension into the temporal, frontal, or posterior fossa; and E) lateral expansion toward the cavernous sinuses (17).

Exept for aggressive prolactinomas in which DA therapy is the first-line treatment choice, transsphenoidal surgery is the first-line treatment option for aggressive tumors, but most of these aggressive tumors reccure after surgery and repeat surgery is needed to achieve control.

DA therapy results in a rapid normalization of serum prolactin concentration and a reduction in tumour size in 70-90% of patients, but resistance to DA's can occur and alternative therapies, such as higher doses of DA, surgery and radiation therapy may be required (18). Even sometimes this therapy methods fail to control gowth, the treatment of such problematic cases are a matter of troublesome for both endocrinologists and neurosegeons and there is no effective treatment options in this situation.

Surgery is also the treatment of choice for patients who harbor corticotroph adenomas, but when surgery fails to achieve control, and as there is no proven effective medical therapy, surgery with radiotherapy is first-line treatment modality up-to-date. Crooke's cell adenoma is another histologic variant of corticotroph adenoma, which is characterized by Crooke's hyaline degeneration in most corticotroph adenoma cells. They are a rare subtype of Cushing's disease with an estimated prevalence of 4.4-14% in all corticotroph adenomas (13). According to studies, 81% of Crooke's cell

adenomas are macroadenomas and 72% of them are highly invasive, resistant to surgery and radiotherapy with high-recurrence rates (13). Corticotroph carcinomas developed in preexisting Crooke's cell adenomas are have been reported (13).

Nelson Syndrome defined as pituitary macroadenoma with elevated plasma ACTH levels occurring in a patient as a possible late complication of bilateral adrenalectomy. It is a life-threatening condition with high morbidity, resulting from local invasion of surrounding tissues, and from excessive secretion of ACTH that causes abnormal skin pigmentation (19). Morbidity and mortality remain high, despite the multimodality treatments including surgery, conventional radiotherapy, focused irradiation and certain medical therapies. Corticotroph carcinomas devloped in preexisting Nelson's adenoma have also been reported (20).

Somatotroph adenomas are usually treated with transsphenoidal surgery which could reduce growth hormone levels in about 85% of microadenomas and in less than 60% of macroadenomas. Somatotroph adenomas respond to somatostatin analogues (SSA) in about 70% of cases and to DA just in about 15%, depending on the profile of hormone production (21). Pegvisomant efficiently decrease insulin-like growth factor-1 (IGF-1) level but tumour shrinkage is not achieved during therapy.

Nonfunctioning pituitary adenomas (NFPA) are frequently of large size at the time of diagnosis. They frequently invade perisellar structures and cause pressure symptoms. The silent corticotroph adenoma subtype 1, 2 and the silent adenoma subtype 3 have more aggressive clinical course with higher reccurence rates than other NFPA subtypes (4). Regrowth of NFPA has been reported in 38-95% of cases and despite of the multimodality treatments, they can progress in some cases, causing theraputic challenges (4).

Pituitary Carcinomas

Pituitary carcinomas are very rare tumours with an estimated incidence of around 2% of all symptomatic pituitary adenomas (5,14). They are defined as pituitary tumors with craniospinal and/or systemic metastasis and to date, approximately 140 cases have been published in English literature (14,15). These carcinomas generally arise from the transformation of initially benign pituitary macroadenomas, most of them are hormonally active and the most common pituitary carcinomas are ACTH- and prolactin-producing carcinomas, followed by GH-secreting carcinomas (15). They have an equal frequency in both sexes and are being diagnosed after a latent period of around 7 years following the diagnosis of an aggressive pituitary adenoma (15). Generally the initial clinical, biochemical and histological features are of minimal usefullness in differentiating benign adenomas from malignant carcinomas (15). Histologically nuclear pleomorphism, mitosis, hemorrhagia and necrosis are not indicative of malignancy (5,22). Pituitary carcinomas are highly resistant to all therapeutic approaches and most of the patients die within the subsequent one year after the diagnosis is made (5). Metastases can occur in every part of the brain, and distant metastases have been reported in liver, lymph nodes, bone and lung (15). It is important to exclude metastatic carcinoma, because it may mimic pituitary adenoma and particular confusion would be encountered when a carcinoma shows neuroendocrine features.

Owing to highly invasive and infiltrative nature of these carcinomas, surgical treatment is rarely curative, recurrences always occurs and repeated different surgical approaches may be nescesary to achieve local control (5). Radiation therapy is effective for achievement of local control, but its effect is temporary, it just provids palliative treatment and there is no study to support that radiation therapy would improve prognosis (5).

Partial and short-lasting responses to chemotheraputic agents such as cyclophosphamide/ adriamycin/ 5-flurouracil, lomustin/procarbazine/ etoposide combinations have been reported, but most pituitary carcinomas respond poorly to these chemotherapeutic combinations (23).

Temozolomide

Recently, temozolomide (TMZ), an alkylating agent, has been used successfully in the treatment of

Table 1: Cases of temozolomide treted aggressive pituitary adenomas and pituitary carcinomas in the literature

Author, Year of Publication	Ref. No.	Tumour type	MGMT expression	p53	Ki 67 LI	metastasis	Primary therapy	TMZ** (dose)	TMZ duration(mo)	response
Fadul 2006	6	NF(Ca)	ND	ND	<%1	spinal,bone	TSS,TCS,RT,	200mg/m^2 RS	12	Yes
Fadul 2006	6	PRL(Ca)	ND	ND	%10	bone	DA,TSS,TCS RS,CT	200mg/m^2	10	Partial
Syro 2006	12	PRL(Ad)	ND	ND	ND	-	TCS,RT,TSS DA	200mg/m^2	7	Yes
Lim 2006	9	PRL(Ca)	ND	ND	-	Craniospinal	TSS,DA,TCS?	200mg/m^2	18	Yes
Kovacs 2007	8	PRL(Ad)	Negative	+	%40-%60	-	DA,TSS,TCS? RT,	200mg/m^2	7	Yes
Neff 2007	10	PRL(Ad)	ND	-	<%5	-	DA,TSS,RT, RS, SERM,SSRA	150mg/m^2	26	Yes
Kovacs 2008	††	NFA (Silent Subtype II)	Positive	ND	ND	ND	ND	ND	ND	No
Debono	††	PRL(MEN 1)	ND	ND	ND	-	DA,TSS,RT RS,CT	ND	7	Yes
Thearle 2009	††	ACTH(Ca*)	ND	ND	%31	bone	TSS,RS,SSRA DA	200mg/m^{2†}	4	No
Hagen 2009	7	PRL+GH(Ca)	Negative	ND	%5	LN	DA,TSS,RT SSRA,RT	150-200mg/m^2	23	Yes
Hagen 2009	7	PRL(Ad)	Negative	ND	%2	-	TSS,DA,SSRA	150- 200mg/m^2	12	Yes
Hagen 2009	7	NFA	very low	ND	%2	-	TSS,TCS,RT SSRA,DA	150- 200mg/m^2	15‡	Yes
Takeshita 2009	13	ACTH(Ca)	low	very low	%3	Liver	TSS,RS,DA Pioglitazone, SSRA	150-190mg/m^2	24‡	Yes
Byrne 2009	36	PRL(Ca)	ND	ND	ND	Craniospinal	DA,TSS,RT TCS	200mg/m^2	12‡	Yes
Syro 2009	11	NFA (Oncocytic adenoma LH+)	+/-	ND	%2-%6	-	TSS, RT	200mg/m^2	5	Yes

TMZ: temozolomide, *: TMZ has been used in combination with Capecitabin, **: TMZ is used in mg/m^2/day for 5 consecutive days, every 4 weeks,
††: unpublished data, ‡: the treatment with TMZ has been continued during publication, ND: no data available, DA: dopamin agonists, SSRA: Somatostatin receptore agonist, SERM: Selective estrogen receptor modulator, TSS: transsphenoidal surgery, TCS: transcranial surgery, RT: radiotherapy, RS: radiosurgery, CT: chemotherapy, Ad: adenoma, Ca: carcinoma, PRL: prolactin, NF: non functional, ACTH: adrenocorticotrophic hormone, LH: lutinizing hormone, GH: grwth hormone, Ref: Reference

resistant and recurrent agrressive pituitary adenomas and piyuitary carcinomas (Table 1). At present, TMZ is used just in cases of pituitary adenomas and pituitary carcinomas refractory to conventional treatment. TMZ has been approved by the US Food and Drug administration (FDA) for the treatment of refractory anaplastic astrocytomas (24). TMZ is an orally available drug that is converted phisyologically to 5-(3-methyltriazen-1-yl) imidazole-4-carboximide, has a cytotoxic effect by methylation of guanine base at the O-6 position in DNA and inhibites DNA replication (24). The advantage of TMZ, as other alkilating agents, is that it is not cell-cycle specific, it can inhibit all stages of tumor cell growth and thus, it is suitable for slow-growing tumors (9). O-6 methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme and removes the alkyl group adducts from the O -6 position of DNA and induces

resistance to TMZ (25). Immunohistochemical studies demonstrated that gliomas with low MGMT expression respond to TMZ, whereas gliomas with high levels are generally resistant to TMZ effect (25). Epigenetic silencing of the MGMT gene by methylation of the MGMT promoter turned out to be the strongest predictive marker of a favorable outcome in patients with glioblastomas treated with TMZ (26). For routine clinical use, MGMT immunohistochemistry is available in most laboratories, easy to perform, and is not expensive.

In 2006, Fadul et al. described the first 2 cases of progressive pituitary carcinomas, which reccured after all treatment approaches and were treated succecfully with TMZ with persistant clinical response (6). After the initial success, TMZ treatment has been administered to many cases of aggreseive pituitary adenomas and pituitary carcinomas (Table 1).

Kovacs et al. treated a patient with TMZ who had an invasive large prolactinoma, which had recurred dispite several surgical approaches and was resistant to DA and radiation therapy. In spite of significant clinical improvment and marked decrese in prolactin level and tumor burden, they also observed a significant morphological changes in tumour cells exposed to TMZ. Necrosis, hemorrhagic foci, deposition of collagen tissue, focal inflamatory infiltrats and neuronal transformation have been seen. Mitotic activity and Ki-67 LI were also markedly decreased (8). With the same purpouse, they treated another patient who had an aggressive silent subtype II corticotroph pituitary tumour. Neither tumor shrinkage or morphological changes, nor clinical improvement observed in the patient. Immunuhistochemical staining showed lack of MGMT expression in TMZ responsive case and high expression in unresponsive case (27). Takeshita et al. reported a case of Crook's cell adenoma who had devloped persistent hypercortisolemia and liver metastasis, despite of the several transsphenoidal surgical approaches, radiosurgery and medical treatments including cabergolin, pioglitazon and octriotide. Further expansion observed after induction of Nelson's syndrome by adrenolytic effect of mitotane. After 6 cycles of treatment with TMZ, they observed clinical improvment, significant decrease in ACTH and cortisol levels, and marked shrinkage of the tumour with dissapearance of metastasis (13). They also demonstrated low MGMT expression in 5 out of 7 cases with invasive Crooke's cell adenoma compared to only 1 out of 17 ordinary type corticotroph adenomas. According to them, in cushing's disease, invasive macroadenomas including Crooke's cell adenomas, usually have low MGMT expression and they wold be candidates for tretment with TMZ, particularly when conventional treatments are ineffective (13). . Recently, Syro et al. reported a case of aggressive oncocytic NFPA, which had MGMT immunpositive and immunnegative cells in the same tumor and was treated with 5 cycles of TMZ. After treatment, MRI showed certain degree of response and tumor necrosis (11). Widhalm et al. studied MGMT expression in 24 regrowing NFPA and 21 surgically removed and tumour-free patients, based on postoperative MRI. They exhibited low MGMT expression in 50% of progressive regrowing NFPA compared to 24% of tumour-free group (4). Zuhur et al. studied MGMT immunoexpression in growth hormone secreting pituitary adenomas and found low levels of MGMT expression in more than 90% of cases (28). These studies suggest that TMZ could be an alternative treatment approach in aggressive and treatment resistant cases of NFPA and growth hormone secreting pituitary adenomas.

TMZ is used in standard dosing schedule (150-200mg/m2 for 5 days, every 4 weeks) and in extended dosing regimens in different cases of central nervous system malignancies (24). The standard dosing schedule has also been used in cases of aggressive pituitary adenomas and pituitary carcinomas (Table1). It is generally a well-tolerated agent and associated side effects could include rash, nausea, nasal suffusion, fatigue, marrow supression including leukopenia, thrombocytopenia and anemia (9,29). At present, serious side effects have not been reported in cases of aggressivev pituitary adenomas and pituitary carcinomas treated with TMZ, but it could cause serious side effects.

Su et al. studied the effect of TMZ in extended dosing schedule (75mg/m2/day for 6 weeks, every 8 weeks) on lymphocytes in metastatic malignant melanoma patients and found CD4+ lymphopenia in

60% of patients. They also observed 2 documented cases of Pneumocystis jiroveci and Aspargillus pneumonia as well as other 21 cases of infections indicative of T-cell dysfunction (24). Altough with this dosing schedule the patient is exposed to approximately 57% higher doses of TMZ than standard dosing schedule, CD4+ lymphocyte difficiency may be seen in standard dosing schedule and because lymphopenia is not always noted as toxicity in clinical studies, it is possible that the true incidence of lymphopenia is underreported.

Ganiere et al. reported a case of a patient who had glioblastoma multiforme (GBM) and was treated for a short period with extended dosing schedule of TMZ. The patient devloped fever, headache and cutaneous lesions during radiotherapy, and subsequent laboratory, cerebral MRI, brain and skin biyopsies revealed the simultaneous opportunistic infections with Pneumocystis jiroveci pneumonia, Listeria monocytogenes brain abscess and cutaneous Kaposi's sarcoma which are indicative of CD4+ lymphopenia (30). According to these studies, prophylaxis against Pneumocystis jiroveci is essential in patients treating with TMZ.

Ferreira et al. reported a case of GBM who was treated with low dose, followed by standard dosing schedule of TMZ. Soon after first cycle, the patient devloped fever and productive cough, and bronchoscopy with lavage revealed the presence of acid-fast bacteria (31). As the patient has taken glucocorticoid therapy at the same time which could lead to immunesupression, it is not known whether TMZ treatment put the patients at higher risk for tuberculosis infection or not.

Binello et al. treated a patient who had GBM with TMZ for 6 years, he has been reccurrence-free, but has devloped tonsillary carcinoma after 6 years of treatment (32). It is not clear that wether it is treatment-related or incidentally diagnosed, but drug-related malignancies should be taken into consideration after treating patients with TMZ, especially for long time. In vivo studies using murine bone marrow cells exhibited that mutational load increased by a factor of 22 with TMZ treatment, mostly point mutations (33). It causes the speculation that TMZ's mutagenic potential may rise the occurence of drug-related cancer, particularly after long term exposure.

Singhal et al. reported 2 cases of severe myelosupression in patints received low-dose TMZ for GBM (29). Su et al. reported a case of treatment-related myelodisplastic syndrome (MDS) after treatment with standard dosing schedule of temozolomide for reccurent high-grade glioma. The MDS has been diagnosed 8.4 months after begining TMZ and evolved into acute leukemia 1 month later, the patient died during induction chemotherapy (34). These cases highlight the importance of monitoring blood count in patients receiving TMZ.

Palmery et al. treated another patient diagnosed as astrocytoma with low dose, followed by standard dosing schedule of TMZ (35). Thirteen months after completing treatment he was fathered a healthy child, this is the unique case in the literature of a patient successfully fathering a baby following treatment with TMZ. With the promising activity seen with TMZ in aggressive pituitary adenomas and pituitary carcinomas, proper monitoring of the effect of this agent in male and famale fertility is very important and further studies are required to investigate the issue of fertility in patients treated with this agent.

CONCLUSION

To date, many cases of aggressive pituitary adenomas and pituitary carcinomas resistant to conventional treatments have been treated with TMZ and existing data emphasize the role of TMZ in aggressive pituitary adenomas and pituitary carcinomas refractory to current available treatment modalities. Although there is no any suggested optimal lenght of treatment and the response rates are different in every case, a significant decrease in hormone level, clinical improvment, marked tumour shrinkage and even in some pituitary carcinomas, dissapearance of metastasis are reported in patients treated with TMZ. According to reported cases, TMZ prolongs survival in this hopeless patient population. Whether TMZ should be administered in combination with conventional medical therapies should be studied further. By now it seems to be effective just in tumours with low MGMT expression, and should be

administered in tumors with low MGMT expression. TMZ is generally a well-tolerated drug with few tolarable side effects, but seldomely it may be associated with occurrence of serious opportunistic infections indicative of CD4+ lymphopenia and serious haematologic side effects. It is reasonable to start prophilaxis for Pneumocystis jiroveci in the begining of treatment with TMZ and the patients should be observed also for other opportunistic infections. The patients must also be observed properly with complet blood count during and long-term after discontinuation of treatment. Therefore, it must be administered in experienced centers familiar with this treatment. It is not clear wither treatment with TMZ put the patient at higher risk for tuberculosis or high-risk groups should be prophylactically treated for tuberculosis should also bee studied further in large patient population.

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