THEMATIC REVIEW

65 YEARS OF THE DOUBLE HELIX

Treatment of pituitary tumors with temozolomide: an update

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Abstract

Temozolomide is an alkylating chemotherapeutic agent used in malignant neuroendocrine neoplasia, melanoma, brain metastases and an essential component of adjuvant therapy in the treatment of glioblastoma multiforme and anaplastic astrocytoma. Since 2006, it has been used for the treatment of pituitary carcinomas and aggressive pituitary adenomas. Here, we discuss the current indications and results of temozolomide therapy in pituitary tumors, as well as frequently asked questions regarding temozolomide treatment, duration of therapy, dosage, tumor recurrence and resistance.

Key Words

- chemotherapy
- neoplasms
- neuroendocrine tumors
- pituitary
- temozolomide

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Introduction

Pituitary adenomas (PAs) arise in different adenohypophyseal cells and represent 15% of intracranial tumors (Melmed 2011, Osamura 2017a). The majority are slow-growing, noninvasive and benign neoplasms; however, several others are more rapidly growing and invade surrounding areas. Very rarely, PAs do metastasize, and these adenomas are called pituitary carcinomas. Mode of treatment of PAs includes drug therapy, surgery and, in some cases, irradiation. In prolactin (PRL)-producing PAs, dopamine agonists are effective and the preferred first line of treatment (Melmed *et al.* 2011). Long-acting somatostatin analogs are useful in growth hormone (GH)- and thyroid-stimulating hormone (TSH)-producing PAs.

No primary medical treatment is currently available for adrenocorticotrophic hormone (ACTH)-producing PAs and for nonfunctional PAs, so that surgery is the first option. In several cases the tumor is not completely resected, resulting in returning symptoms and the patient requiring further surgical intervention and additional treatment. Irradiation – conformal external beam radiation therapy or stereotactic radiosurgery – a third option, may not always be successful and could cause side effects. Two issues must be considered. The first is the mass effect; in this case surgery, or cabergoline in PRL-producing PAs, offer a chance to reduce quickly mass-related symptoms. The second is the hormonal secretion. Here, effective

drugs directed to the tumor function can be used (i.e., somatostatin analogs in acromegaly), or in case of severe symptoms of endocrine excess, medical treatment that does not impact the tumor can be chosen (i.e., pegvisomant in acromegaly or steroidogenesis inhibitors in Cushing's disease). Currently, the quest of many researchers, clinical endocrinologists and neurosurgeons is to find other options of treatment, especially in cases of large, invasive and recurrent tumors and pituitary carcinomas.

Temozolomide (TMZ) is an alkylating chemotherapeutic agent used as an essential component of adjuvant therapy in the treatment of glioblastoma multiforme (GBM) and anaplastic astrocytoma (Stupp *et al.* 2005, van den Bent *et al.* 2017). Since 2006, TMZ has been found to be an effective treatment of pituitary carcinomas (Fadul *et al.* 2006, Lim *et al.* 2006) and aggressive PAs (Syro *et al.* 2006). The present study discusses the current indications and results of TMZ therapy in PAs, examines the pathways involved in its action and attempts to answer frequently asked questions about TMZ treatment, duration of therapy, dosage, tumor recurrence and resistance (Bruno *et al.* 2015).

Aggressive adenomas and pituitary carcinomas

PAs are a heterogenous group of lesions with different clinical manifestations and a wide range of proliferative and invasive behaviors. Most PAs are controlled by current treatment protocols which, according to their functional activity, include surgery, radiotherapy and/or drug therapy. Some PAs invade bone, dura or adjacent structures, precluding their resection. They may also recur during follow-up despite repeated surgeries, radiotherapy, and pharmacologic treatments. From a pragmatic and clinical perspective, they have been called aggressive PAs and their exact prevalence is not known (Buchfelder 2009, Di Ieva *et al.* 2014, Raverot *et al.* 2018).

In an attempt to differentiate tumors with clinical aggressive behavior, the previous World Health Organization (WHO) classification (2004) of PAs, characterized a subtype of adenomas as 'atypical adenomas' if they presented an elevated mitotic index, a Ki-67 labeling index greater than 3%, and extensive nuclear staining for p53 immunoreactivity (Lloyd 2004). It was assumed that these atypical adenomas may have an uncertain clinical and biological behavior. This assumption has not been proven and, to date, it also has not been able to accurately predict tumor recurrence or resistance to therapy (Miermeister *et al.* 2015). In the recent WHO classification of PAs (2017)

(Osamura 2017b), the term 'atypical adenomas' is no longer recommended. To identify adenomas that may behave in a clinically aggressive manner, assessment of tumor proliferation markers and invasion – evaluated by MRI, surgical and/or morphological findings – is now suggested. This classification also recognizes some subtypes of PAs as 'high-risk' PAs due to their previously reported clinical aggressive behavior (Gomez-Hernandez *et al.* 2015, Lopes 2017, Osamura 2017a). These include sparsely granulated somatotroph adenomas, lactotroph adenomas in men, Crooke's cell adenomas, silent corticotroph adenomas and plurihormonal Pit-1-positive adenomas (formerly classified as silent subtype III adenomas) (Mete & Lopes 2017).

As in the previous classification, the current WHO classification (2017) characterizes pituitary carcinomas only when craniospinal or systemic metastases are found, independent of their histological appearance (Roncaroli 2017). Pituitary carcinomas are rare and account for approximately 0.12% of PAs in the German Pituitary Tumor Registry (Saeger *et al.* 2007). Its etiology is not clear and two possible mechanisms have been proposed: (i) step-wise transformation from an adenoma to an invasive adenoma and to a carcinoma, or alternatively, (ii) *de novo* development of carcinoma from either a normal gland or from a slow growing adenoma (Melmed 2011, Roncaroli 2017).

The term *adenoma* is applied to benign epithelial neoplasms that produce gland-like structures. It is considered *benign* because its macroscopic and microscopic features suggest that it will remain localized and amenable to be surgically resected. Conversely, the term *malignant* is applied to a neoplasm that can invade and destroy adjacent structures, and spread to distant sites. PAs are considered *benign* tumors, even if some of them behave in a clinically aggressive manner, whereas pituitary carcinoma – *malignant* – is only applied when metastases are found. In this context, the so-called aggressive adenomas would be a group of *benign* lesions with *malignant* potential. Different designations have been used to describe them: premetastatic lesions in the sellar phase (Scheithauer *et al.* 2006), carcinoma *in situ* (Heaney 2011), localized pituitary carcinomas (Syro 2015), and invasive/proliferative tumors with high risk of recurrence and suspect of malignancy (Trouillas *et al.* 2013).

The terms *atypical*, *invasive* and *aggressive* have been used synonymously when evaluating PAs. This has led to different interpretations and it has become clear that standardized definitions are required. PAs can then be classified according to their pathologic features, radiological findings or clinical behavior such as typical or

atypical, invasive or noninvasive, and aggressive or non-aggressive. Thus, the terms *typical* and *atypical* adenoma should refer only to pathologic features, *invasive* and *noninvasive* to radiological, surgical and/or morphological findings of invasion, and, *aggressive* and *non-aggressive* to their clinical behavior (Sav *et al.* 2015). The classification of pituitary tumors must include not only morphologic characteristics, but also radiologic and clinical features. The focus must be on early diagnosis and treatment of these aggressive adenomas (Ceccato *et al.* 2018).

Temozolomide

TMZ was synthesized in 1987 (Stevens *et al.* 1987). It is a pro-drug that, after administration, is pharmacologically inactive until it is hydrolyzed within the body. It has important features such as low molecular weight, hydrophobicity and the ability to undergo rapid conversion to its active form, methyl-triazeno-imidazole-carboxamide (MTIC), after it is absorbed (Neidle & Thurston 2005). Its cytotoxic effect is exerted through methylation of deoxyribonucleic acid (DNA) at the O⁶ position of guanine, which mispairs with thymine during the next cycle of DNA replication. If it is not repaired, the sequence of mismatch-repair events leads to apoptosis (Sabharwal & Middleton 2006).

The action of TMZ depends on its accumulation in the tumor and the capacity for O⁶-methylguanine-DNA methyltransferase (MGMT), present in the cells, to repair its effects (Kaina *et al.* 2007, Sharma *et al.* 2009). MGMT is an enzyme that removes the methylated base, transferring the methyl group, from the methylated DNA to an internal cysteine residue thereby restoring guanine. It can only catalyze a single turnover, and for this reason, it is called a 'suicide enzyme' (Kaina *et al.* 2007). MGMT is therefore an important DNA repair system, which influences the mechanism of action of TMZ. Common, non-hematologic adverse effects, mild to moderate in severity, can occur in more than 30% of the patients taking TMZ. These include nausea, vomiting, fatigue, headache and constipation. Not every patient experiences all the side effects, they are reversible and will go away after treatment is complete. The hematologic toxicities of TMZ are managed with dose reduction or temporary suspension. Severe, TMZ-related myelodysplastic syndrome and aplastic anemia have been reported in GBM cases, but to date, not in pituitary tumor patients (Scaringi *et al.* 2013).

To our knowledge, approximately 160 cases of PAs and pituitary carcinomas have been treated with TMZ. Recent publications describing case reports, retrospective patient

studies, clinical practice guidelines, and an international survey also review the effect of TMZ treatment on pituitary tumors (Bengtsson *et al.* 2015, Ji *et al.* 2016, Losa *et al.* 2016, Almalki *et al.* 2017, Halevy & Whitelaw 2017, Lasolle *et al.* 2017, McCormack *et al.* 2018, Raverot *et al.* 2018).

MGMT expression and MGMT promoter methylation

Effectiveness or resistance to TMZ treatment may be the result of the presence of MGMT. Many studies have shown an inverse relationship between MGMT immunoexpression and innate sensitivity to TMZ (Kovacs *et al.* 2008, Wiewrodt *et al.* 2008, Salehi *et al.* 2010). Low-level expression of MGMT may be due to epigenetic silencing, by hypermethylation of the MGMT gene promoter in a wide spectrum of human tumors (Esteller *et al.* 2000, Jacinto & Esteller 2007, Sharma *et al.* 2009, Gusyatiner & Hegi 2017). It has been shown that low-level MGMT expression is a prognostic marker of favorable outcome in patients with TMZ treated GBM (Esteller *et al.* 2000). MGMT expression may be analyzed using immunohistochemistry (IHC), methylation-specific PCR (MSP), pyrosequencing (PSQ) and by high-resolution melting (HRM) analysis (Switzeny *et al.* 2016). Although MGMT status in GBM has been evaluated by identification of MGMT promoter methylation, in pituitary tumors, IHC has proven to be reliable, inexpensive, and accessible to most laboratories (Salehi *et al.* 2011).

The inverse relationship between MGMT immunoexpression and TMZ response was first reported in two patients with aggressive PAs (Kovacs *et al.* 2008). Other studies have not shown a conclusive relationship between the MGMT expression and response to treatment, but this may be attributed to the technical differences in tissue fixation, processing, immunostaining and the fact that published studies are retrospectively conducted. Nevertheless, it appears that low MGMT immunoexpression is mostly associated with a better response to TMZ treatment, and it may be used as predictive marker of TMZ response (Bengtsson *et al.* 2015, Raverot *et al.* 2018). MGMT expression may also be used as a prognostic marker in pituitary tumors. Two recent studies (Dai *et al.* 2017, Micko *et al.* 2017) have shown that progression and recurrence of PAs are associated with loss of MGMT immunoexpression. This is in concordance with earlier publications that suggested the same association between progression, recurrence, and MGMT immunoexpression (Widhalm *et al.* 2009, Lau *et al.* 2010).

Thus, low MGMT immunoexpression could be both a predictive marker for TMZ response, and a prognostic marker of tumor recurrence and poor prognosis in PAs.

How can TMZ response be defined?

Clinical and radiographic changes

Studies have shown that in TMZ-responsive cases, the clinical response has been rapid with decreased chiasmic compression and mass effects. In patients with functional tumors, an important reduction of plasma hormone values became apparent after commencement of therapy (Ji *et al.* 2016, Losa *et al.* 2016, Halevy & Whitelaw 2017, Lasolle *et al.* 2017). Response can be seen after 3–6 months of therapy; therefore, the first evaluation of treatment response can be performed after 3 cycles (Raverot *et al.* 2018).

In patients who respond to TMZ treatment, several patterns of radiographic changes have been seen on MRI: tumor necrosis and hemorrhage, cystic change, and shrinkage of the tumor (Syro *et al.* 2011). These changes can be seen as early as two months after the onset of

treatment. To evaluate the response to treatment, Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), MacDonald criteria of response for supratentorial glioma, and Response Assessment in Neuro-Oncology Criteria (RANO) may be used (Macdonald *et al.* 1990, Eisenhauer *et al.* 2009, Wen *et al.* 2010) (Table 1). It is advisable to standardize the reports for future prospective studies, and RANO criteria are recommended for its feasibility. According to these, the response is classified as complete response, partial response, stable disease and progressive disease. Comparison of these criteria is presented in Table 1. The effectiveness of TMZ in aggressive PAs and pituitary carcinomas according to tumor pathological subtype is presented in Table 2.

Morphologic changes

Although only few cases studied have compared their pathology before and after TMZ treatment, it has been shown that TMZ produces edema, necrosis, hemorrhage, accumulation of connective tissue, inflammatory

Table 1 Criteria for response to treatment.

Response	MacDonald	RECIST (version 1.1)	RANO
Complete response (CR)	<i>Imaging features:</i> Disappearance of all enhancing disease Sustained for at least 4 weeks No new lesions <i>Clinical features:</i> Clinically stable or improved	Disappearance of all target lesions Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	Disappearance of the lesion for at least 4 weeks Stable or improved clinically
Partial response (PR)	<i>Imaging features:</i> 50% or more decrease of all measurable enhancing lesions Sustained for at least 4 weeks No new lesions <i>Clinical features:</i> Clinically stable or improved	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters	A decrease of more than 50% compared with baseline Stable or improved clinically
Stable disease (SD)	<i>Imaging features:</i> Does not qualify for complete response, partial response or progression <i>Clinical features:</i> Clinically stable	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study	Does not qualify for complete response, partial response or progression A decrease of less than 50%, stabilization of the lesion or increase less than 25% Stable clinically
Progressive disease (PD)	<i>Imaging features:</i> 25% or more increase in enhancing lesions Any new lesions <i>Clinical features:</i> Clinical deterioration	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (note: the appearance of one or more new lesions is also considered progression)	Increased more than 25% of the lesion Appearance of new lesions Clinical deterioration

Data from Macdonald *et al.* (1990), Eisenhauer *et al.* (2009), Wen *et al.* (2010).

RANO, Response Assessment in Neuro-Oncology Criteria; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2 Aggressive adenomas and pituitary carcinomas. Response to temozolomide treatment according to tumor pathological subtype.

Tumor	Complete response (CR) (%)	Partial response (PR) (%)	Stable disease (SD) (%)	Progressive disease (PD) (%)	Total (%)
PRL	2 (7)	17 (45)	10 (26)	9 (22)	38 (100)
ACTH	6 (8)	22 (30)	20 (27)	25 (35)	73 (100)
NPPA	0 (0)	4 (14)	15 (54)	9 (32)	28 (100)
GH+TSH	1 (6)	6 (33)	7 (39)	4 (22)	18 (100)
Total	9 (6)	49 (31)	52 (33)	47 (30)	157 (100)

Data from [McCormack *et al.* \(2018\)](#).

ACTH, adrenocorticotrophic hormone; GH, growth hormone; NPPA, nonfunctioning pituitary adenoma; PRL, prolactin; TSH, thyroid-stimulating hormone.

infiltrates, larger and more differentiated tumor cells, and neuronal transformation ([Kovacs *et al.* 2007](#), [Bush *et al.* 2010](#)). Analysis of tissue following TMZ treatment shows a decrease in Ki67 labeling index with a corresponding reduction in mitotic activity ([Kovacs *et al.* 2007](#)). Operative findings include tumor softening and friability, both of which may facilitate resection at re-intervention post TMZ treatment ([Syro *et al.* 2011](#)). In a single study, tissue obtained after TMZ therapy showed heterogenous response, with areas of tumor cell destruction as well as viable, non-damaged, MGMT immunopositive cells, which probably were resistant to TMZ ([Ersen *et al.* 2012](#)).

When to start TMZ treatment?

Based on published literature and reported response rates, there is no doubt that patients with pituitary carcinomas are the first indication for TMZ treatment. Unfortunately, there are differences among studies regarding TMZ response rates because there is overlapping information, since some patients are included in more than one study. Not all the studies differentiate response rates between carcinomas and aggressive PAs. Lack of standardization regarding the criteria to evaluate response rate is another issue, since some studies consider only complete and partial response as successful TMZ treatment ([Table 1](#)). Nevertheless, the overall survival (OS) at 5 years in pituitary carcinomas after TMZ therapy is approximately 56.2% ([Ji *et al.* 2016](#)). Comparing this with OS in patients with pituitary carcinomas treated before TMZ – when almost all the patients died within one year and had a mean survival rate of 1.9 years ([Pernicone *et al.* 1997](#), [Kaltsas *et al.* 2005](#), [Scheithauer *et al.* 2006](#)) – TMZ represents an enormous advancement in therapeutic options. In this context, facing the ominous evolution of pituitary carcinomas, one can conclude that a stable disease response is a good response as well ([Tables 1 and 2](#)). Whether stable disease is included or not, the response rate of pituitary carcinomas with TMZ varies from 50 to 87.6% ([Hirohata *et al.* 2013](#),

[Bengtsson *et al.* 2015](#), [Ji *et al.* 2016](#), [Almalki *et al.* 2017](#), [Lasolle *et al.* 2017](#), [McCormack *et al.* 2018](#)).

In cases of aggressive PAs, the decision to start TMZ treatment is not as easy and some considerations must be contemplated. Comparing demographic characteristics, age, sex, time of duration of disease, previous radiotherapy, number of surgeries, functional status of the tumors and Ki67, there are no statistically significant differences between aggressive PAs and pituitary carcinomas, except for the presence of metastases ([Bengtsson *et al.* 2015](#), [Ji *et al.* 2016](#), [McCormack *et al.* 2018](#), [Raverot *et al.* 2018](#)). Perhaps aggressive PAs and pituitary carcinomas are two faces on the same coin? Due to the lack of morphologic, biochemical or molecular biomarkers that can indicate in advance which tumors will behave in an aggressive manner, the decision to start TMZ will always be a difficult task ([Lin *et al.* 2016](#), [Halevy & Whitelaw 2017](#)). Age, previous medical therapy, radiotherapy, number of previous surgical interventions, invasion, proliferation markers, and histologic subtype of the tumor must be considered ([Ceccato *et al.* 2018](#)). The benefits of starting TMZ must outweigh the risks of repeated surgeries, re-irradiation and potential complications with standard treatments ([Lin *et al.* 2016](#)). The decision must be considered from an interdisciplinary perspective ([Raverot *et al.* 2018](#)).

In a recent meta-analysis, the 5-year OS for aggressive PAs treated with TMZ was 57.4% ([Ji *et al.* 2016](#)). The lack of standardization regarding tumor response criteria gave a response rate from 50% to 80.6% whether stable disease is included or not ([Ji *et al.* 2016](#), [Raverot *et al.* 2018](#)). In aggressive PAs, TMZ is often used as a last resort after standard medical therapies, repeated surgeries and radiotherapy have been unsuccessful. Therefore, it should be taken into consideration that a stable disease response after TMZ therapy, may be considered a good response as well. Interestingly, no statistically significant differences in OS and progression-free survival (PFS) were found between patients with aggressive PAs and those

with pituitary carcinomas. The 5-year PFS was 21.9% for patients with aggressive PAs and 36.1% for patients with pituitary carcinomas. This suggests that aggressive PAs and pituitary carcinomas are closer in identity than previously perceived.

It is advisable to perform MGMT immunoexpression before starting TMZ therapy. A low MGMT immunoexpression has been correlated with a positive response to TMZ. If it is not possible to perform MGMT IHC, or if MGMT immunoexpression is high, then, TMZ can be started for 3–6 cycles to determine the response of the tumor to therapy (Raverot *et al.* 2018).

What should the starting and maintenance doses be?

The standard therapeutic dose of TMZ is 150–200 mg/m²/day for 5 of every 28 days (5/28). TMZ response is schedule dependent and alternative dosing regimens may enhance its efficacy (Mrugala & Chamberlain 2008). TMZ can be administered on a continuous daily metronomic schedule as well, thus achieving MGMT depletion and improving response. In this case, the dose is 50 mg/m²/day without interruption (28/28). Other TMZ schedules include its administration every other week (7/14) and on a 21-consecutive-day regimen administered every 28 days (21/28). Both are considered dose-dense regimens: they increase the dose intensity of the regimen by delivering standard-dose chemotherapy with shorter intervals between the treatment cycles. This improves the efficacy by minimizing the opportunity for cellular regrowth between cycles (Liu & Gerson 2006). In these dose-dense regimens, TMZ is administered at 150 mg/m²/day for 7 days every other week (7/14) or at 85–100 mg/m²/day for 21 consecutive days (21/28).

In most pituitary cases (87.8%), TMZ has been used according to the standard regimen (5/28) (Ji *et al.* 2016). If external beam radiation therapy is needed, TMZ may be used concomitantly as in the Stupp protocol for GBM at 75 mg/m²/day for 6 weeks. This could not be applicable for stereotactic radiosurgery. TMZ absorption is minimally affected by food. No serious side effects have been reported with its use in pituitary tumors. In cases of dose-dense regimens, the secondary effects can be more severe.

A small number of patients in different series have received a combination of TMZ with another medication: capecitabine (Zacharia *et al.* 2014), pasireotide (Bode *et al.* 2010, Ceccato *et al.* 2015), octreotide (Bush *et al.* 2010, Vieira Neto *et al.* 2013), bevacizumab (Touma *et al.* 2017) and thalidomide (Raverot *et al.* 2018). In patients with

functional tumors, the addition of a second medication can be useful. The small number of patients does not allow proper analysis of the effects of these combinations and their use must be decided according to each patient.

How long should the treatment be given?

In patients with GBM, the duration of treatment is 6–12 months and, in some cases, it may be extended for several years (Mannas *et al.* 2014). In pituitary tumors, 73% of patients have received short-term therapy (1–12 months). On average, they received 13 cycles of TMZ (range, 1–45 cycles). In patients with short-term treatment, the median number of TMZ cycles was 8 (range, 1–12 cycles) and 26 (range, 14–45 cycles) for those in long-term therapy (more than 12 cycles) (Ji *et al.* 2016). In patients who responded to TMZ, there was a trend toward benefit from long-term therapy. The 5-year OS rate was 91.7% and the 5-year PFS rate 61.3% in patients with long-term treatment vs 54.1% and 16.3% respectively, in patients with short-term treatment (Ji *et al.* 2016). Although not statistically significant, it seems that patients can benefit from extended TMZ therapy. It was shown that patients receiving long-term treatment, stayed free of disease progression up to 120 months (Ji *et al.* 2016).

In patients with pituitary carcinomas, TMZ treatment can be extended according to their tolerance, clinical and radiological response. In aggressive Pas, the benefits to extended therapy must outweigh the risks of secondary effects and may be continued if therapeutic benefit is observed. Relapse after TMZ suspension has been observed in some patients and a second attempt of TMZ usually has not been successful (Raverot *et al.* 2018). Based on these findings, and in the fact that there are no alternative drugs, an extended or lifelong treatment may be justified, especially in pituitary carcinomas.

What to do with TMZ resistant tumors?

Tumors that were initially sensitive to chemotherapeutic agents can develop resistance. This condition is known as acquired resistance and may be caused by genetic or epigenetic alterations in particular genes, that provide tumor cells with a survival advantage to continue to replicate (Alvino *et al.* 2006). In this scenario, if a heterogenous tumor is treated using chemotherapy, only the sensitive tumor cells would be killed, thereby leaving behind the resistant tumor cells to continue to grow and replicate. Studies have shown that acquired resistance

is conferred by a variety of mechanisms that result in TMZ treatment having little or no effect on the specific tumors (Longley & Johnston 2005, Bradshaw *et al.* 2008). Moreover, certain glioma cases may contain various multi-drug resistant proteins that are able to diminish or tolerate the effects of TMZ (Calatozzolo *et al.* 2005).

In pituitary tumors non-responsive to TMZ, progressive disease under treatment, or relapse after discontinuation of therapy, a second-line option has been used with limited success. Anti-angiogenic therapy with bevacizumab has been successful in one case (Ortiz *et al.* 2012) and the patient is still alive after 7 years of continuous therapy. Everolimus, lapatinib, sunitinib and erlotinib have also been tried without success (Jouanneau *et al.* 2012, Donovan *et al.* 2016, Raverot *et al.* 2018). Re-irradiation can be another option, but the risk of secondary effects must be balanced against the possible benefits.

Suggested indications for TMZ treatment

Based on current data, TMZ continues to be used as the last resort and as a salvage treatment in many cases. The suggested indications are:

1. Pituitary carcinomas (Melmed *et al.* 2011, Syro *et al.* 2011, Raverot *et al.* 2018).
2. Aggressive PRL-producing PAs resistant to bromocriptine or cabergoline, which undergo continued growth after surgery and radiotherapy. In some cases, TMZ may be used before radiotherapy (Hagen *et al.* 2009, Whitelaw *et al.* 2012).
3. Aggressive ACTH-producing PAs, especially the Crooke's cell and Nelson syndrome variants, not cured by surgery and radiotherapy. TMZ may be used alone or concomitant with pasireotide (Ceccato *et al.* 2015).
4. Aggressive, recurrent, nonfunctional PAs exhibiting continued growth after repeated surgeries and radiotherapy. TMZ may be used concomitantly with external beam radiation therapy as in the Stupp protocol for GBM patients (Raverot *et al.* 2018).
5. Aggressive GH-producing PAs, without biochemical control after combination therapies. TMZ may be used alone or concomitantly with cabergoline, somatostatin analogs and pegvisomant (Lim & Fleseriu 2017).
6. Recurrent PAs with repeated surgeries and previous unsuccessful resection due to hard, fibrous consistency of the tumor. In such cases, TMZ may serve to soften the lesion prior to another attempt of resection (Syro *et al.* 2006, Ersen *et al.* 2012).

Future directions

TMZ has documented to be of value in the treatment of aggressive PAs and pituitary carcinomas. After twelve years of its use, prospective, clinical trials are needed. With the advancement in research and clinical techniques, future studies involving TMZ can be expanded on many levels. First and foremost, research should focus on establishing novel reliable markers, beyond MGMT methylation and IHC analysis, in order to improve accuracy in predicting TMZ response rate in individual cases. This is an ongoing issue with current TMZ treatment. Another possibility is to study whether TMZ response increases if used alone or concurrently with radiotherapy. Studies should focus whether TMZ response improves when different radiation therapy methods are used.

Researchers studying genetic mutations in PAs and pituitary carcinomas should collaborate with clinicians to correlate whether TMZ therapy response varies with the existence of other genetic mutations, present in various pituitary tumors. It may be that certain genetic mutations may make some tumors resistant or less responsive to TMZ therapy. There is also a crucial need to further explicate the mechanisms that confer tumor resistance to TMZ in PAs and pituitary carcinomas, as well as in all other tumor types. Increased knowledge of the molecular mechanisms and processes present within these tumors may reveal novel targets that would increase the effectiveness of TMZ therapy especially in cases of TMZ resistant cases. Perhaps the secret to increasing TMZ effectiveness lies in the simple fact that novel mechanisms or agents are needed to deplete MGMT levels within the tumor cells in order to heighten the effect of TMZ.

While the identification of genetic mutations in pituitary tumors is a step in the right direction, future research should seek to determine why certain tumors are drug resistant. Here, studies should include whether prolonged TMZ dosing regimens will overcome TMZ resistance in both recurring tumors, and tumors where MGMT immunoexpression is strong. They can also look at whether TMZ therapy applied earlier in the treatment process (i.e. after initial diagnosis) is more effective in these types of tumors as opposed to using TMZ therapy as a 'last resort' (Lin *et al.* 2016).

Along with using genetic information to determine effect of TMZ treatment, future studies should look at whether response rates improve if TMZ is used in combination with drugs/antibodies that are known enzyme/protein blockers in tumor cell growth. Capecitabine may augment the effects of TMZ if it is

administered some days before, but more studies are needed. Studies should focus on VEGF and rapamycin effects when used along with TMZ to treat tumors. Along with this, emphasis should be given to whether immunotherapy can be combined with TMZ therapy to treat recurrent aggressive PAs and pituitary carcinomas.

Although TMZ may be the 'best' therapy as a last resort in many cases of aggressive PAs and pituitary carcinomas, more work on a greater number of cases should be of the utmost importance to establish the true capabilities of this agent. The lack of clinical trial data for TMZ effectiveness, and the establishment of the indications, doses and duration of TMZ administration needed in tumors, necessitates multidisciplinary approaches to provide patients with the most informed and best treatment options. The use of TMZ as neoadjuvant therapy in cases of recurrent PAs should be explored.

To conclude, the fact that TMZ treatment, a chemotherapeutic agent, has been effective in both aggressive PAs (considered *benign*) and pituitary carcinomas (considered *malignant*), and that the studies have shown clinical similarities in both groups, a new paradigm of benignity, aggressiveness and malignancy in pituitary tumors emerges. Perhaps their boundaries are not so clear. This can lead us to find the missing link between them and help us to clarify their pathogenesis and their management.

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