Cytotoxic Chemotherapy and Targeted Therapy for Aggressive Pituitary Tumors

34

Alissa A. Thomas and Camilo E. Fadul

Introduction

Pituitary tumors are usually benign entities that can be treated with surgery, radiation, and medical therapy, including dopamine agonists and hormonal therapy. Despite judicious implementation of these treatment modalities, a subset of pituitary tumors may become aggressive with local invasive recurrence or with metastases. Cytotoxic chemotherapy is not traditionally considered an effective therapeutic option because even when the tumor has an aggressive biologic behavior, the cancer cells are well differentiated and have a low proliferation rate. In 2006, however, our group and others reported on the response of aggressive pituitary tumors to temozolomide, an alkylating cytotoxic agent. Since then, chemotherapy has been used off-label in multiple cases, and although there are no controlled trials to date, the therapeutic benefit, as measured by response rate, has been consistent. Furthermore, as the cell-signaling mechanisms responsible for tumor growth are elucidated and in the advent of targeted therapies, we have an opportunity to improve the outcomes for patients diagnosed with aggressive pituitary tumors.

In this chapter we will discuss the medical oncologic management of aggressive pituitary adenomas and pituitary carcinomas. We will review the published experience using cytotoxic chemotherapy, anti-angiogenic therapy, and targeted therapy for pituitary tumors, and we will discuss biomarkers that are potentially predictive of response, keeping in mind two caveats. First, there are no controlled trials that evaluate the outcomes of these treatments, and, therefore, their effectiveness is based on anecdotal case studies. Second, the categorical designation of "aggressive

A.A. Thomas, MD
Department of Neurology, University of Vermont College of Medicine, Burlington, VT, USA

C.E. Fadul, MD, FAAN (✉)
Department of Neurology, University of Virginia, Charlottesville, VA, USA
e-mail: CEF3W@hscmail.mcc.virginia.edu

E.R. Laws, Jr. et al. (eds.), *Transsphenoidal Surgery*,
DOI 10.1007/978-3-319-56691-7_34

pituitary tumor" includes a heterogeneous group of diseases that, although histologically similar, may have very different mechanisms of tumorigenesis and therapeutic response.

The malignant behavior of pituitary tumors is determined by biologic characteristics as well as invasion into surrounding structures. Pituitary tumors constitute about 15% of all intracranial neoplasms [1], and 35–50% of these tumors are locally invasive [2]. Some invasive tumors are resistant to standard medical therapies, including dopaminergic agents and hormonal therapy. Others may recur after initial response to treatment. When the cellular proliferation rate exceeds 3%, these recurrent aggressive tumors are classified by the World Health Organization (WHO) as atypical pituitary adenomas. Though these neoplasms are locally invasive and histologically may differ from typical tumors, atypical pituitary adenomas rarely metastasize. It is estimated that 25–55% of pituitary adenomas are clinically aggressive, and display such features as invasion into surrounding tissue, as well as rapid growth, large size, and rapid recurrence [3]. After standard therapeutic options have been exhausted, patients who suffer from recurrence of these malignant tumors are presented with very limited options.

Pituitary carcinomas are a rare subgroup of pituitary tumors defined by the WHO as having systemic metastases or craniospinal dissemination. These aggressive cancers account for an estimated 0.2% of all pituitary tumors. Between 1961 and 2012 less than 150 cases were reported in the literature [4, 5]. From the histologic and endocrinologic perspectives, these tumors may be indistinct from benign pituitary tumors. Pituitary carcinomas most often secrete prolactin (36%) or adrenocorticotrophin (ACTH, 30%), while a smaller number are nonfunctional (23%) [5]. The most frequent sites of metastases are within the brain and spinal cord, but extracranial spreading of the neoplasm can also occur. There are no endocrinologic or pathologic characteristics known to predict which patients will develop metastases from a pituitary tumor. The molecular mechanisms that allow the tumor to metastasize also remain unknown. Although, in most patients, pituitary carcinomas behave aggressively with functional impairment leading to death, a few patients have reportedly lived for several years without medical treatment [2, 6]. In the majority of patients with pituitary carcinoma, the only treatment option is supportive care.

Pituitary tumors with certain histologic subtypes and biologic characteristics are associated with more malignant behavior. For example, prolactinomas are often more aggressive and less responsive to dopamine agonist therapy in men than women [3]. Another inherently aggressive pituitary neoplasm is the Crooke cell tumor, a corticotroph adenoma that undergoes massive accumulation of perinuclear cytokeratin in the presence of glucocorticoids [3]. In a study of 36 cases of this type of tumor, 60% of patients had recurrent disease with an average time to recurrence of 3.6 years [7]. Of the 25 patients who were followed for more than 1 year, two developed metastatic carcinoma. Silent corticotroph adenomas are even more aggressive than either their hormone-secreting counterparts (ACTH-secreting tumors) or other nonfunctioning adenomas. Though morphologically similar to ACTH-secreting tumors [3], they are characterized by higher rates of recurrence and more frequent invasion into the cavernous sinus [3]. Other pituitary tumors reported to

Table 34.1 Chemotherapy drugs that have been reported for the treatment of invasive pituitary tumors

Chemotherapy
5-fluorouracil with lomustine[a]
Gliadel wafers
Temozolomide[a]
Carboplatin
Paclitaxel
Etoposide
Capecitabine and temozolomide[a]

[a]Indicates that clinical or radiographic responses were reported

have an aggressive clinical course include gonadotropin-secreting pituitary adenomas, sparsely granulated somatotroph adenomas, densely granulated lactotroph adenomas, acidophil stem-cell adenomas, thyrotroph adenomas, plurihormonal adenomas, silent adenomas, and null cell adenomas [3]. These types of pituitary tumors should alert the clinician about a potentially more malignant behavior.

No standard-of-care recommendation exists for patients with aggressive pituitary tumors and carcinomas. Pituitary tumors that are invasive, recurrent, or metastatic pose a therapeutic challenge, as these neoplasms are often not manageable with local treatments such as surgery or radiation therapy. In most cases, dopamine agonists and hormonal therapies have limited benefit. Although the potential for systemic therapy with cytotoxic and targeted agents to improve outcomes for patients with malignant pituitary tumors is unknown, the reports to date suggest that these therapies could become an effective addition to the therapeutic armamentarium.

Cytotoxic Chemotherapy

Multiple cytotoxic chemotherapy agents have been used for the treatment of patients with recurrent aggressive pituitary tumors and pituitary carcinomas (Table 34.1). The benefit of chemotherapy in this patient population can be measured by response rate, as determined by tumor size in imaging studies, reduction in hormone concentration, progression-free survival, and overall survival. It is difficult to compare outcomes among studies because of the heterogeneity of the tumors treated and the variability in survival rates between locally invasive pituitary adenomas and pituitary carcinomas. As previously mentioned, some patients may experience prolonged survival without treatment. Of the aforementioned outcome measurements, radiographic response rate is the most consistently reported in studies using chemotherapy for malignant pituitary tumors.

Early publications on the use of chemotherapy for aggressive pituitary tumors were restricted to a few single case reports. The diversity of administered drugs limits the assessment of clinical utility [8]. The first series reported on seven patients with highly aggressive or malignant pituitary tumors who showed a disappointing response rate of only 14% after treatment with a combination of

5-fluorouracil (5-FU) and cyclo-hexyl-chloroethyl-nitrosourea (lomustine, CCNU) [9]. Three of these seven patients received single-agent carboplatin after progression with 5-FU/CCNU, but none responded on the basis of imaging assessment. In another trial, Gliadel wafers (1, 3-bis (2-chloroethyl)-1-nitrosourea [BCNU] and a biodegradable polyanhydride copolymer) were implanted postresection in nine patients with aggressive recurrent pituitary adenomas. Although potential benefits could not be determined from this single study, the patients tolerated the treatment without significant adverse reactions [10].

In 2006, we reported two cases of patients with pituitary carcinoma [11] who had remarkable responses on MRI to treatment with temozolomide. The first patient had a luteinizing-hormone-secreting pituitary adenoma with several local recurrences despite treatment with fractionated radiation and radiosurgery in addition to multiple surgical resections. About 8 years after his initial diagnosis, he was found to have multiple intradural and extramedullary lesions in the cervical and thoracic spinal cord. Biopsy of one of these lesions confirmed a typical pituitary tumor similar to the samples previously resected. Staging studies showed metastases in the ribs and right tibia, as well as growth of the original sellar tumor. He underwent radiation to the spinal lesions and received octreotide without effect. He was then enrolled in a Phase I study combining temozolomide and pegylated interferon. The interferon was stopped after 1 month due to Grade 4 fatigue. He continued temozolomide 200 mg/m^2/day on days 1–5 of 28-day cycles for 12 cycles. He tolerated the treatment well and had clinical improvement, as well as radiographic response (Fig. 34.1). Sixteen months after stopping chemotherapy, he remained asymptomatic. The second patient was a 26-year-old man with a prolactin-secreting pituitary adenoma who had progression with disseminated disease in the cervical and thoracic cord after treatment with dopamine agonists, surgery, and radiation therapy. He had previously received treatment for the metastatic disease, including bromocriptine, octreotide, carboplatin, paclitaxel, and etoposide, without response. Based on our experience with the prior case, the patient was treated with oral temozolomide 200 mg/m^2/day on days 1–5 of a 28-day cycle. He finished 10 of 12 planned cycles (stopped early due to fatigue), with improvement in symptoms, decreased prolactin concentration, and a partial radiographic response. Both patients had clinical and radiographic responses that were durable for more than 1 year after discontinuing the treatment, but both cases ultimately progressed without response after restarting temozolomide. Since then, several other reports have confirmed the sensitivity of aggressive pituitary tumors and pituitary carcinomas to temozolomide [11].

Temozolomide is an alkylating chemotherapy agent that works by methylating DNA at the O6 position of guanine (Fig. 34.2) leading to mispairing with thymine during the next cycle of DNA replication and ultimately results in non-cell-cycle-specific apoptosis. In 2005, the FDA approved temozolomide for newly diagnosed glioblastoma after a randomized trial demonstrated improvement in overall survival in patients treated with radiation and temozolomide as compared to patients treated with radiation therapy alone [12]. The effect was modest with a median overall survival of 14.6 months (compared with 12.1 months) and an increase in 2-year survival to 26.5% from 10.4% [12]. A retrospective analysis revealed that patients

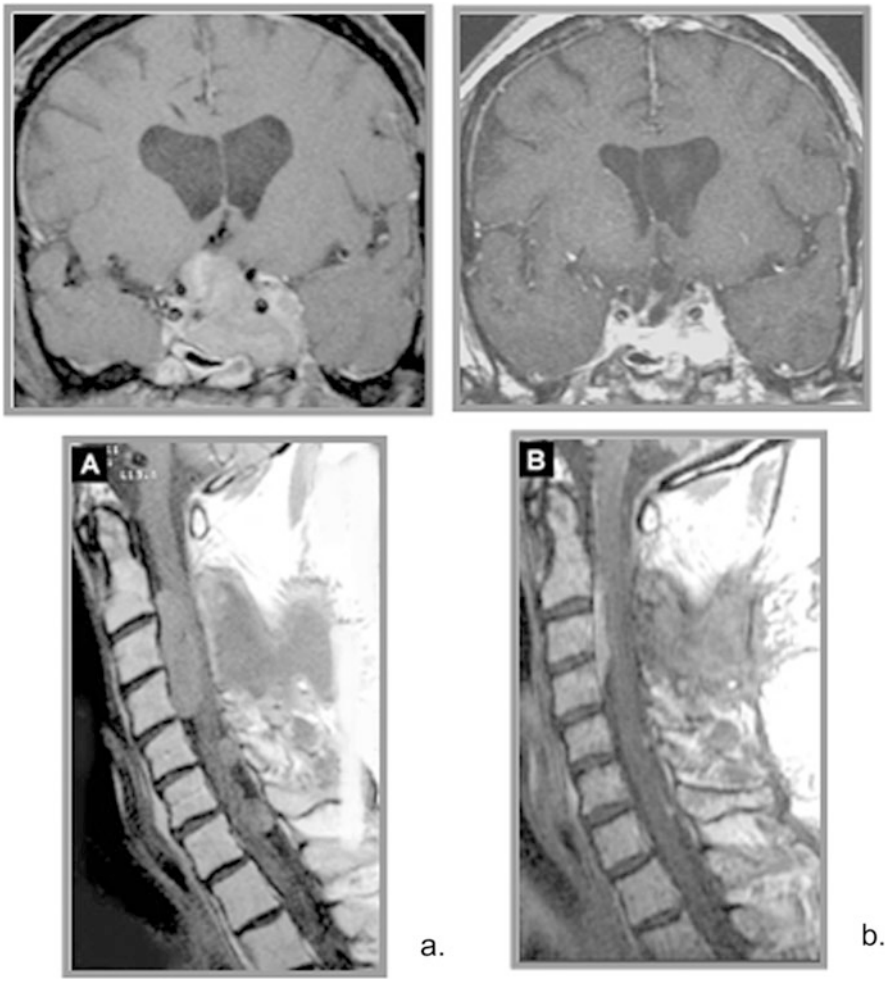

Fig. 34.1 A: Coronal contrast-enhanced T1-weighted MR image of the brain obtained before treatment, revealing an invasive pituitary mass with suprasellar extension. B: Sagittal contrast-enhanced T1-weighted MR image of the spine obtained before treatment, demonstrating three extramedullary masses, the largest at C2–4. C and D: Coronal (C)and sagittal (D) contrast-enhanced T1-weighted MR images showing decreases in the pituitary mass and spinal metastases, respectively, after 12 cycles of chemotherapy. (Reproduced with permission from: Fadul CE, Kominsky AL, Meyer LP, et al. Long-term response of pituitary carcinoma to temozolomide. Report of two cases. J Neurosurg. 2006;105(4):621–6.)

whose tumors harbored hypermethylation of the gene promoter of the DNA-repair enzyme O6-methylguanine-methyltransferase (MGMT) had a significantly better response to treatment; the median overall survival was 21.7 months, and 2-year survival rate was 46% [13]. MGMT repairs DNA by removing the methyl group from guanine, thereby undoing the damage caused by temozolomide. When the promoter region of MGMT is methylated, the gene is epigenetically silenced, and temozolomide has greater activity.

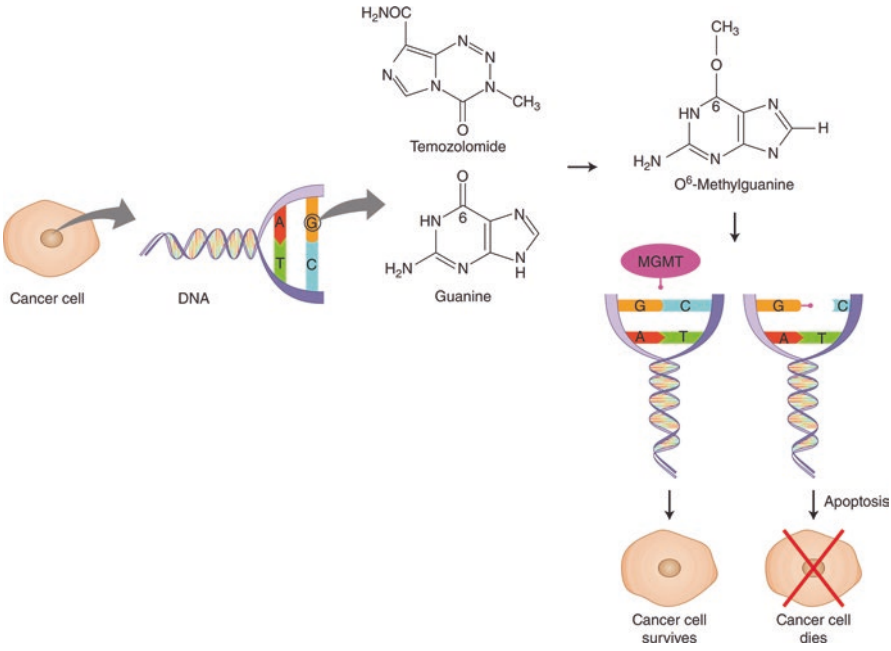

Fig. 34.2 Schematic representation of temozolomide mechanism of action. Temozolomide acts by adding a methyl group to the O6 position of guanine on the DNA of cancer cells. The O6-methylguanine is unable to pair with cytosine and the DNA cannot replicate, so the cell is forced to undergo apoptosis and die. MGMT is a DNA-repair enzyme that removes the methyl groups, repairing the damage done by temozolomide and allowing the cell to survive

The reports supporting the use of temozolomide in patients with aggressive pituitary tumors have been growing in the past decade [14, 15]. Overall, these studies suggest that the drug may have activity against a variety of subtypes of pituitary tumors, including Crooke's cell tumors [16], prolactinomas [17], and nonfunctioning pituitary adenomas [18], as well as tumors secreting luteinizing hormone (LH) as previously described [11]. Temozolomide may also be effective in treating extraneural metastases [19]. However, not all tumors are sensitive, as demonstrated by a case series of four patients with somatotropic pituitary adenomas that did not respond to temozolomide [20]. Therefore, in the absence of controlled trials, the challenge is to deepen our understanding of the mechanisms of cytotoxicity and resistance in order to determine which patients are more likely to benefit from temozolomide and what combinations of cytotoxic chemotherapy agents have the most favorable outcomes.

Since most reports include single cases or small series, meta-analysis of the cases is used to better assess the effectiveness of temozolomide in this disease. One meta-analysis included 46 patients, 30 with pituitary adenomas and 16 with carcinomas, who received treatment with temozolomide [21]. Clinical and radiographic responses occurred in 60% of the adenomas and 69% of the carcinomas. Another meta-analysis [4] of 21 additional patients from three studies [22–24] reported that seven patients (33%) with aggressive pituitary tumors responded to temozolomide and five more had stable disease, suggesting an overall disease control rate of 57%. The most recent

Table 34.2 Cases published of patients with aggressive pituitary adenoma or pituitary carcinoma treated with at least two cycles of temozolomide

		Response by MRI			Hormone response	
Type of pituitary tumor	*N*	CR + PR (%)	SD (%)	PD (%)	*N*	Decrease (%)
Aggressive invasive[a]	62	38 (61%)	6 (10%)	18 (29%)	13	11 (85%)
Carcinoma[b]	38	24 (63%)	4 (11%)	10 (26%)	14	11 (79%)
Aggressive/Carcinoma[c]	31	11 (35%)	14 (45%)	6 (19%)	21	15 (71%)
Total[d]	131	73 (56%)	24 (18%)	34 (26%)	48	37 (77%)

CR Complete Response, *PR* Partial Response, *PD* Progressive Disease
[a][15, 16, 20, 22–24, 26–28, 34, 41, 43–54]
[b][11, 14, 19, 22–24, 34, 36, 44, 49, 55–60]
[c]This reference includes six cases of pituitary carcinoma and 25 cases of locally aggressive pituitary tumor, but report does not discriminate response by type of tumor [25]
[d]Only included cases that received at least two cycles of temozolomide

meta-analysis reported an 80% response rate among 31 patients with aggressive pituitary tumors (six with carcinoma and 25 with adenoma) treated with temozolomide [25]. Of the 25 temozolomide responders, 13 had tumor growth after the temozolomide was discontinued. In our review of the published literature, 131 patients with aggressive pituitary adenoma or pituitary carcinoma have been treated with temozolomide for at least two cycles (Table 34.2). The radiographic response rate was 56% with an additional 18% of patients with stable disease, for a total of a 74% disease control rate. Among secretory tumors, 77% had a response as determined by a decrease in hormone secretion. Although the combination of these case reports and case series suggests that temozolomide may be an effective therapy for treatment-refractory pituitary adenoma and carcinoma, the optimal duration of therapy and the influence in progression-free and overall survival remain unanswered questions.

In most cases, progression has been observed after months to more than a year after stopping temozolomide [11, 26]. The mechanisms of resistance have not been elucidated, but it has been suggested that like in glioblastoma, temozolomide can cause secondary mutations. In our first two patients with pituitary carcinoma treated with temozolomide, both had recurrence more than 18 months after having completed 12 cycles of temozolomide. There was no response when the patients received temozolomide again. Another case report described a patient with an atypical aggressive pituitary adenoma that responded well to treatment with temozolomide, but then recurred after 6 months of stopping therapy [27]. A mutation in the mismatch repair gene MSH6, not present in the initial specimen, was found at recurrence.

Temozolomide has been combined with other cytotoxic chemotherapy for the treatment of aggressive pituitary tumors in an attempt to circumvent resistance. Four patients with aggressive ACTH-secreting pituitary tumors that progressed after surgeries, radiation, and hormonal therapy [28] were treated with a regimen of temozolomide (150 mg/m^2/day administered on days 10–14 of a 28-day cycle) and capecitabine (1000 mg BID on days 1–14) (CAPTEM). Of the four patients, two had radiographic complete responses, one had a 75% tumor regression, and the other had stable disease without progression after 4.5 years of follow-up. All tumors had low MGMT

expression by immunohistochemistry. Two other patients treated with CAPTEM have been reported, one with a corticotroph adenoma [29] and one with a prolactinoma associated with multiple endocrine neoplasia (MEN) [30]; both had a clinical and hormonal response to treatment [31]. The benefit of adding other chemotherapy agents to temozolomide in patients with aggressive pituitary tumors has not been established, but molecular profiling may provide the rationale for more effective combinations.

Similar to the experience in glioblastoma, patients with pituitary tumors tolerate treatment with temozolomide well. Grade 1 and 2 fatigue and thrombocytopenia are the most frequently reported side effects. Only one report of a severe temozolomide-related adverse event in a patient with a pituitary carcinoma has been published. A 58-year-old man with an ACTH-secreting pituitary carcinoma presented to the hospital with severe headache, blindness, and nuchal rigidity 27 days after starting temozolomide. He was found to have profound thrombocytopenia with multiple intraparenchymal cerebral hemorrhages from brain metastases. He died a few months later. This event highlights the potential life-threatening complications of temozolomide and the need for close monitoring when the disease and treatment combination have not been well characterized.

Biomarkers Predictive of Response

As with any other therapeutic decision, there is a need to identify patients with aggressive pituitary tumors who would benefit the most from temozolomide. The DNA-repair enzyme MGMT is a well-validated biomarker that predicts response to temozolomide and overall survival in patients with glioblastoma [13]. MGMT expression can be determined by a number of different assays, but there is no consensus on the measurement methodology that will provide the best correlation with response to this agent. Methylation assays, including methylation-specific polymerase chain reaction (PCR), real-time quantitative methylation-specific PCR, and methylation-specific multiplex ligation-dependent probe amplification, detect MGMT promoter methylation at CpG islands. Methylated MGMT represents the inactivated form of the enzyme, while unmethylated MGMT retains its enzymatic activity. MGMT protein expression can be determined by immunohistochemistry.

The correlation of MGMT methylation detected by PCR and protein expression by immunohistochemistry has been poor. One study of aggressive pituitary adenomas and carcinomas attempted to correlate MGMT protein expression with MGMT promoter methylation [32]. Among 14 carcinomas, 33% exhibited MGMT promoter methylation, while low MGMT protein expression was found in 50% by immunohistochemistry. Similarly, among the 12 aggressive adenomas, 42% had a methylated MGMT promoter region, while immunohistochemistry for MGMT was negative in 92% of the tumors. The lack of concordance between MGMT methylation and immunohistochemistry for protein expression is similar to that which has been reported with glioblastoma, where the methylation status is the predictor of response [33].

Most studies reporting on MGMT activity in pituitary tumors have relied on immunohistochemical assays [28, 34–37], with the suggestion that MGMT protein deficiency predicts response to temozolomide [35]. In the largest series to date, tissue

from 24 patients with aggressive pituitary tumors (16 aggressive adenomas and eight metastatic pituitary carcinomas) treated with temozolomide was retrospectively analyzed for hormone status, response to temozolomide, and MGMT protein expression by immunohistochemistry [34]. Of the 24 patients, 10 had a response to treatment (two radiographic complete responses, seven partial responses, and 1 hormonal response with 71% decrease in prolactin). Among the ten responders, median MGMT expression was 9% (range of 5–20%), compared with 93% in nonresponders (range 50–100%). A study of 197 pituitary adenomas revealed MGMT expression was low in the majority of tumors (86.3%) [38]. Although these studies suggest that aggressive pituitary adenomas with low MGMT protein expression by immunohistochemistry may respond to temozolomide, the glioblastoma literature suggests that the MGMT methylation status of the promoter may be a better predictive biomarker for response.

Loss of the DNA mismatch repair protein MSH6 has been implicated in the development of temozolomide resistance even when MGMT expression is low [27]. The presence of MSH6 by immunohistochemistry positively correlated with response to temozolomide in 13 cases of atypical pituitary adenomas and pituitary carcinomas. In another series, there was one case with absent MSH6 in which there was resistance to the drug, but several other cases also had rapid progression in spite of having expression by immunohistochemistry [34]. The small number of retrospective cases precludes any conclusions about its value as a biomarker of responsiveness to temozolomide.

Anti-angiogenic Therapy

Vascular endothelial growth factor (VEGF) is a pro-angiogenic cytokine that drives neovascularization in many cancers. Bevacizumab, a monoclonal antibody that targets VEGF, is FDA approved for the treatment of several solid tumors, including recurrent glioblastoma. VEGF has been reported to be present at high concentrations in 59% of pituitary adenomas [38]. The presence of VEGF and the invasive behavior of some pituitary adenomas provide rationale for the use of bevacizumab for the treatment of refractory disease. There has been one case report showing stabilization of an aggressive pituitary adenoma after bevacizumab treatment [39]. A 44-year-old man presented with an aggressive silent corticotroph cell pituitary adenoma, which was refractory to multiple treatments and progressed despite the use of temozolomide. Bevacizumab was initiated, and after 10 months of therapy the tumor remained stable. Bevacizumab was continued for another 16 months with ongoing disease control for the duration of follow-up (26 months). Though this is only a single case, the successful long-term disease control is encouraging. It is possible that the combination of temozolomide and bevacizumab could be an effective option for refractory disease.

Targeted Therapy

There has been limited experience combining temozolomide with the somatostatin analog, pasireotide. The first report described a patient with an ACTH-secreting pituitary carcinoma with widespread intracranial, spinal, and systemic metastases

despite repeated surgical treatment, bilateral adrenalectomy, medical treatment, and chemotherapy [40]. The patient received temozolomide and pasireotide combination therapy for 12 months. The combination was well tolerated, and the patient had improvement in symptoms and reduction of ACTH levels. Pasireotide was continued for 9 months as monotherapy after temozolomide was discontinued. A case series of five patients with aggressive pituitary adenomas treated with temozolomide included two patients with secreting tumors who received both temozolomide and pasireotide [41]. One of the two patients responded to combination therapy with a decrease in both cortisol concentration and tumor volume.

Preclinical studies suggest that aggressive pituitary adenomas may be sensitive to treatment with PIK3/mTOR inhibitors and that these drugs may augment the response to temozolomide [42]. Hyperactivity of the PIK3/Akt/mTOR pathway is thought to contribute to chemotherapy resistance. In pituitary adenoma cell lines, XL756, a novel dual PIK3/mTOR inhibitor, given in combination with temozolomide inhibited adenoma cell growth and induced apoptosis to a significantly greater extent than temozolomide alone. The combination of XL756 and temozolomide synergistically inhibited tumor growth and resulted in decreased serum growth hormone and prolactin concentrations in a murine xenograft model [42]. This suggests that dual inhibition of PIK3 and mTOR may enhance alkylating agent-mediated cytotoxicity in pituitary tumors, but there is no clinical experience with this combination.

One patient with an ACTH pituitary carcinoma resistant to temozolomide has been treated with everolimus (an mTOR inhibitor) in combination with octreotide. Treatment failed to control tumor growth and hormone secretion, with the lack of response thought to be explained by the weak mTOR activation in ACTH tumors. It must be determined whether mTOR inhibition is a more prominent mechanism of tumorigenesis in other types of aggressive pituitary tumors and if response to inhibition will correlate with its activation.

Indications for Chemotherapy

Invasive pituitary adenomas and pituitary carcinomas are uncommon pituitary neoplasms with high rates of recurrence and responsible for significant morbidity and mortality. In these aggressive tumors, it may be impossible to achieve local control with radiation therapy or surgery due to infiltration into surrounding tissues or metastatic dissemination. In the absence of a clear hormonal target with established endocrine therapy, temozolomide may be considered for the treatment of these tumors. Controlled prospective data is lacking to support the use of temozolomide for this indication, but several case reports and case series demonstrate both safety and clinical, hormonal, and imaging efficacy, sometimes with prolonged and durable responses. Temozolomide is most likely to be effective when the tumor has a methylated MGMT promoter. Although the adverse side effects of temozolomide are usually mild to moderate, close monitoring is still imperative.

The Future of Chemotherapy for Pituitary Tumors

To better understand the indications for cytotoxic chemotherapy, controlled prospective data is needed with attention to the subtypes of pituitary cancers that most often develop an invasive phenotype and the biomarkers that may be predictive of response. Because these tumors are uncommon, it may be necessary to establish a referral center of excellence or involve cooperative groups in order to develop clinical trials that assess the efficacy of chemotherapy for this disease.

Case reports and case series of temozolomide have been encouraging, but there are many unanswered questions about the use of this drug for invasive pituitary cancers. In most case reports, patients received a standard dose of temozolomide [12], but it is unclear whether this is the optimal dosing schedule for pituitary tumors or if an alternative schedule such as continuous daily dosing or dose-dense treatment may be better. The duration of therapy is also unknown. In glioblastoma, 6 months of adjuvant temozolomide is recommended, but in practice temozolomide may be continued for 12, 18, or 24 cycles or longer. In several reports patients who initially had a response to temozolomide had recurrent disease after the temozolomide was stopped [11, 25]. A prospective trial could better establish the duration of treatment as well as the duration of response.

Combinations of temozolomide with anti-angiogenic therapy, targeted therapy (such as PIK3/mTOR inhibitors), and hormonal therapy need to be studied to determine the safety and clinical efficacy in pituitary tumors. We had observed that after an initial response to temozolomide, recurrent pituitary carcinoma may be resistant to additional treatment with temozolomide [11]. Patients with relapsed pituitary carcinoma who remain fit enough for therapy are rare, so designing clinical trials for this small population of patients is challenging, but this may be a population that benefits from combination therapy or from anti-angiogenic therapy. Invasive pituitary tumors are known to express VEGF, but there is only one case report of treating a patient with bevacizumab [39]. Larger studies may be able to confirm therapeutic benefit.

Some studies have started to elucidate the genetic contributors of invasiveness in pituitary cancers, but more data is needed to understand the pathways and mutations that drive tumor growth and invasion. Pituitary tumors are a heterogeneous group of tumors with different cells of origin and variable hormonal secretory status. With histologic diagnostic tools, it is not possible to predict which of these tumors are likely to become invasive or refractory to standard treatments. Molecular profiling and genotyping may be able to identify drivers of invasiveness and help to predict the tumors likely to transform to a malignant phenotype. With increased understanding of the molecular biology of pituitary cancers, we may be able to identify therapeutic targets.

Conclusions

Invasive pituitary adenomas and pituitary carcinomas are rare tumors that are often resistant to radiation and hormonal therapy and are surgically unresectable. Early clinical experience suggests that a majority of these tumors may respond to

chemotherapy with temozolomide. Limited molecular data points to some oncogenic pathways that may provide other targets for treatment. Though challenging to design, clinical trials are needed to optimize treatment in a way that can predictably improve patient outcomes.

References

1. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. Neuro-Oncology. 2015;17 Suppl 4:iv1–iv62.
2. Pernicone PJ, Scheithauer BW, Sebo TJ, et al. Pituitary carcinoma: a clinicopathologic study of 15 cases. Cancer. 1997;79(4):804–12.
3. Di Ieva A, Rotondo F, Syro LV, Cusimano MD, Kovacs K. Aggressive pituitary adenomas – diagnosis and emerging treatments. Nat Rev Endocrinol. 2014;10(7):423–35.
4. Raverot G, Castinetti F, Jouanneau E, et al. Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. Clin Endocrinol. 2012;76(6):769–75.
5. Dudziak K, Honegger J, Bornemann A, Horger M, Mussig K. Pituitary carcinoma with malignant growth from first presentation and fulminant clinical course – case report and review of the literature. J Clin Endocrinol Metab. 2011;96(9):2665–9.
6. Kaltsas GA, Grossman AB. Malignant pituitary tumours. Pituitary. 1998;1(1):69–81.
7. George DH, Scheithauer BW, Kovacs K, et al. Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. Am J Surg Pathol. 2003;27(10):1330–6.
8. Asai A, Matsutani M, Funada N, Takakura K. Malignant growth hormone-secreting pituitary adenoma with hematogenous dural metastasis: case report. Neurosurgery. 1988;22(6 Pt 1):1091–4.
9. Kaltsas GA, Mukherjee JJ, Plowman PN, Monson JP, Grossman AB, Besser GM. The role of cytotoxic chemotherapy in the management of aggressive and malignant pituitary tumors. J Clin Endocrinol Metab. 1998;83(12):4233–8.
10. Laws ER Jr, Morris AM, Maartens N. Gliadel for pituitary adenomas and craniopharyngiomas. Neurosurgery. 2003;53(2):255–69; discussion 259–60.
11. Fadul CE, Kominsky AL, Meyer LP, et al. Long-term response of pituitary carcinoma to temozolomide. Report of two cases. J Neurosurg. 2006;105(4):621–6.
12. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
13. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997–1003.
14. Lim S, Shahinian H, Maya MM, Yong W, Heaney AP. Temozolomide: a novel treatment for pituitary carcinoma. Lancet Oncol. 2006;7(6):518–20.
15. Syro LV, Uribe H, Penagos LC, et al. Antitumour effects of temozolomide in a man with a large, invasive prolactin-producing pituitary neoplasm. Clin Endocrinol. 2006;65(4):552–3.
16. Mohammed S, Kovacs K, Mason W, Smyth H, Cusimano MD. Use of temozolomide in aggressive pituitary tumors: case report. Neurosurgery. 2009;64(4):E773–774; discussion E774.
17. Kovacs K, Horvath E, Syro LV, et al. Temozolomide therapy in a man with an aggressive prolactin-secreting pituitary neoplasm: morphological findings. Hum Pathol. 2007;38(1):185–9.
18. Zhong C, Yin S, Zhou P, Jiang S. Pituitary atypical adenoma or carcinoma sensitive to temozolomide combined with radiation therapy: a case report of early identification and management. Turk Neurosurg. 2014;24(6):963–6.
19. Annamalai AK, Dean AF, Kandasamy N, et al. Temozolomide responsiveness in aggressive corticotroph tumours: a case report and review of the literature. Pituitary. 2012;15(3):276–87.

20. Ghazi AA, Rotondo F, Kovacs K, et al. Treatment of invasive silent somatotroph pituitary adenoma with temozolomide. Report of a case and review of the literature. Endocr Pathol. 2015;26(2):135–9.
21. Ortiz LD, Syro LV, Scheithauer BW, et al. Temozolomide in aggressive pituitary adenomas and carcinomas. Clinics (Sao Paulo). 2012;67(Suppl 1):119–23.
22. Raverot G, Sturm N, de Fraipont F, et al. Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. J Clin Endocrinol Metab. 2010;95(10):4592–9.
23. Bush ZM, Longtine JA, Cunningham T, et al. Temozolomide treatment for aggressive pituitary tumors: correlation of clinical outcome with O(6)-methylguanine methyltransferase (MGMT) promoter methylation and expression. J Clin Endocrinol Metab. 2010;95(11):E280–90.
24. Losa M, Mazza E, Terreni MR, et al. Salvage therapy with temozolomide in patients with aggressive or metastatic pituitary adenomas: experience in six cases. Eur J Endocrinol. 2010;163(6):843–51.
25. Losa M, Bogazzi F, Cannavo S, et al. Temozolomide therapy in patients with aggressive pituitary adenomas or carcinomas. J Neurooncol. 2016;126(3):519–25.
26. Campdera M, Palacios N, Aller J, et al. Temozolomide for aggressive ACTH pituitary tumors: failure of a second course of treatment. Pituitary. 2016;19(2):158–66.
27. Murakami M, Mizutani A, Asano S, et al. A mechanism of acquiring temozolomide resistance during transformation of atypical prolactinoma into prolactin-producing pituitary carcinoma: case report. Neurosurgery. 2011;68(6):E1761–7; discussion E1767.
28. Zacharia BE, Gulati AP, Bruce JN, et al. High response rates and prolonged survival in patients with corticotroph pituitary tumors and refractory Cushing disease from capecitabine and temozolomide (CAPTEM): a case series. Neurosurgery. 2014;74(4):E447–55; discussion E455.
29. Thearle MS, Freda PU, Bruce JN, Isaacson SR, Lee Y, Fine RL. Temozolomide (Temodar(R)) and capecitabine (Xeloda(R)) treatment of an aggressive corticotroph pituitary tumor. Pituitary. 2011;14(4):418–24.
30. Gulati AP, Krantz B, Moss RA, et al. Treatment of multiple endocrine neoplasia 1/2 tumors: case report and review of the literature. Oncology. 2013;84(3):127–34.
31. Liu JK, Patel J, Eloy JA. The role of temozolomide in the treatment of aggressive pituitary tumors. J Clin Neurosci. 2015;22(6):923–9.
32. Salehi F, Scheithauer BW, Kros JM, et al. MGMT promoter methylation and immunoexpression in aggressive pituitary adenomas and carcinomas. J Neuro-Oncol. 2011;104(3):647–57.
33. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nat Rev Neurol. 2010;6(1):39–51.
34. Bengtsson D, Schroder HD, Andersen M, et al. Long-term outcome and MGMT as a predictive marker in 24 patients with atypical pituitary adenomas and pituitary carcinomas given treatment with temozolomide. J Clin Endocrinol Metab. 2015;100(4):1689–98.
35. Kulke MH, Hornick JL, Frauenhoffer C, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. Clin Cancer Res. 2009;15(1):338–45.
36. Moshkin O, Syro LV, Scheithauer BW, et al. Aggressive silent corticotroph adenoma progressing to pituitary carcinoma: the role of temozolomide therapy. Hormones (Athens). 2011;10(2):162–7.
37. Salehi F, Scheithauer BW, Moyes VJ, et al. Low immunohistochemical expression of MGMT in ACTH secreting pituitary tumors of patients with Nelson syndrome. Endocr Pathol. 2010;21(4):227–9.
38. Wang Y, Li J, Tohti M, et al. The expression profile of dopamine D2 receptor, MGMT and VEGF in different histological subtypes of pituitary adenomas: a study of 197 cases and indications for the medical therapy. J Exp Clin Cancer Res. 2014;33:56.
39. Ortiz LD, Syro LV, Scheithauer BW, et al. Anti-VEGF therapy in pituitary carcinoma. Pituitary. 2012;15(3):445–9.
40. Bode H, Seiz M, Lammert A, et al. SOM230 (pasireotide) and temozolomide achieve sustained control of tumour progression and ACTH secretion in pituitary carcinoma with widespread metastases. Exp Clin Endocrinol Diabetes. 2010;118(10):760–3.

41. Ceccato F, Lombardi G, Manara R, et al. Temozolomide and pasireotide treatment for aggressive pituitary adenoma: expertise at a tertiary care center. J Neuro-Oncol. 2015;122(1):189–96.
42. Dai C, Zhang B, Liu X, et al. Inhibition of PI3K/AKT/mTOR pathway enhances temozolomide-induced cytotoxicity in pituitary adenoma cell lines in vitro and xenografted pituitary adenoma in female nude mice. Endocrinology. 2013;154(3):1247–59.
43. Neff LM, Weil M, Cole A, et al. Temozolomide in the treatment of an invasive prolactinoma resistant to dopamine agonists. Pituitary. 2007;10(1):81–6.
44. Hagen C, Schroeder HD, Hansen S, Hagen C, Andersen M. Temozolomide treatment of a pituitary carcinoma and two pituitary macroadenomas resistant to conventional therapy. Eur J Endocrinol. 2009;161(4):631–7.
45. McCormack AI, McDonald KL, Gill AJ, et al. Low O6-methylguanine-DNA methyltransferase (MGMT) expression and response to temozolomide in aggressive pituitary tumours. Clin Endocrinol. 2009;71(2):226–33.
46. Dillard TH, Gultekin SH, Delashaw Jr JB, Yedinak CG, Neuwelt EA, Fleseriu M. Temozolomide for corticotroph pituitary adenomas refractory to standard therapy. Pituitary. 2011;14(1):80–91.
47. Whitelaw BC, Dworakowska D, Thomas NW, et al. Temozolomide in the management of dopamine agonist-resistant prolactinomas. Clin Endocrinol. 2012;76(6):877–86.
48. Batisse M, Raverot G, Maqdasy S, et al. Aggressive silent GH pituitary tumor resistant to multiple treatments, including temozolomide. Cancer Investig. 2013;31(3):190–6.
49. Hirohata T, Asano K, Ogawa Y, et al. DNA mismatch repair protein (MSH6) correlated with the responses of atypical pituitary adenomas and pituitary carcinomas to temozolomide: the national cooperative study by the Japan Society for Hypothalamic and Pituitary Tumors. J Clin Endocrinol Metab. 2013;98(3):1130–6.
50. Zemmoura I, Wierinckx A, Vasiljevic A, Jan M, Trouillas J, Francois P. Aggressive and malignant prolactin pituitary tumors: pathological diagnosis and patient management. Pituitary. 2013;16(4):515–22.
51. Asimakopoulou A, Tzanela M, Koletti A, Kontogeorgos G, Tsagarakis S. Long-term remission in an aggressive Crooke cell adenoma of the pituitary, 18 months after discontinuation of treatment with temozolomide. Clin Case Rep. 2014;2(1):1–3.
52. Bruno OD, Juarez-Allen L, Christiansen SB, et al. Temozolomide therapy for aggressive pituitary tumors: results in a small series of patients from Argentina. Int J Endocrinol. 2015;2015:587893.
53. Kurowska M, Nowakowski A, Zielinski G, et al. Temozolomide-induced shrinkage of invasive pituitary adenoma in patient with Nelson's syndrome: a case report and review of the literature. Case Rep Endocrinol. 2015;2015:623092.
54. Strowd R, Salvatori R, Laterra J. Temozolomide retreatment in a recurrent prolactin-secreting pituitary adenoma: hormonal and radiographic response. J Oncol Pharm Pract. 2016;22(3):517–22.
55. Byrne S, Karapetis C, Vrodos N. A novel use of temozolomide in a patient with malignant prolactinoma. J Clin Neurosci. 2009;16(12):1694–6.
56. Takeshita A, Inoshita N, Taguchi M, et al. High incidence of low O(6)-methylguanine DNA methyltransferase expression in invasive macroadenomas of Cushing's disease. Eur J Endocrinol. 2009;161(4):553–9.
57. Curto L, Torre ML, Ferrau F, et al. Temozolomide-induced shrinkage of a pituitary carcinoma causing Cushing's disease – report of a case and literature review. ScientificWorldJournal. 2010;10:2132–8.
58. Jouanneau E, Wierinckx A, Ducray F, et al. New targeted therapies in pituitary carcinoma resistant to temozolomide. Pituitary. 2012;15(1):37–43.
59. Philippon M, Morange I, Barrie M, et al. Long-term control of a MEN1 prolactin secreting pituitary carcinoma after temozolomide treatment. Ann Endocrinol (Paris). 2012;73(3):225–9.
60. Vieira Neto L, Chimelli L, Pereira PJ, et al. The role of temozolomide in the treatment of a patient with a pure silent pituitary somatotroph carcinoma. Endocr Pract. 2013;19(6):e145–9.