

REVIEW

How and when to use temozolomide to treat aggressive pituitary tumours

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Abstract

Temozolomide is an oral chemotherapy used to treat aggressive pituitary tumours since 2006. It is inexpensive and well tolerated, the main side effects are fatigue, nausea and cytopenia. Overall the studies demonstrate approximately 70% response rate for temozolomide, if response is defined radiologically as complete, partial response or stable disease. Using the more stringent criteria of complete or partial response, the success rate is near 40%. Functioning tumours respond more frequently than non-functioning tumours. Tumours which are depleted of methyl guanine methyltransferase (MGMT), as assessed by immunohistochemistry, also are more likely to respond. Temozolomide has an established role in treating pituitary tumours which have demonstrated metastases or which are refractory and progressing, despite all conventional treatment (so-called salvage treatment). The challenge is to offer temozolomide earlier in the pathway if appropriate. Tumours which demonstrate aggressive clinical behaviour (defined as clinically relevant growth despite optimal treatment) should be considered for temozolomide. One common situation when this might occur is tumour progression after surgery and radiotherapy. It is unnecessary to wait until salvage treatment is required. Anticipated (but not yet demonstrated) aggressive behaviour can be regarded as a potential indication for temozolomide, but there is currently insufficient evidence to recommend this. Ideally a trial should assess this potential indication. Early treatment could be considered in selected cases when high levels of proliferation and invasion were demonstrated, causing significant clinical concern.

Key Words

- ▶ pituitary tumour
- ▶ aggressive
- ▶ temozolomide
- ▶ methyl guanine methyltransferase (MGMT)

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Temozolomide is an oral chemotherapy which has an established role in treating glioblastoma multiforme (GBM) and has since 2006 been used to treat aggressive and malignant pituitary tumours (O'Reilly *et al.* 1993, Raverot *et al.* 2012, Syro *et al.* 2018). The clinical experience has grown over that time and there has been evolving evidence for temozolomide from case reports to case series and most recently a meta-analysis

(Raverot *et al.* 2018) and an international survey of clinical practice (McCormack *et al.* 2018).

Mechanism of action

Temozolomide is an alkylating agent. It works by covalently attaching a methyl group to guanine bases within the DNA of a tumour. This causes mispairing of the DNA during cell replication and, through the action of the

mismatch repair system, leads to tumour cell apoptosis and tumour regression (Syro *et al.* 2018).

The intracellular enzyme methyl guanine methyltransferase (MGMT) acts as a repair mechanism to remove the methyl group from guanine bases and to therefore counteract the effects of temozolomide. MGMT is sometimes referred to as a suicide enzyme because in the process of removing the methyl group, the molecule of enzyme is destroyed. MGMT is ubiquitously expressed in cells but sometimes cells express low levels of this enzyme.

Evidence of clinical efficacy

There have been several case series of temozolomide-treated pituitary tumours published in the past decade (Bush *et al.* 2010, Raverot *et al.* 2010, Hirohata *et al.* 2013, Bengtsson *et al.* 2015, Bruno *et al.* 2015, Ceccato *et al.* 2015, Losa *et al.* 2016, Lasolle *et al.* 2017). They demonstrate that temozolomide is an effective treatment. If we define a clinically successful outcome as achieving either a complete response, partial response or stable disease, then the studies, overall, demonstrate a 69% success rate for temozolomide (Table 1). The recent international survey of temozolomide use for pituitary tumours reported a success rate of 70% by these criteria (McCormack *et al.* 2018).

If we use a more stringent standard for clinical success and include only cases which have shown clear tumour volume reduction (complete response or partial response), then the success rate from the studies is about 40%. Aggregating figures from nine recent case series (Table 1) gives an overall response of 42%. There was a recently published meta-analysis of a selection of cases which concluded that 47% of cases show significant tumour volume reduction (Raverot *et al.* 2018). The international survey showed 37% of cases

demonstrated tumour volume reduction (McCormack *et al.* 2018).

Data from the French pituitary series was used to analyse overall survival in patients treated with temozolomide (Lasolle *et al.* 2017). The patients who responded to temozolomide had a median survival of 44 months, whereas non-responders had a median survival of 16 months. This finding emphasises that temozolomide treatment, when associated with a tumour response, greatly increases the chance of a significantly improved outcome.

Side effects

Clinically relevant side effects occur in about 20% of patients taking temozolomide (McCormack *et al.* 2018). The main side effects are fatigue, nausea, with or without vomiting, and cytopenia, including leukopenia, thrombocytopenia or combination. The cytopenia is normally transient and can often be managed by delaying the next cycle and/or using a dose reduction. Cessation of temozolomide due to severe cytopenia is reasonably rare but most case series report at least one example of this occurring (Bruno *et al.* 2015, Losa *et al.* 2016, Lasolle *et al.* 2017).

The effect of temozolomide on fertility is uncertain but, as with other chemotherapy agents, there is some risk of gonadal toxicity which is difficult to quantify. If clinically relevant, fertility consultation and sperm or oocyte/embryo preservation should be considered (Raverot *et al.* 2018).

Severe side effects from temozolomide are rare and have not been reported in the group of pituitary tumours treated. They include aplastic anaemia, acute liver injury, Stevens–Johnson syndrome (Syro *et al.* 2018). There is thought to a very low long-term risk of haematological malignancy from temozolomide use, with the risk

Table 1 Case series reporting radiological tumour response to temozolomide.

Author	Year	Location	Number of cases	Response rate (CR, PR SD) (%)	Response rate (CR, PR) (%)
Lasolle	2017	France	43	51	51
Losa	2016	Italy	31	81	35
Bengtsson	2015	Sweden	24	48	46
Hirohata	2013	Japan	13	85	69
Raverot	2010	France	8	38	38
Bush	2010	Virginia, USA	7	86	29
Losa	2010	Milan, Italy	6	67	33
Bruno	2015	Argentina	6	33	33
Ceccato	2015	Padua, Italy	5	60	40

estimated as 1 in 10,000 persons treated (Kim *et al.* 2009, Chou *et al.* 2014).

Case selection: can we identify which tumours will respond?

The published data indicate that aggressive pituitary tumours and pituitary carcinoma have the same response rate to temozolomide treatment (Raverot *et al.* 2018). This is surprising since one might expect carcinoma to be more difficult to treat and to be less responsive.

The case series show that functioning tumours, especially prolactinomas and corticotroph tumours, have a better response to temozolomide (Halevy & Whitelaw 2017). Conversely non-functioning tumours are less likely to respond to temozolomide.

From an understanding of the mechanism of action of temozolomide and from parallel clinical experience in GBM we would expect pituitary tumours which are depleted of MGMT and which have normal functioning mismatch repair (MMR) proteins to show an optimal response to treatment. This has been investigated by several studies with some partially contradictory results.

It is agreed that MGMT status of pituitary tumours needs to be assessed by direct immunohistochemistry (Raverot *et al.* 2018). The indirect method of assessment using promoter methylation status, while useful in GBM, is not helpful in pituitary tumours (McCormack *et al.* 2011).

The initial case reports and analysis of small series do indicate an association between low% MGMT immunostaining and response to temozolomide (Kovacs *et al.* 2008, McCormack *et al.* 2009). This is also the finding of a large Swedish study (Bengtsson *et al.* 2015) and is supported by both a review of 99 cases from the literature (Raverot *et al.* 2018) and also an international survey of temozolomide cases (McCormack *et al.* 2018).

Conversely the French series did not find an association between MGMT status and temozolomide response (Lasolle *et al.* 2017). Only a subgroup of patients in that series 13/43 had MGMT immunohistochemistry assessed; nevertheless, it has raised doubt over the clinical use of MGMT to predict temozolomide response.

The 2018 guidelines recommend that MGMT immunohistochemistry is assessed in patients in whom temozolomide therapy is being considered (Raverot *et al.* 2018). This may enable them to be stratified into a category of more likely or less likely to respond; however, there are exceptions and, at present, patients should not

be denied a trial of temozolomide therapy solely on the basis of unfavourable MGMT status. Future treatment algorithms may suggest treatment adjustment on the basis of MGMT status.

The other histological markers which might predict response to temozolomide are the proteins which form the mismatch repair (MMR) system, particularly MSH2 (mutS homolog 2) and MSH6 (mutS homolog6). It would be predicted that an intact MMR system would be needed for temozolomide to have an effective response. A Japanese case series demonstrated that MSH6 immunohistochemistry predicted temozolomide treatment response (Hirohata *et al.* 2013). However the Swedish case series did not replicate this finding and so it remains an open question as to whether MSH2 and MSH6 are useful for predicting temozolomide response.

Case selection: when in the clinical pathway should temozolomide be used?

If we attempt to describe the phases of treatment of a pituitary tumour – the early phase would include initial presentation and initial management: often medical management, initial surgery and perhaps radiotherapy. For many pituitary tumours there will be no need for tumour management beyond this first phase.

A second phase (or middle phase) could be where a tumour, after initial treatment(s), demonstrates progression and/or recurrence requiring additional treatment which currently is often additional surgery and/or radiotherapy.

The late phase is the management of an advanced tumour when the pituitary tumour has perhaps shown metastatic spread or is refractory to multiple surgery and radiotherapy. This includes salvage therapy when all other standard treatments are felt to be exhausted.

Many of the initial case reports relate to this late phase. They explicitly use the term ‘salvage treatment’ to convey that temozolomide was being used for progressive disease after all conventional treatments have been tried and failed (Losa *et al.* 2010). Temozolomide has been shown to be effective in this context and now has an established role in the management of advanced pituitary tumours, the late phase of management in the scheme outlined above. This is reflected in some recent guidelines: including the European guidelines on aggressive pituitary tumours which name temozolomide as the first-line chemotherapy for pituitary carcinoma (Raverot *et al.* 2018). Temozolomide is also suggested as a treatment

for malignant prolactinoma in the Endocrine Society guidelines on prolactinoma management (Melmed *et al.* 2011). Temozolomide is recognised to be 'the best therapy of last resort' (Syro *et al.* 2018).

The use of temozolomide earlier in the treatment pathway has recently been suggested (Lin *et al.* 2016). European Society of Endocrinology clinical practice guidelines defined an aggressive pituitary tumour as one which shows clinically relevant growth despite optimal treatment (Raverot *et al.* 2018). They offer the alternative definition: radiologically invasive tumour with rapid growth. The same guidelines indicate that temozolomide is the first-line chemotherapy for treating this type of tumour, but they do not make the indication for treatment totally explicit (Raverot *et al.* 2018). However, it is reasonable to offer temozolomide treatment on the basis that a tumour has demonstrated aggressive behaviour, meaning growth despite optimal initial treatment. Recent expert reviews propose the use of temozolomide in tumours which show growth after surgery and radiotherapy (Syro *et al.* 2011, 2018, Lin *et al.* 2016).

Using temozolomide even earlier in the treatment pathway is rare and is not currently part of standard clinical practice. There are reasons it might be considered advantageous but also potential disadvantages (see below). The potential indication for early use of temozolomide is anticipated future aggressive behaviour based on radiological and histological assessment.

The grading system for pituitary tumours, developed by Trouillas and colleagues, offers a method of evaluating both invasion and proliferation to predict future recurrence or progression (Trouillas *et al.* 2013). Invasion is primarily evaluated by MRI (defined as significant cavernous sinus or sphenoid sinus invasion). Proliferation is evaluated by increased Ki67, p53 expression and/or mitoses. The overall grade is determined by whether the tumours are invasive (1 or 2) and/or proliferative (a or b). The combination of both invasion and proliferation (grade 2b) strongly predicts recurrence or progression (Asioli *et al.* 2019).

This grading system can identify a high-risk subgroup of pituitary tumours with anticipated future aggressive behaviour. A high-grade tumour (e.g. grade 2b) with a significant residual after initial surgery should be considered for additional treatment, normally radiotherapy but under some circumstances temozolomide might be considered.

Case examples of early (anticipatory) treatment with temozolomide are relatively rare. One case (case 1 from series) shows a corticotroph adenoma with very elevated Ki67 (50%) treated with surgery and both radiotherapy

and temozolomide in quick succession (Bengtsson *et al.* 2015). It appears, in that case, that temozolomide is offered on the basis of anticipated aggressive future behaviour. Another series shows two prolactinoma tumours, resistant to dopamine agonist therapy, treated with first surgery and then temozolomide due to a need for tumour control, in preference to radiotherapy and in anticipation of aggressive future behaviour (Whitelaw *et al.* 2012).

The largest published case series (Lasolle *et al.* 2017) reports that a short interval between diagnosis and temozolomide initiation is associated with a positive response to temozolomide. This finding relates to a heterogeneous group of 43 cases but in general suggests earlier temozolomide treatment may be associated with better outcomes and therefore is not harmful.

One of the advantages of considering temozolomide early in the treatment pathway is the possibility of combining treatment with radiotherapy (such as in the Stupp protocol). There is some evidence that concurrent use of temozolomide and radiotherapy gives better outcomes (Raverot *et al.* 2018).

Conversely it can be argued that the early use of temozolomide is potentially unnecessary and/or harmful. By intervening early, on the basis of anticipated future progression and recurrence, there are a proportion of patients who will have received temozolomide chemotherapy but might never have required it, had they been managed more conservatively. Temozolomide is well tolerated but its use exposes patients to the small risk of rare serious side effects.

There is no indication in the literature that temozolomide promotes aggressive tumour behaviour and the extent to which temozolomide promotes tumour epigenetic methylation or tumour mutation is uncertain (Barciszewska *et al.* 2015, Lin *et al.* 2018). Theoretically the early use of chemotherapy (or radiotherapy) treatment agents could encourage mutation or hypermethylation of a tumour which might have an adverse effect on their clinical behaviour and response to future treatments. This would be an argument for reserving temozolomide treatment for later, rather than early, use in the treatment pathway.

There are some other rarer situations in which temozolomide might be considered. A frail patient with co-morbidity who was thought to be unsuitable for surgery and radiotherapy but who was perhaps losing vision and independence due to tumour progression could be offered temozolomide as a first-line therapy with the aim of restoring or protecting vision and promoting independence (Halevy & Whitelaw 2017).

In summary, there are four broad areas of potential indication for temozolomide treatment (shown in Table 2). The late stage indication of salvage and/or metastases (C) is well established. The earlier indication of demonstrated aggression (B) is becoming accepted as an indication, which is a welcome development and means patients do not need to wait to a salvage phase (all other treatment exhausted) before being offered temozolomide.

Anticipated (but not yet demonstrated) aggression (A) remains a controversial potential indication which is not currently part of general clinical practice. It could be argued that, in selected cases, where a tumour showed both invasion and proliferation, temozolomide could be offered early to avoid losing tumour control and to potentially allow for combined treatment with radiotherapy. Conversely, there is no evidence base for this early intervention at present. Surveillance for aggressive clinical behaviour is the current standard practice and would minimise iatrogenic harm.

The fourth group of other indications (X) represent special cases such as problematic hormone hypersecretion and/or frail patients with co-morbidity.

What is the relapse rate?

Despite a good initial response to temozolomide therapy some case series have demonstrated a high relapse rate (Losa *et al.* 2016). For example 10/22 cases show relapse in a large French series with 14–16 months median follow-up (Lasolle *et al.* 2017). However the same series shows that, despite the relapse rate, temozolomide responders overall have a significantly better median survival of 44 months,

compared with 16 months for non-responders. Conversely other series have not identified high relapse rates (Bengtsson *et al.* 2015).

Practical aspects of temozolomide use

Temozolomide is an oral medication. The standard dose is 200 mg/m² per day for 5 days. This delivers one cycle of temozolomide and the cycles are normally repeated every 28 days. This dose is recommended in the ESE guidelines (Raverot *et al.* 2018). During each cycle safety blood tests are performed to assess for cytopenia or other side effects or toxicity. Clinical assessment is made of side effects and patients are normally given antiemetics to take at least during the 5 days that they take temozolomide. If patients develop cytopenia then they normally have a delay in taking the next cycle of temozolomide and sometimes a dose reduction is considered.

The initial tumour response after 3 months of temozolomide is strongly predictive of overall response (Lasolle *et al.* 2017). Therefore after three cycles, repeat neuroimaging (MRI scan) is performed to assess the radiological response (Raverot *et al.* 2018). If prior to this there is clear clinical progression or new symptoms of progression a decision may be taken to scan earlier and/or to discontinue treatment. If the initial scan shows either stable disease or a response then further cycles will be given, normally completing 12 cycles in total.

The ESE guidelines advise giving at least six cycles of treatment (Raverot *et al.* 2018) but internationally there is a preference to give 12 or more cycles in patients

Table 2 Indications for temozolomide treatment.

Code	Indication	Strength of indication	Explanation	Comments
A	Anticipated aggression	Possible indication	Histological, clinical and/or radiological evidence of future risk of tumour progression and resistance to treatment	Normally after first surgery. May be offered as an alternative to radiotherapy (RT) if RT is declined or contra-indicated
B	Demonstrated aggression	Recommended indication	Histological, clinical and/or radiological evidence of tumour progression and resistance to treatment	Progression after surgery and radiotherapy is a common example
C	Salvage or Metastases	Established indication	The point when conventional therapy (surgery radiotherapy and medical treatments) has been exhausted Radiological evidence of metastatic tumour spread	'Last resort' after multiple surgery and radiotherapy interventions ± medical treatments
X	Other	Specific to circumstances	Primary therapy in a patient with multiple comorbidities Problematic hormone hypersecretion	

who are tolerating the medication and who appear to be showing some response (Lasolle *et al.* 2017, McCormack *et al.* 2018). The evidence for this is not strong. Some retrospective analysis indicates that longer term treatment (12 or more months) is associated with a trend towards better progression-free survival (Ji *et al.* 2016). However, it has been pointed out that this type of retrospective data is subject to survival bias, since non-responders and those who rapidly progress will discontinue temozolomide early (Lasolle *et al.* 2017).

Practice has also been influenced by the observation that re-challenge with temozolomide tends to be ineffective, encouraging a tendency to ensure the first course of temozolomide is substantial and increase the number of cycles offered during the primary course of treatment (Raverot *et al.* 2018).

The use of temozolomide concurrently with radiotherapy is appealing since there may be synergistic effect. This would involve either commencing temozolomide within 4 months of radiotherapy or possibly using the Stupp protocol (daily low-dose temozolomide given during 6 weeks of radiotherapy) (Raverot *et al.* 2018).

Who should prescribe temozolomide?

Temozolomide should be prescribed by a doctor who has the knowledge, competence and experience to appreciate the clinical indications for its use and who understands the side effect profile and toxicity. Because it is a chemotherapy it should be prescribed within the appropriate oncology governance structures. However the fact that it is oral and well tolerated means that it does not need to be administered by a chemotherapy specialist unit.

Within the United Kingdom, it is prescribed by both oncologists and endocrinologists provided the doctor has the appropriate training and experience. The decision to give temozolomide should be taken by a pituitary multidisciplinary team who have the experience to consider both whether temozolomide is an appropriate treatment and to consider the alternative surgical, radiotherapy and medical treatments (Raverot *et al.* 2018).

Training should be offered to endocrinologists and/or oncologists to ensure that they feel confident to consider temozolomide treatment in both the early and later phases of tumour management. Regional or national expert networks should be developed to allow for support with challenging cases.

Beyond temozolomide

If a tumour fails to respond to temozolomide or recurs after treatment, the next line therapy is unclear. Further surgery and radiotherapy will always be considered if appropriate and not exhausted. Repeat treatment with temozolomide has a generally disappointing clinical effect, review of the published cases showed 13 of 16 cases treated showed progression (Raverot *et al.* 2018).

Temozolomide in combination with capecitabine showed a good response in a case series of four patients with aggressive corticotroph adenomas (Zacharia *et al.* 2014). Three of the four cases (75%) showed complete or partial response to the treatment. However, this good clinical response may have been entirely due to temozolomide. Other case reports have shown no response to treatment with this combination and it is unclear whether there is any true advantage in adding capecitabine (Bengtsson *et al.* 2015). The current guidelines indicate temozolomide monotherapy remains first line (Raverot *et al.* 2018).

Knowledge of the MGMT and MSH status of the tumour might in the future allow for modification of the temozolomide regime to increase effectiveness. For example a tumour with high expression of MGMT might be treated with a dose-dense regime of temozolomide to deplete MGMT. The addition of an agent, such as withaferin A, to deplete MGMT has also been proposed but evidence for this is at a pre-clinical phase only (Grogan *et al.* 2014).

The current range of proposed treatments for temozolomide-resistant tumours has been recently reviewed and is summarised in Table 3 (Dworakowska & Grossman 2018).

The most promising recent case report concerns a 35-year-old woman with pituitary carcinoma (Lin *et al.* 2018). She had Cushing's syndrome and was treated with two surgical procedures, radiotherapy and multiple medical therapies. Temozolomide was used as monotherapy and then in combination with cabecitabine; however, there was progression of the primary tumour and liver metastases. Cushing's was controlled with bilateral adrenalectomy. The patient was then treated with two combined checkpoint inhibitors (ipilimumab and nivolumab) and showed a dramatic reduction in tumour volume. ACTH fell from 45,550pg/mL to 66pg/mL. Other studies have shown immunotherapy targets in pituitary tumours (Wang *et al.* 2018). Although very promising, the use of combination immunotherapy will need replication to see if it is consistently effective.

Table 3 Treatment options after temozolomide resistance.

Proposed treatment after temozolomide resistance	Notes
Repeat temozolomide	Unlikely to be effective
Repeat temozolomide with MGMT depletion	There is no established MGMT depletion agent currently
Temozolomide with capecitabine	Mixed results, see text
Pasireotide	Some case reports of tumour control
Radionuclide (PPRT)	Few case reports – some of stable disease others show rapid tumour progression
Cytotoxic chemotherapy – lomustine/5FU	Used in pre-temozolomide era. Response rate estimated 14%
Everolimus/octreotide	Not effective in one case report
Gefitinib/lapatinib	Case reports showing radiological and/or biochemical response (in ACTH and PRL tumours). Clinical trial results are pending.
Bevacizumab	Stable disease achieved in case reports
Nivolumab and ipilimumab	Dramatic response in one case report, see text

Conclusions

Temozolomide has established itself as the chemotherapy of choice for treatment of advanced pituitary tumours. It is effective and well tolerated. It is important to ensure pituitary MDTs feel confident to consider and initiate temozolomide treatment and are supported to do this. The point at which temozolomide treatment should be actively considered is when a tumour has demonstrated aggressive behaviour (meaning growth despite standard treatment). Often this time point will be when growth is seen after radiotherapy. It is unnecessary to wait until the point of salvage therapy when all other options are exhausted.

Anticipated (but not yet demonstrated) aggressive behaviour can be regarded as a potential indication for temozolomide, but there is currently insufficient evidence to recommend this. Ideally a trial should assess this potential indication. Treatment could be considered in selected cases when high levels of proliferation and invasion were demonstrated, causing significant clinical concern. One advantage of early identification of the potential need to use temozolomide is that concurrent use with radiotherapy becomes more of an option.

There is a need to develop and agree standardised methods of reporting MGMT and MSH tumour status, ideally on a prospective basis, to allow for the development of greater clinical understanding of the significance of these markers.

Clinical trials are needed and pending there establishment, national and international registries should continue to be promoted to facilitate our understanding of clinical practice and progress.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References

- Asioli S, Righi A, Iommi M, Baldovini C, Ambrosi F, Guaraldi F, Zoli M, Mazzatenta D, Faustini-Fustini M, Rucci P, *et al.* 2019 Validation of a clinicopathological score for the prediction of post-surgical evolution of pituitary adenoma: retrospective analysis on 566 patients from a tertiary care centre. *European Journal of Endocrinology* **180** 127–134. (<https://doi.org/10.1530/EJE-18-0749>)
- Barciszewska AM, Gurda D, Głodowicz P, Nowak S & Naskręć-Barciszewska MZ 2015 A new epigenetic mechanism of temozolomide action in glioma cells. *PLoS ONE* **10** e0136669. (<https://doi.org/10.1371/journal.pone.0136669>)
- Bengtsson D, Schroder HD, Andersen M, Maiter D, Berinder K, Feldt Rasmussen U, Rasmussen ÅK, Johannsson G, Hoybye C, van der Lely AJ, *et al.* 2015 Long-term outcome and MGMT as a predictive marker in 24 patients with atypical pituitary adenomas and pituitary carcinomas given treatment with temozolomide. *Journal of Clinical Endocrinology and Metabolism* **100** 1689–1698. (<https://doi.org/10.1210/jc.2014-4350>)
- Bruno OD, Juarez-Allen L, Christiansen SB, Manavela M, Danilowicz K, Vigovich C & Gomez RM 2015 Temozolomide therapy for aggressive pituitary tumors: results in a small series of patients from Argentina. *International Journal of Endocrinology* **2015** 1–8. (<https://doi.org/10.1155/2015/587893>)
- Bush ZM, Longtine JA, Cunningham T, Schiff D, Jane JA, Vance ML, Thorne MO, Laws ER & Lopes MB 2010 Temozolomide treatment for aggressive pituitary tumors: correlation of clinical outcome with O(6)-methylguanine methyltransferase (MGMT) promoter methylation and expression. *Journal of Clinical Endocrinology and Metabolism* **95** E280–E290. (<https://doi.org/10.1210/jc.2010-0441>)
- Ceccato F, Lombardi G, Manara R, Emanuelli E, Denaro L, Milanese L, Gardiman MP, Bertorelle R, Scanarini M, D'Avella D, *et al.* 2015 Temozolomide and pasireotide treatment for aggressive pituitary adenoma: expertise at a tertiary care center. *Journal of Neuro-Oncology* **122** 189–196. (<https://doi.org/10.1007/s11060-014-1702-0>)
- Chou KN, Lin YC, Liu MY & Chang PY 2014 Temozolomide-related acute lymphoblastic leukemia with translocation (4;11)(q21;q23) in a glioblastoma patient. *Journal of Clinical Neuroscience* **21** 701–704. (<https://doi.org/10.1016/j.jocn.2013.07.032>)
- Dworakowska D & Grossman AB 2018 Aggressive and malignant pituitary tumours: state-of-the-art. *Endocrine-Related Cancer* **25** R559–R575. (<https://doi.org/10.1530/ERC-18-0228>)

- Grogan PT, Sarkaria JN, Timmermann BN & Cohen MS 2014 Oxidative cytotoxic agent withaferin A resensitizes temozolomide-resistant glioblastomas via MGMT depletion and induces apoptosis through Akt/mTOR pathway inhibitory modulation. *Investigational New Drugs* **32** 604–617. (<https://doi.org/10.1007/s10637-014-0084-7>)
- Halevy C & Whitelaw BC 2017 How effective is temozolomide for treating pituitary tumours and when should it be used? *Pituitary* **20** 261–266. (<https://doi.org/10.1007/s11102-016-0745-y>)
- Hirohata T, Asano K, Ogawa Y, Takano S, Amano K, Isozaki O, Iwai Y, Sakata K, Fukuhara N, Nishioka H, *et al.* 2013 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. *Journal of Clinical Endocrinology and Metabolism* **98** 1130–1136. (<https://doi.org/10.1210/jc.2012-2924>)
- Ji Y, Vogel RI & Lou E 2016 Temozolomide treatment of pituitary carcinomas and atypical adenomas: systematic review of case reports. *Neuro-Oncology Practice* **3** 188–195. (<https://doi.org/10.1093/nop/npv059>)
- Kim SJ, Park TS, Lee ST, Song J, Suh B, Kim SH, Jang SJ, Lee CH & Choi JR 2009 Therapy-related myelodysplastic syndrome/acute myeloid leukemia after treatment with temozolomide in a patient with glioblastoma multiforme. *Annals of Clinical and Laboratory Science* **39** 392–398.
- Kovacs K, Scheithauer BW, Lombardero M, McLendon RE, Syro LV, Uribe H, Ortiz LD & Penagos LC 2008 MGMT immunorexpression predicts responsiveness of pituitary tumors to temozolomide therapy. *Acta Neuropathologica* **115** 261–262. (<https://doi.org/10.1007/s00401-007-0279-5>)
- Lasolle H, Cortet C, Castinetti F, Cloix L, Caron P, Delemer B, Desaillood R, Jublanc C, Lebrun-Frenay C, Sadoul JL, *et al.* 2017 Temozolomide treatment can improve overall survival in aggressive pituitary tumors and pituitary carcinomas. *European Journal of Endocrinology* **176** 769–777. (<https://doi.org/10.1530/EJE-16-0979>)
- Lin AL, Sum MW & Deangelis LM 2016 Is there a role for early chemotherapy in the management of pituitary adenomas? *Neuro-Oncology* **18** 1350–1356. (<https://doi.org/10.1093/neuonc/nov059>)
- Lin AL, Jonsson P, Tabar V, Yang TJ, Cuaron J, Beal K, Cohen M, Postow M, Rosenblum M, Shia J, *et al.* 2018 Marked response of a hypermutated ACTH-secreting pituitary carcinoma to ipilimumab and nivolumab. *Journal of Clinical Endocrinology and Metabolism* **103** 3925–3930. (<https://doi.org/10.1210/jc.2018-01347>)
- Losa M, Mazza E, Terreni MR, McCormack A, Gill AJ, Motta M, Cangi MG, Talarico A, Mortini P & Reni M 2010 Salvage therapy with temozolomide in patients with aggressive or metastatic pituitary adenomas: experience in six cases. *European Journal of Endocrinology* **163** 843–851. (<https://doi.org/10.1530/EJE-10-0629>)
- Losa M, Bogazzi F, Cannavo S, Ceccato F, Curto L, De Marinis L, Iacovazzo D, Lombardi G, Mantovani G, Mazza E, *et al.* 2016 Temozolomide therapy in patients with aggressive pituitary adenomas or carcinomas. *Journal of Neuro-Oncology* **126** 519–525. (<https://doi.org/10.1007/s11060-015-1991-y>)
- McCormack AI, McDonald KL, Gill AJ, Clark SJ, Burt MG, Campbell KA, Braund WJ, Little NS, Cook RJ, Grossman AB, *et al.* 2009 Low O6-methylguanine-DNA methyltransferase (MGMT) expression and response to temozolomide in aggressive pituitary tumours. *Clinical Endocrinology* **71** 226–233. (<https://doi.org/10.1111/j.1365-2265.2008.03487.x>)
- McCormack AI, Wass JA & Grossman AB 2011 Aggressive pituitary tumours: the role of temozolomide and the assessment of MGMT status. *European Journal of Clinical Investigation* **41** 1133–1148. (<https://doi.org/10.1111/j.1365-2362.2011.02520.x>)
- McCormack A, Dekkers OM, Petersenn S, Popovic V, Trouillas J, Raverot G, Burman P & ESE Survey Collaborators 2018 Treatment of aggressive pituitary tumours and carcinomas: results of a European Society of Endocrinology (ESE) survey 2016. *European Journal of Endocrinology* **178** 265–276. (<https://doi.org/10.1530/EJE-17-0933>)
- Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA & Endocrine Society 2011 Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* **96** 273–288. (<https://doi.org/10.1210/jc.2010-1692>)
- O'Reilly SM, Newlands ES, Brampton M, Glaser MG, Rice-Edwards JM, Illingworth RD, Richards PG, Kennard C, Colquhoun IR, Lewis P, *et al.* 1993 Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. *European Journal of Cancer* **29A** 940–942.
- Raverot G, Sturm N, De Fraipont F, Muller M, Salenave S, Caron P, Chabre O, Chanson P, Cortet-Rudelli C, Assaker R, *et al.* 2010 Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. *Journal of Clinical Endocrinology and Metabolism* **95** 4592–4599. (<https://doi.org/10.1210/jc.2010-0644>)
- Raverot G, Castinetti F, Jouanneau E, Morange I, Figarella-Branger D, Dufour H, Trouillas J & Brue T 2012 Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. *Clinical Endocrinology* **76** 769–775. (<https://doi.org/10.1111/j.1365-2265.2012.04381.x>)
- Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, Trouillas J, Dekkers OM & European Society of Endocrinology 2018 European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *European Journal of Endocrinology* **178** G1–G24. (<https://doi.org/10.1530/EJE-17-0796>)
- Syro LV, Ortiz LD, Scheithauer BW, Lloyd R, Lau Q, Gonzalez R, Uribe H, Cusimano M, Kovacs K & Horvath E 2011 Treatment of pituitary neoplasms with temozolomide: a review. *Cancer* **117** 454–462. (<https://doi.org/10.1002/cncr.25413>)
- Syro LV, Rotondo F, Ortiz LD & Kovacs K 2018 65 YEARS OF THE DOUBLE HELIX: Treatment of pituitary tumors with temozolomide: an update. *Endocrine-Related Cancer* **25** T159–T169. (<https://doi.org/10.1530/ERC-18-0015>)
- Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Viennet G, Bonneville JF, Assaker R, Auger C, Brue T, *et al.* 2013 A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. *Acta Neuropathologica* **126** 123–135. (<https://doi.org/10.1007/s00401-013-1084-y>)
- Wang PF, Wang TJ, Yang YK, Yao K, Li Z, Li YM & Yan CX 2018 The expression profile of PD-L1 and CD8(+) lymphocyte in pituitary adenomas indicating for immunotherapy. *Journal of Neuro-Oncology* **139** 89–95. (<https://doi.org/10.1007/s11060-018-2844-2>)
- Whitelaw BC, Dworakowska D, Thomas NW, Barazi S, Riordan-Eva P, King AP, Hampton T, Landau DB, Lipscomb D, Buchanan CR, *et al.* 2012 Temozolomide in the management of dopamine agonist-resistant prolactinomas. *Clinical Endocrinology* **76** 877–886. (<https://doi.org/10.1111/j.1365-2265.2012.04373.x>)
- Zacharia BE, Gulati AP, Bruce JN, Carminucci AS, Wardlaw SL, Siegelin M, Remotti H, Lignelli A & Fine RL 2014 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* **74** E447–E455; discussion E455. (<https://doi.org/10.1227/NEU.0000000000000251>)

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