Treatment of Aggressive Pituitary Adenomas and Carcinomas – An Overview

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Abstract

Most pituitary tumours are non-invasive, benign adenomas that remain confined to the sella turcica. Some of them recur, have a rapid growth rate, and invade surrounding tissues. These adenomas, considered aggressive pituitary tumours, are difficult to manage and present problems due to incomplete resection. A pituitary carcinoma is diagnosed when craniospinal and/or systemic metastases are documented. Treatment options for pituitary adenomas are surgery, radiation and drugs. Recent publications report the efficacy of temozolomide in the treatment of aggressive pituitary adenomas and carcinomas. Indications for, results with, and side effects of temozolomide therapy in aggressive pituitary tumours and pituitary carcinomas are reviewed here. Alternative treatment options for resistant or recurrent pituitary tumours are also discussed.

Keywords

Pituitary adenoma, pituitary carcinoma, O6-methylguanine-DNA methyltransferase (MGMT), temozolomide, everolimus, bevacizumab

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Most pituitary tumours are non-invasive, benign adenomas that remain confined to the sella turcica. Although there is, at present, no accepted definition of aggressive pituitary adenomas, one would suggest that these have a tendency to recur after initial surgery. They have a rapid growth rate and invade surrounding structures such as the sphenoid and cavernous sinus as well as the skull base bone. They are clinically difficult to manage and present major problems due to incomplete resection.[1]

Pituitary carcinomas are rare – 0.2 % of all pituitary tumours. They present major diagnostic and therapeutic challenges. They may initially appear as benign pituitary adenomas subsequently transforming into an aggressive neoplasm, or they may be aggressive tumours from the beginning.[2–4] A pituitary carcinoma is diagnosed when craniospinal and/or systemic metastases are documented.[5] Predicting pituitary tumour behaviour remains a real challenge. Studies suggest that increased mitotic activity, high Ki-67, nuclear labelling index and P53 expression might be associated with tumour progression.[3,5]

Multiple treatment approaches – including surgery, external beam radiotherapy, gamma knife, drugs and various chemotherapeutic agents – have been used. Until recently, the treatment of pituitary carcinomas was mainly palliative and did not seem to increase overall survival. Progression of disease after a diagnosis of pituitary carcinoma was variable; approximately 75 % of patients with systemic metastasis died of the disease within one year.[4] Recent publications report efficacy of temozolomide, an alkylating agent used to treat gliomas, in the management of aggressive pituitary adenomas and carcinomas.[6–36] As in gliomas, the outcome of treatment might depend on the expression of O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme that counteracts the action of temozolomide.[6,13,37]

Temozolomide

Temozolomide is an alkylating chemotherapeutic agent related to a series of imidazotetrazines. Orally administered, it readily crosses the blood–brain barrier. It exerts its cytotoxic effect through methylation of DNA at the O6 position of guanine,[38] which then mispairs with thymine during the next cycle of DNA replication. Temozolomide is accepted as an effective drug in the treatment of glioblastoma multiforme and other tumours of the central nervous system.[39] Recent reports point out its efficacy in malignant neuroendocrine neoplasms,[40] melanomas[41,42] and colorectal carcinomas.[43]

The standard therapeutic dose of temozolomide is 150–200 mg/m^2 on Days 1–5 of a 28-day cycle (5/28). Depletion of MGMT has been proposed as a means of tumour response to temozolomide.[44] Experimental and clinical data have shown that response to temozolomide is schedule-dependent and that alternative dosing

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regimens may enhance the drug's efficacy.[45,46] The antiangiogenic effect of the drug is optimised by administering low doses on a frequent or continuous schedule without extended interruptions ('metronomic' chemotherapy), thus achieving MGMT depletion and improving response. Thus the recommended dose is 50 mg/m^2/day without interruption over a 28-day cyle (28/28). Temozolomide absorption is minimally affected by food. Furthermore, no serious side effects have been reported when using temozolomide to treat patients with pituitary tumours. Common, non-haematologic adverse effects include nausea, vomiting, fatigue, headache and constipation, most of which are mild-to-moderate.

As previously stated, MGMT is a DNA repair protein reversing the effect of temozolomide[47] by removing alkylating adducts, counteracting its effect[48] and conferring resistance.[49] Low-level expression in a wide spectrum of human tumours is thought to result from epigenetic silencing, by hypermethylation of the *MGMT* gene promoter.[49,50] Low-level MGMT immunoexpression is considered a predictive and prognostic marker in patients with temozolomide-treated glioblastomas.[51] This observation has been extended to aggressive adenohypophysial tumours and carcinomas.[6,13,37]

Pituitary Carcinomas Treated with Temozolomide

Pituitary carcinomas are difficult to manage despite the use of various therapies, including repeated surgeries, radiation and drugs.[3,5,52] Initial reports of the successful use of temozolomide in pituitary carcinoma were published in 2006.[8,9]

To date, 20 cases have been treated.[8,9,16,19,20,24–26,28] The time between disease presentation and temozolomide administration varied between five and 23 years (mean time 10.7). The group included eight PRL-secreting, eight ACTH-secreting, three clinically non-functional, and one silent corticotroph carcinomas. Fourteen of the 20 patients (70 %) showed a clinical and radiological response to temozolomide.

Aggressive Pituitary Adenomas Treated with Temozolomide

After the successful treatment reports in pituitary carcinomas, the first case of a pituitary adenoma treated with temozolomide was reported in 2006.[10,11] The tumour, an aggressive prolactin (PRL)-secreting pituitary adenoma, with no MGMT immunoexpression, was investigated before and after temozolomide treatment by histology, immunohistochemistry and electron microscopy. Significant clinical improvement, tumour skrinkage, and morphological changes were evident. A 41-year-old patient with an aggressive silent subtype 2 corticotroph adenoma was subsequently described with no morphological changes after temozolomide treatment. In that tumour, the cell nuclei were immunopositive for MGMT. Based upon these results, it was suggested that MGMT immunoexpression may predict responsiveness to temozolomide therapy.[13]

To our knowledge, 32 cases of pituitary adenomas have been treated with temozolomide to date.[10–19,21–23,25–29,31,32,36] The patients' age varied from 20–71 years (mean age 51). Among the 32 cases, there were 11 PRL-secreting adenomas, 10 adrenocorticotropic hormone (ACTH)-secreting adenomas, seven clinically non-functioning adenomas, two silent ACTH adenomas and two growth hormone (GH)-secreting adenomas. The time between clinical presentation and introduction of temozolomide treatment was two to 23 years (mean time 10 years). Almost all tumours were irradiated and operated before starting temozolomide therapy. The rate of response to temozolomide was 62.5 % (20 of 32 patients).

Response to Treatment and Indications

In three out of 52 cases, morphological comparison was possible. These tumours had been investigated before and after temozolomide treatment. Two tumours responded to treatment temozolomide and showed haemorrhage, necrosis, focal fibrosis, inflammatory infiltration, fewer mitoses and a lower Ki-67 nuclear labelling index.[11,26] The third tumour showed no changes.[13]

In patients responding to temozolomide, the clinical response was rapid and associated with a fast decrease in tumour volume. In patients with PRL- and ACTH-secreting tumours, an almost immediate reduction of plasma hormone levels was seen after the commencement of therapy, allowing the rapid evaluation of treatment response. Three basic patterns of radiographic changes were described on magnetic resonance imaging: tumour necrosis and haemorrhage,[10,11] cystic change[22] and shrinkage.[12,14–17] Within two or three months, it was possible to assess the response to treatment based on clinical, biochemical and radiographic changes.

An inverse relationship between MGMT immunoexpression and response to temozolomide has been noted in several studies. Tumours with low-level MGMT immunoexpression showed a better clinical and radiologic response to temozolomide therapy than tumours with high-level MGMT immunoexpression.[6] Demonstration of MGMT immunoreactivity appears to be useful in identifying non-responders to temozolomide treatment. However, some studies concluded that MGMT immunoexpression is not reliable and does not properly predict success of temozolomide therapy. Therefore, due to these contradictory results and also to the lack of other available medications, temozolomide therapy may be introduced independently of MGMT status.[6,25]

Based on the published cases and the reported response rates, temozolomide therapy could be used in:

- aggressive PRL-secreting pituitary tumours resistant to bromocriptine or cabergoline that continue to grow after surgery and radiotherapy;[53]
- aggressive ACTH-secreting tumours – especially Crooke's cell neoplasms and Nelson's syndrome variants – not cured by surgery and radiotherapy;
- recurrent, clinically non-functional pituitary tumours exhibiting continued growth after repeated surgeries and radiotherapy; and
- pituitary carcinomas.

Due to the lack of long-term follow-up, it has not yet been possible to define the most appropriate dosing regimen or duration of treatment. In patients resistant to temozolomide, new targeted therapies have been proposed such as everolimus (a mammalian target of rapamycin inhibitor)[54] or bevacizumab (a recombinant, humanised, antivascular endothelial growth factor monoclonal antibody).[55]

Conclusion

Temozolomide has been proven to be of value in the treatment of aggressive pituitary adenomas and carcinomas. The clinical and radiologic response rates are encouraging – 62.5 % in aggressive pituitary adenomas and 70 % in pituitary carcinomas. According

to several reports, an inverse correlation exists between MGMT immunoexpression and therapeutic response to temozolomide. There are studies, however, that do not support this conclusion. Based upon published cases, a significant proportion of adenohypophysial tumours responsive to temozolomide show low-level MGMT immunoexpression. Due to the lack of other available medications, temozolomide may be used independently of MGMT status.

According to the earlier paradigm, every tumour cell is the same in every tumour. Recent evidence indicates tumour cell heterogeneity. Various parts of the tumour undergo mutations and not every tumour cell has the same genetic profile.[56] Thus some tumour cells will respond to chemotherapy while others will not. Despite tumour cell heterogeneity, we hope that, in the future, targeted and personalised therapies will be available for temozolomide-resistant patients.[57,58] ■

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