CASE REPORT

Temozolomide treatment of a pituitary carcinoma and two pituitary macroadenomas resistant to conventional therapy

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Abstract

Objective: Aggressive pituitary tumours may be difficult to treat. Temozolomide (TMZ) is an alkylating cytostaticum. In a small number of cases, TMZ therapy has been reported to reduce pituitary tumour size and hormone hypersecretion.

Design: We present three patients with pituitary tumours treated with TMZ. One tumour was initially a macroprolactinoma that developed into a mixed GH- and prolactin-secreting carcinoma (patient A). To our knowledge, this is the first published in English literature. Two adenomas, a macroprolactinoma (patient B) and a clinically non-functioning pituitary adenoma (patient C), were highly invasive. The three patients suffered from extensive tumour mass effects, and all tumours were resistant to conventional treatment.

Method: TMZ, 150–200 mg/m² of body surface area was administered orally for 5 days during each 28-day cycle.

Result: During TMZ therapy, tumour sizes were significantly reduced, hormone levels normalized and symptoms of mass effects decreased in all three cases. The carcinoma was treated from 2004 to 2006 (23 months). Three years after the terminating treatment, the tumour has not regrown and hormone levels are normalized. Immunohistochemical staining for methylguanine DNA methyltransferase (MGMT) was negative in two patients (A and B), and in one patient (C) a few nuclei stained positive.

Conclusion: TMZ therapy significantly decreased tumour volume, hormone hypersecretion and symptoms in all three patients, corresponding to the pathological findings regarding MGMT. TMZ therapy may be a new option for the treatment of resistant pituitary adenomas.

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Introduction

The behaviour of pituitary adenomas varies considerably, ranging from slow intrasellar growth through microscopic dural infiltration to radiographically and/or operatively apparent invasion (1). Transsphenoidal surgery is first line treatment of non-functioning pituitary adenomas (NFAs) causing mass effects (2). Adjunctive radiotherapy may be necessary in patients who experience significant tumour recurrence (3). NFAs contain dopamine (D2) and somatostatin receptors, but the effect of dopamine receptor agonist (DA) and somatostatin analogues (SSA) are limited when used separately (4). Recent data indicate that a combination of DA and SSA could be effective (5, 6). GH-secreting adenomas are usually treated with transsphenoidal surgery, which reduce hormone levels to acceptable levels in about 85% of microadenomas and in <60% of macroadenomas (7, 8). GH adenomas respond to SSA in about 70% of cases and to DA in about 15%, depending on the profile of hormone

hypersecretion (9). Pegvisomant efficiently decrease insulin-like growth factor 1 (IGF1) levels; however, tumour size is usually not decreased during therapy (10, 11). In most centres, radiotherapy is reserved for tumours resistant to surgery and pharmacological therapy (12).

The majority of macroprolactinomas respond well to cabergoline (13, 14). However, a few aggressive macroprolactinomas are resistant to conventional therapy (15). Radiotherapy is given to invasive adenomas that do not respond to pharmacological or surgical therapy (16). Resistance to DA may be defined as failure to normalize prolactin (PRL) levels and a tumour reduction <50% (17). Invasive macroprolactinomas developing DA resistance, indicate aggressive tumour biology and possibly future malignancy (18). Combined octreotide and cabergoline therapy may be efficient in DA-resistant macroprolactinomas (19).

With an incidence of 0.2% of symptomatic pituitary tumours, pituitary carcinomas are extremely rare. Given the rarity of pituitary carcinomas, there is no

consensus regarding treatment. Surgical excision, radiotherapy and hormonal treatment with DA, SSA and tamoxifen generally provide palliation only (20, 21). Long-term survival after conventional therapy has been reported (22, 23).

There has been partial and short-lasting responses to chemotherapy such as cyclophosphamide/adriamycin/5-fluorouracil (24), lomustin/procarbazine/etoposide (25, 26), 5-fluorouracil/adriamycin/cyclophosphamide (27), lomustin/adriamycin (28). Most carcinomas, however, respond poorly (29). Recently, a limited number of aggressive pituitary adenomas and carcinomas resistant to conventional treatment have been reported to respond to temozolomide (TMZ) therapy (Table 1) (30–36).

We present a pituitary carcinoma and two highly invasive macroadenomas, which were all resistant to conventional treatment. Tumour size and symptoms of mass effect were significantly reduced by TMZ in all three patients.

Methods

Pathology

Sections of 4 µm in thickness were cut from paraffin-embedded tissue and stained with hematoxylin and eosin. Immunohistochemical (IHC) stainings were performed using LSAB and Envision (Dako, Glostrup, Denmark) as detections systems. Antibodies directed against adrenocorticotropin (ACTH) (Dako-A0571), human growth hormone (hGH) (BioGenex, San Ramon, CA, USA, MU028-UC), PRL (Dako, A0569), luteinizing hormone (LH) (Dako M3502), follicle-stimulating hormone (FSH) (Dako, M3504), thyroid stimulating hormone (TSH) (Dako, M3503). α -subunit (Immunotech, Beckman Coulter, Fullerton CA, USA, 0375), Ki67 (Dako M7240), methylguanine DNA methyltransferase (MGMT; Neomarkers, Fremont, CA, USA, MS-470) were applied.

TMZ therapy

TMZ was administered by conventional schedule in all cases, i.e. 150–200 mg/m² of body surface area for 5 days during each 28-day cycle (37).

Case reports

Patient A

Initial examination and conventional treatment

A 48-year-old woman presented with visual disturbances, facial loss of sensibility, headache and nausea. Computed tomography of cerebrum (CTC) and elevated PRL indicated an invasive pituitary macroprolactinoma. Cabergoline (0.5 mg × 1 daily; month 1) had no effect, so transsphenoidal surgery was performed (month 3). After 5 months, patient A developed peripheral oedemas and arterial hypertension. GH and IGF1 levels were increased and sandostatin was administered (100 µg × 3 daily s.c.; start month 5) in combination with cabergoline. There was no significant response to the combined therapy. Radiotherapy was given (54 Gy, month 27) and medical therapy was continued. Clinical symptoms and hormone hypersecretion were reduced during the following years.

Eight and a half years after diagnosis, metastases were found in lymph nodes in the left side of the neck. There was no communication between the nodes and the primary tumour in the sella turcica region on magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) scans. Radical surgery of the metastases revealed pituitary tissue with identical staining pattern as primary tumour and a few cells staining for hGH. Cabergoline and sandostatin treatment were continued. After 7 months, a new metastasis occurred in a lymph node on the opposite side of the neck, and the pituitary tumour grew rapidly. The primary tumour reached a size of 68 × 48 mm (WHO criteria (38)), and the lymph

Table 1 Temozolomide treatment of pituitary tumours.

Author (year)	Tumour	Hormone	MGMT	Temozolomide dose – series	Response hormonal	Response tumour	Response clinical
Zhu (2004) (51)	Carcinoma	PRL	NA	NA	NA	Reduced	Improvement
Lim <i>et al.</i> (2006) (32)	Carcinoma	PRL	NA	200 mg/m ² – 18	7.3 × 10 ³ –6.1 IU/l	Reduced	Improvement
Fadul <i>et al.</i> (2006) (30)	Carcinoma	LH	NA	200 mg/m ² – 12	NA	Reduced	Improvement
	Carcinoma	PRL	NA	200 mg/m ² – 10	694–<50 ng/ml ^a	Recurred ^a	Improvement
Syro <i>et al.</i> (2006) (34)	Adenoma	PRL	NA	200 mg/m ² – 7	1838–30 ng/ml	Reduced	NA
Neff <i>et al.</i> (2007) (33)	Adenoma	PRL	NA	150 mg/m ² – 26	7000–260 ng/ml	Reduced	Improvement
Kovacs <i>et al.</i> (2007) (31)	Adenoma	PRL	Negative	200 mg/m ² – 7	1838–30 ng/ml	Reduced	Improvement
Kovacs <i>et al.</i> (2008) (41)	Adenoma	NFA	Positive	NA	NA	NR	NR
Moyes <i>et al.</i> (2009) (36)	Adenoma	ACTH	Negative	200 mg/m ² – 6	2472–389 pmol/l	Reduced	Improvement
Mohammed <i>et al.</i>	Adenoma	ACTH	Negative	150 mg/m ² – 12	NA	Reduced	Improvement
(2009) (35)	Adenoma	ACTH	Positive	NA – 12	140–21 pmol/l	Carcinoma ^b	Response ^b
	Adenoma	NFA	NA	200 mg/m ² – 12	NA	Reduced	NA

NA, no data available; NR, no response.

^aInitially positive response. Fifteen months after termination of TMZ, prolactin level increased and metastasis recurred.

^bInitially positive response. Four months after termination of TMZ, tumour transformed to a carcinoma and headache returned.

node measured 30×13 mm (RECIST criterias (39)). The patient suffered from headache, nausea and vomiting, and the visual field was further impaired.

Pathology The pituitary tumour was composed of a moderate pleomorphic cell population with round to oval nuclei containing one or two distinct nucleoli and with varying amounts of cytoplasm. With IHC, the neoplastic cells stained for PRL but were negative for other hormones. Ki-67 index was ~5%. MGMT was negative.

In a cervical lymph node metastasis, an identical staining pattern was seen with PRL positivity. In addition, a few cells stained for hGH. Ki-67 index was ~10%. MGMT was negative.

Biochemistry At the time of diagnosis, the PRL was 790 µg/l (normal <20), IGF1 was 184 µg/l (normal 80–265). The T-4 index and the Synacthen test were normal, and LH and FSH levels were low.

At months 4–33, IGF1 levels increased to a maximum of 1156 µg/l, and the nadir GH during an oral glucose tolerance test was 16 mU/l (normal <1 mU/l).

At the time of surgery on the metastases, the PRL level was 738 µg/l and the IGF1 level was 372 µg/l.

TMZ treatment TMZ treatment was initiated in 2004 according to conventional schedule. A total of 23 cycles were administered. Cabergoline in combination with sandostatin was continued during and after TMZ treatment. The primary tumour was reduced 62% to a size of 28×44 mm with maximum reduction reached after 10 cycles. The metastatic lymph node on the right side of the neck disappeared completely on MRI scan. Headache was noticeably reduced and the visual deficits improved. During the time of TMZ treatment, PRL decreased from 738 to 14 µg/l and IGF1 went from 372 to 78 µg/l. Thirty-four months after termination of TMZ, remnant tumour size (MRI scan) was unchanged and hormone levels stayed suppressed.

Patient B

Initial examination and conventional treatment A 60-year-old male presented with headache, visual disturbances and impotence. CTC demonstrated a pituitary macroadenoma invading the suprasellar region. Transsphenoidal surgery (month 1) left a very small tumour mass. Pathology and hormone levels revealed a prolactinoma of the pituitary gland. Bromocriptine (2.5 mg×3 daily; months 1–195) was effective for 15 years. Tumour recurred and PRL levels increased despite cabergoline therapy (alternating 2 mg/1 mg daily; month 195 onwards). During the following

4 years, patient B experienced clinical deterioration with headache, impaired visual fields and complex partial epileptic seizures with secondary generalisation. A MRI scan revealed an invasive supra-, para- and infrasellar pituitary adenoma measuring 31×29 mm in near vicinity to the brainstem and optical tract. No metastases were seen on PET-CT scan. The risk of damaging essential brain structures by surgery or radiotherapy was high. Sandostatin LAR (20 mg i.m. every 4 weeks; months 229–256) was administered in combination with cabergoline without reduction of tumour size or hormone hypersecretion.

Pathology A uniform cell population arranged in sheets or lobules was found in the adenoma. IHC staining was positive for PRL but negative for other pituitary hormones. Ki-67 index: ~2% MGMT negative.

Biochemistry At the time of diagnosis, PRL level was 1075 µg/l. TSH, tri-iodothyronine and thyroxine (T₄) levels were low. Other pituitary hormones were unaffected. Secondary hypothyroidism was treated with T₄. PRL was 650 µg/l before TMZ treatment.

TMZ treatment Twelve cycles of TMZ were administered according to conventional schedule. Cabergoline treatment was continued during and after TMZ treatment. The TMZ dose was reduced after the first cycle and after the sixth cycle due to adverse effects – leukocytopenia, thrombocytopenia and nausea.

Headache was noticeably reduced, improvements of visual fields on both eyes were registered by Goldman perimetri, and there have been no further epileptic seizures. Tumour was reduced 80% to a size of 16×11 mm. PRL declined from 650 to 18 µg/l. Twelve months after treatment, the remnant tumour had not increased in size, and the PRL level was normal.

Patient C

Initial examination and conventional treatment

A 20-year-old male developed headache, nausea, vomiting and visual disturbance acutely. CTC demonstrated a highly invasive pituitary macroadenoma showing signs of pituitary apoplexia. Transsphenoidal surgery was performed (acutely). Pathology revealed a NEA. After 3 years, the NEA recurred. To preserve visus and visual fields, transsphenoidal and transcranial surgical procedures were performed five additional times (years 3, 10, 12, 14 and 15). Radiotherapy was given (50 Gy, 3.5 years), sandostatin LAR (30 mg every 4 weeks i.m., years 12–17) was administered, and cabergoline therapy (0.5 mg×1 daily, years 4–5) was

Figure 1 MRI cerebrum, sagittal view. From the top: patient A, B and C. Left to right: before and after temozolomide treatment.

not tolerated. The adenoma was not controlled. Before TMZ treatment, the tumour was 45×43 mm on MRI scan. A PET-CT scan showed no metastasis.

Pathology The adenoma consisted of a uniform cell population, which was arranged without a particular growth pattern. IHC of the adenoma cells stained negative for pituitary hormones including α -subunit, while remnants of the pituitary stained as a normal,

mixed population for the various hormones. Ki-67 index: $\sim 2\%$. MGMT showed few positive nuclei.

Biochemistry At the time of diagnosis, levels of T_4 , ACTH, LH, FSH and GH were low. The patient was treated with T_4 , hydrocortisone and testosterone.

TMZ treatment Fifteen cycles of TMZ were administered according to the conventional schedule.

The adenoma was reduced from 55% to 40×22 mm, and the patient experienced improvement concerning headache and visual field. At the time of publishing, the patient was still treated with TMZ.

Discussion

The three pituitary tumours were different concerning malignancy, invasiveness, sizes and hormone secretion. At the time of TMZ therapy, the age of the patients ranged from 39 to 82 years. All patients suffered from extensive mass effect, and the tumours were resistant to conventional therapy.

TMZ is an alkylating cytostaticum with great ability to cross the blood–brain barrier. Combined with radiotherapy, TMZ is known to be effective in some patients with glioblastoma multiforme (37). At the time of initiating TMZ treatment of patient A, there was no data concerning TMZ treatment of pituitary tumours. No other cytostatic agents had proven effective in pituitary carcinomas, and TMZ was chosen due to the efficacy in patients with glioblastoma multiforme and due to low toxicity. Recently, several cases of effective TMZ treatment of pituitary tumours have been reported (Table 1).

The effect of TMZ depends on methylation of a specific guanine in DNA. MGMT is a DNA repair enzyme removing the alkyl group from the guanine. High expression of MGMT in gliomas indicates resistance to TMZ (40), and high expression of MGMT has been reported in a pituitary tumour not responding to TMZ (41) and in an adenoma transforming to a carcinoma after TMZ therapy (35) (Table 1). Kovacs *et al.* have suggested that MGMT expression should be immunohistochemically assessed to predict the effect of TMZ (41). Thirteen percent of pituitary adenomas present low expression of MGMT, independent of tumour invasiveness and postoperative recurrence (42). MGMT levels in all three cases were negative or very low, correlating with efficient TMZ treatment.

All patients experienced worsening of nausea, but only patient B experienced haematological adverse effects which normalized after dose reduction. No other symptoms of cytotoxic adverse effects were reported.

Treatment response of pituitary tumours are usually evaluated by reduction of tumour mass, improvement of neurological symptoms and normalization of hormone or α -subunit levels in cases of hypersecretion. There is no published definition of a responder to cytostatic treatment of pituitary adenomas. According to MacDonald's response criteria, which are used for the evaluation of gliomas (43), all three patients responded partially to TMZ. Tumours were reduced by 62, 80 and 55% in patients A, B and C respectively (Fig. 1). The responses were progressive and recognized after the first series of treatment, and maximum

tumour reduction was reached after ~10 cycles in all cases. Regarding patient A, the metastasis responded completely to TMZ therapy, according to RECIST response criteria (39). Visual fields were improved in all patients, and hormone hypersecretion in patients A and B was normalized. There are no published data on long-term follow-up of pituitary tumours treated with TMZ. We found stable parameters concerning tumour size and hormone levels in patients A and B after 3 years and 1 year respectively.

The two PRL-producing tumours were treated with cabergoline in combination with TMZ. It seems unlikely that cabergoline was the reason for the tumour mass reductions, bearing in mind that patient A and B were treated with cabergoline continuously for 10 and 20 years respectively before TMZ therapy was initiated. Patients A and C were treated with radiotherapy 8 and 13 years respectively, before TMZ treatment. It is unlikely that radiotherapy should play a role in the observed tumour reductions.

At debut, patient A presented a prolactinoma. Acromegaly was diagnosed clinically and biochemically after 33 months, despite cabergoline and sandostatin treatment. This is probably due to the ability of pituitary mammosomatotroph cells to produce both hormones (44–46).

Invasive and malignant tumours exhibit higher Ki-67 labelling indices than benign adenomas (20, 47, 48), but there is no difference in the expression of Ki-67 between mono and plurihormonal adenomas (49). Ki-67 indices were elevated in all three cases. Concerning the primary tumours, highest Ki-67 index was found in the tumour that transformed to a carcinoma.

Pituitary carcinomas are extremely rare, only ~140 cases have been reported. Distant metastases are accepted as the only true diagnostic hallmark of pituitary carcinomas (21). MRI and PET–CT scans revealed no physical connection between the primary tumour and metastases in the lymph nodes in the neck region. The metastases produced both PRL and GH, which could be the reason why the PRL levels were more moderate than expected (22). This is the first pituitary carcinoma producing both PRL and GH ever reported in English literature. There is a report of a carcinoma producing GH and expressing D2R, but it did not secrete PRL (50).

Primary tumour and metastases were both monoclonal, and two of three examined genes in the metastases were partly methylated (data not shown). Ki67 index level was doubled in the metastases compared with the primary tumour (patient A). These findings, combined with the fact that 8.5 years passed from the diagnosis of the primary tumour to the appearance of metastases, support the theory of a malignant transformation of an adenoma into a carcinoma (21).

Conclusion

We presented a pituitary carcinoma and two highly invasive macroadenomas, which were resistant to conventional treatment. The effect of TMZ therapy was significant in the three cases and follow up revealed stable parameters. This, combined with the existing literature, emphasize that TMZ may be considered for aggressive pituitary tumours that are resistant to conventional therapy.

Considering the significant effect and the few adverse effects, there might be a wider indication for TMZ treatment of aggressive pituitary adenomas. Whether TMZ should be administered in combination with conventional medical treatment should be thoroughly studied.

Our cases showed low MGMT values and they partially responded to TMZ therapy; however, more data are necessary to decide whether MGMT immunostaining should be used as a surrogate marker for predicting tumour TMZ sensitivity.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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