Long-term response of pituitary carcinoma to temozolomide

Report of two cases


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Pituitary carcinoma is a rare tumor characterized by poor responsiveness to therapy, leading to early death. Reported responses to standard chemotherapy have only been anecdotal, with no single agent or combination demonstrating consistent efficacy in the treatment of patients with this disease. The authors report rare examples of a persistent response to cytotoxic chemotherapy in two patients with pituitary carcinoma.

One patient was a 38-year-old man with visual field loss caused by a luteinizing hormone–secreting pituitary carcinoma that had recurred despite multiple surgeries and radiation therapy. Intradural metastases to the spine that had failed to respond to radiation therapy were pathologically confirmed. The second patient was a 26-year-old man with hyperprolactinemia from a prolactin-secreting pituitary tumor. Spine magnetic resonance images obtained to search for causes of neck pain showed a vertebral tumor, which was later confirmed through pathological analysis to be a metastatic pituitary carcinoma. His disease progressed despite radiation therapy, high-dose bromocriptine, and chemotherapy.

Both patients were treated monthly with temozolomide, which was administered orally on the first 5 days of a 28-day cycle. The patient in the first case underwent all 12 treatment cycles without serious side effects, and his visual field deficits improved. The patient in the second case had undergone only 10 cycles when the drug was stopped because of his severe fatigue. Nonetheless, his pain disappeared and his serum prolactin concentration decreased. Both patients continue to have partial responses and have been employed full-time for more than 1 year after discontinuing temozolomide therapy. These two examples demonstrate that temozolomide may be effective in treating pituitary carcinomas and thus should be considered in the treatment algorithm for these difficult cases.

KEY WORDS • pituitary carcinoma • temozolomide • chemotherapy

Although pituitary adenomas may be found in as many as one in 10 persons and invasion may be a factor in 10% of clinically active adenomas, pituitary carcinomas are exceedingly rare. Authors of a recently published review stated that fewer than 140 cases have been described in the literature to date. Defined as primary neoplasms of the hypophysis that undergo craniospinal and/or systemic spread, pituitary carcinomas are usually hormonally active with more than one half secreting either prolactin or adrenocorticotropic hormone. Although the time between onset of the initial adenoma and diagnosis of the carcinoma averages several years, once a carcinoma has been documented mean survival is typically measured in months. This tumor usually does not respond to radiation therapy or cytotoxic chemotherapy.

We report two cases of pituitary carcinomas that responded to temozolomide.

Case Reports

Case 1

History and Initial Examination. This 38-year-old man presented in 1993 with headaches and left temporal visual field loss. Magnetic resonance images demonstrated a sellar mass with sphenoid and cavernous sinus invasion.

Treatments and Pathological Analyses. The patient underwent transsphenoidal resection, and results of a pathological analysis revealed a pituitary adenoma that stained for luteinizing hormone. The serum luteinizing hormone concentration was mildly and inconsistently elevated. Several months later, because adenoma progression had been radiologically demonstrated, a craniotomy was performed, followed by external-beam radiation therapy.
Case 2

History and Initial Examination. This 26-year-old man presented in 1995 with headaches and a progressive decrease in visual acuity. He was found to have bitemporal hemianopia with a prolactin concentration of 181 ng/ml (normal range 0–28 ng/ml). An MR image revealed a large pituitary mass, which was diagnosed as a prolactin-secreting pituitary macroadenoma.

Treatments and Pathological Analyses. Bromocriptine was administered, which led to a resolution of the patient’s symptoms and a decrease in prolactin levels to 37 ng/ml. After 2 years, cabergoline was substituted for bromocriptine, but the headaches returned and visual field testing revealed worsening bitemporal hemianopia. Magnetic resonance images showed that the mass had grown. Treatment with bromocriptine was restarted, but the patient’s symptoms worsened. A transsphenoidal debulking resection was performed, followed several months later by a craniotomy. Results of a pathological analysis in both instances were consistent with an invasive pituitary tumor as well as bone invasion, numerous mitoses, and an elevated MIB-1 proliferation index at 10%. The tissue stained positively for prolactin but not for growth hormone. Proton beam radiation therapy was applied to the pituitary gland. While on this treatment, the patient had intractable headaches and neck pain that were only relieved with high-dose opioid analgesic agents. Magnetic resonance images of the spine showed multiple discrete lesions involving cervical and thoracic spine vertebrae. A biopsy of a cervical spine lesion demonstrated histological characteristics identical to those of the pituitary tumor. The patient’s symptoms did not respond to an escalated dose of the bromocriptine or radiation therapy to the spine. A trial of octreotide and two cycles of chemotherapy, including carboplatin, paclitaxel, and etoposide, were also ineffective. Several months later a positive MIBG scan led to treatment with 131I-MIBG; this therapy produced some improvement in pain, although prolactin levels did not decline. Five months later, despite having received high doses of bromocriptine, his symptoms progressed and the prolactin levels increased to 694 ng/ml. A PET scan revealed progression of the spinal disease, whereas a repeated MIBG scan demonstrated no lesions.

Temozolomide Treatment. In view of the benefits observed in the patient in Case 1, we administered temozolomide at 200 mg/m² every day for 5 days on and 23 days off, for 10 cycles. Chemotherapy was well tolerated, but the last two cycles were withheld because of the patient’s persistent fatigue. He became pain free and the hyperprolactinemia diminished. Fifteen months after his last cycle of temozolomide, his condition remains clinically stable and his serum prolactin levels are less than 50 ng/ml (Fig. 3). He is asymptomatic and working full time. Follow-up MR images confirmed a partial response that has remained stable (Fig. 4), and his visual fields are normal.

Discussion

Pituitary carcinoma is usually a lethal disease, with more than one half of patients dying within 1 year after a diagnosis. Long-term survivors have been reported, and perhaps the courses in the two described cases were the result of the...
natural history of the disease. Despite multiple treatment approaches, both of the patients had progressive disease, which was objectively determined based on prolactin concentration and PET scanning results in one case and on MR imaging studies and visual fields in the other. One of the patients underwent two cycles of systemic chemotherapy, which exacerbated his symptoms and produced no radiological evidence of a treatment response. Although there

Fig. 2. Case 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. Response was stable more than 1 year after stopping treatment.
was some pain relief after MIBG treatment, prolactin levels
did not decrease. Only after receiving temozolomide did the
prolactin level decline 10-fold. There was no hormonal tu-
mor marker to follow in the patient in the first case, but he
had progressive visual impairment despite multiple treat-
ments. Once he started taking temozolomide, his visual
field deficits improved and the tumor decreased in size. In
both cases the benefit lasted for more than 1 year after dis-
continuation of the therapy. Moreover, the drug was well
tolerated except for fatigue.

In a review of chemotherapy for pituitary carcinoma,
very few individuals showed an objective response to cyto-
toxic treatment. Although exceptions have been report-
ed, the response has been transient and dependent on
continuing chemotherapy. Despite having a high prolifera-
tion index, pituitary carcinomas usually do not respond to
chemotherapy regimens known to be effective against ade-
nocarcinomas or sarcomas, perhaps because pituitary carci-
nomas are well differentiated. Bromocriptine may produce
some benefit in prolactin-producing tumors, but most of
these lesions develop resistance to this drug. Tamoxifen has
been suggested for use in this patient subgroup. The persis-
tence of a therapeutic response after discontinuing treat-
ment is therefore a notable feature in the cases we describe.

Based on the outcome in these patients, who had not
significantly responded to any other treatment, it seems
plausible that these tumors were uniquely sensitive to temo-
zolomide. This drug is an orally prescribed dacarbazine ana-
log that crosses the blood–brain barrier. Furthermore, it has
been shown to have activity against numerous malignan-
cies, particularly intracerebral primary and metastatic tu-
mors. Cytotoxic activity against systemic adenocarcino-
mas, including pancreatic, renal cell, colorectal, and prostate
carcinomas, has been disappointing. Results of an in
vitro study of temozolomide for human tumors have sug-
gested that this drug may have activity against neoplasms
that did not respond to other agents such as dacarbazine,
etoposide, and vinblastine. In the patients in the present re-
port, both the systemic and the craniospinal metastases re-
sponded to treatment, and this response was independent of
whether or not the tumor was hormone secreting. Thus, we
suggest that the location of the metastases and their hor-
mone production status do not correlate with the response to
temozolomide.

Although not ideal, treatment recommendations for rare
tumors are often based on case reports. Given the lack of
effective alternatives, a trial of temozolomide may be indi-
cated before more toxic combinations of chemotherapy for
the treatment of pituitary carcinoma. Only with more ex-
perience can we determine the response rates and durability
of effectiveness associated with temozolomide treatment. If
proven effective, this therapy could be studied in other pa-
tient subsets, such as those with invasive pituitary adenomas
unresponsive to other treatments or with a high potential for
aggressive behavior.

**Addendum**

Since this paper was submitted, the patient described in Case 2
Response of pituitary carcinoma to temozolomide

Fig. 4. Case 2.  A: Coronal contrast-enhanced T₁-weighted MR image of the brain revealing an enhancing pituitary mass infiltrating the cavernous sinus.  B: Sagittal contrast-enhanced T₁-weighted MR image of the spine obtained at baseline, demonstrating areas of marrow replacement within the T-1 and T-2 (arrows) vertebral bodies.  C and D: Coronal (C) and sagittal (D) contrast-enhanced T₁-weighted MR images obtained after 10 cycles of chemotherapy, exhibiting a pituitary mass stable in size and less apparent spine lesions (arrows) with a return of fat within the vertebral bodies, respectively.
had an increase in prolactin levels 15 months after temozolomide was discontinued. He exhibited no symptoms, but a PET scan revealed increased activity in the T-2 vertebral body as the only site of neoplastic activity. The patient has begun taking temozolomide again, but his prolactin levels have continued to increase.

References

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