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Case Report

A Case Series of Temozolomide in the Management of Refractory Prolactinomas

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Abstract:

Objective: To report three cases of refractory prolactinomas treated with Temozolomide (TMZ)**.**

Background: Prolactinomas account for 40% of pituitary adenomas. Dopamine agonists (DA) are the first line of treatment followed by surgical resection and radiation. TMZ is an oral chemotherapeutic agent used in gliomas, which has been given to patients with prolactinomas refractory to conventional treatments.

Methods: Retrospective chart review was conducted for refractory prolactinoma patients treated between 2008 and 2018 at UT Southwestern Medical Center (UTSW). Three patients with refractory prolactinomas received oral TMZ at UTSW.

Results: All three patients demonstrated improvement in symptoms upon TMZ treatment, markedly decreased serum prolactin levels (SPRL), as well as radiographic decrease in tumor size.

Conclusion: TMZ is well tolerated and is a potentially effective treatment for refractory prolactinomas.

Keywords
Refractory prolactinomas; temozolomide; pituitary adenomas; stereotactic radiosurgery; serum prolactin level

1. Introduction

Prolactinomas comprise 40% of pituitary adenomas [1]. They cause headaches, visual field defects, hypogonadism, galactorrhea and infertility. Most prolactinomas respond to Dopamine agonists (DA) [2]. Surgery is indicated for patients who failed DA treatment or are intolerant to DA. Prolactinomas unresponsive to DA or surgery may need radiosurgery.[3]. Despite multimodal treatments, a subset of prolactinomas progress with rapid growth and invasion into surrounding tissue. TMZ is an oral alkylator used in malignant gliomas which readily crosses the blood brain barrier. Nausea, vomiting, constipation, thrombocytopenia and leucopenia are side effects. Successful management of prolactinomas with TMZ was first reported in 2006 [4, 5]. Approximately 50% of prolactinomas respond to treatment with TMZ.[6]. A case series evaluating use of TMZ in refractory prolactinomas reported a response in 4 out of 9 patients. [7]. A recently published large study of 166 patients with aggressive pituitary tumors treated with TMZ of which majority were corticotroph tumors confirmed that TMZ is an effective first line treatment of aggressive pituitary tumors and carcinomas. In this retrospective review, patients received TMZ for multiple subtypes of pituitary tumors. Patients with functioning tumors and those who received TMZ concurrently with radiation therapy had a better response rate [8]. This study is our institutional experience in management of refractory prolactinomas.

2. Methods

Retrospective chart reviews were conducted as part of an Institutional Board review exempt study and three refractory prolactinoma patients treated between 2008 and 2018 at UTSW were identified. All patients had at least 3 relapses prior to starting TMZ treatment. They consented to publication of their clinical data. TMZ was dosed at 150 to 200 mg/m²/day for five days during each 28-day cycle. All patients had monthly serum prolactin level (SPRL) and bimonthly gadolinium enhanced brain magnetic resonance imaging (MRI) scans.

Patient: 1:

A 40-year-old female diagnosed with a prolactinoma in 1996 failed treatment with DA, surgery, Cyber knife® and Gamma Knife® radiosurgery. In May 2013, she developed diplopia. Brain MRI showed enlargement of the prolactinoma measuring 3.1x3.4x4.0 cm (anteroposterior by transverse by craniocaudal (APxTRxCC) with SPRL of 3044.8 ng/ml (normal range in non-pregnant females: 5-40

ng/ml or 106-850 mIU/L). On completion of 18 cycles of monthly TMZ, her tumor decreased to 2.3 cmx1.7cmx1.8 cm APxTRxCC. She was monitored with SPRL and brain MRIs every 2 months off TMZ. TMZ was restarted in October 2016 for progression (Figure 1 C). She completed 21 cycles of TMZ by February 2018 and has stable disease with a SPRL of 8.3 ng/ml. (Figure 2).

Patient 2:

A 70-year-old female was diagnosed with a refractory prolactinoma in 2008. She had failed previous treatment with Dopamine agonists, stereotactic radiosurgery and surgical resection. In June 2014, her SPRL was 3591 ng/ml. (normal range in non-pregnant females: 5-40 ng/ml or 106-850 mIU/L). She completed 14 cycles of TMZ treatment in August 2015. Her tumor has remained stable off TMZ with normal SPRL in October 2017.

Patient 3:

A 76-year-old male underwent resection and Cyber Knife® radiosurgery of a prolactinoma in October 2009. He was not given DA due to a history of paranoid schizophrenia. He completed 9 cycles of TMZ at a reduced dose of 100 mg/m²/day due to pancytopenia. His tumor has remained stable off TMZ with normal SPRL in July 2017.

3. Discussion

Our series confirmed the reports of previous patients with refractory prolactinomas having good responses and acceptable side effects from TMZ. Optimum dosage of TMZ and duration of treatment (number of cycles) is not known. In our institution, dosage of TMZ was based on the treatment regimen for glioblastoma also known as the “Stupp Protocol” [9]. Patients with refractory prolactinomas in our institution underwent bimonthly gadolinium enhanced brain and pituitary MRI and SPRL measurements every month. In patient 1, after successful completion of TMZ treatment for 12 months, the patient opted to continue TMZ treatment for an additional 6 months given her excellent clinical and radiological response. At recurrence while off TMZ therapy, the patient opted to receive a total of 24 cycles of TMZ treatment and had completed 21 cycles at the time of preparation of this report. Patient 2 opted to discontinue TMZ treatment after 14 cycles due to fatigue. Patient 3 received a reduced dose of TMZ due to pancytopenia with eventual discontinuation after 9 cycles due to several delays and dose reductions of TMZ. All three patients demonstrated clinical stability, decrease in tumor size radiologically and decreasing SPRL. Previous studies have published favorable responses of corticotroph tumors with TMZ treatment, however, the optimal dose, and the number of cycles is unclear for these other subtypes as well. Long-term TMZ treatment could be tolerated and may be necessary for some refractory prolactinomas, as Patient 1 recurred on surveillance after 18 monthly cycles of TMZ, and again had a good response to TMZ re-challenge, hence making this is a unique case as previously published case series have shown that response to retreatment of refractory pituitary tumors with TMZ is poor. [8]. In addition, for patients with refractory prolactinomas with concurrent paranoid schizophrenia who cannot receive DA, TMZ may be considered earlier in the treatment course. The tumor tissue was not tested for MGMT status in our patient cohort and therefore is a limitation of this study. Larger prospective studies are needed to

ascertain whether earlier treatment with TMZ may spare standard treatment modalities, such as radiation.

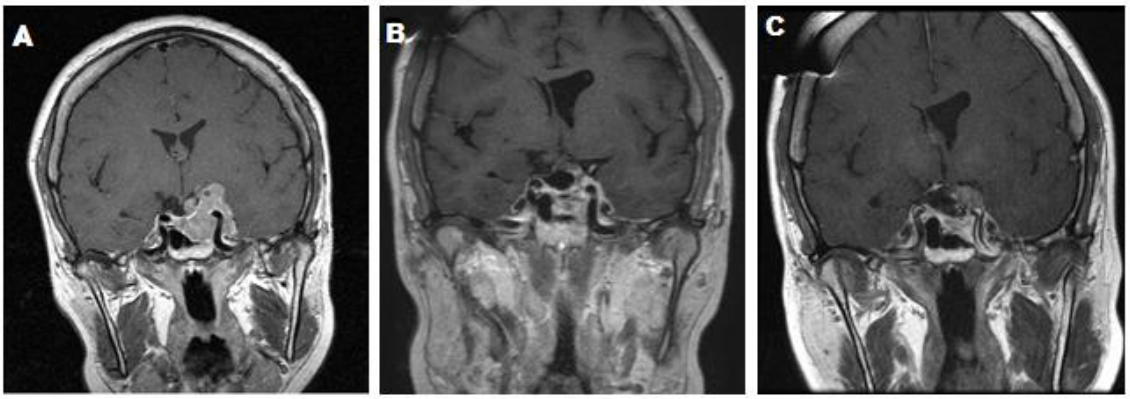

Figure 1 Patient 1 Images A to C: Contrast-enhanced coronal brain MRIs. A: 10 years after initial diagnosis. The patient failed prior DA therapy, surgery and radiosurgery. B: Decrease in tumor size 6 months into TMZ therapy. C: Extension of left suprasellar enhancement during TMZ holiday.

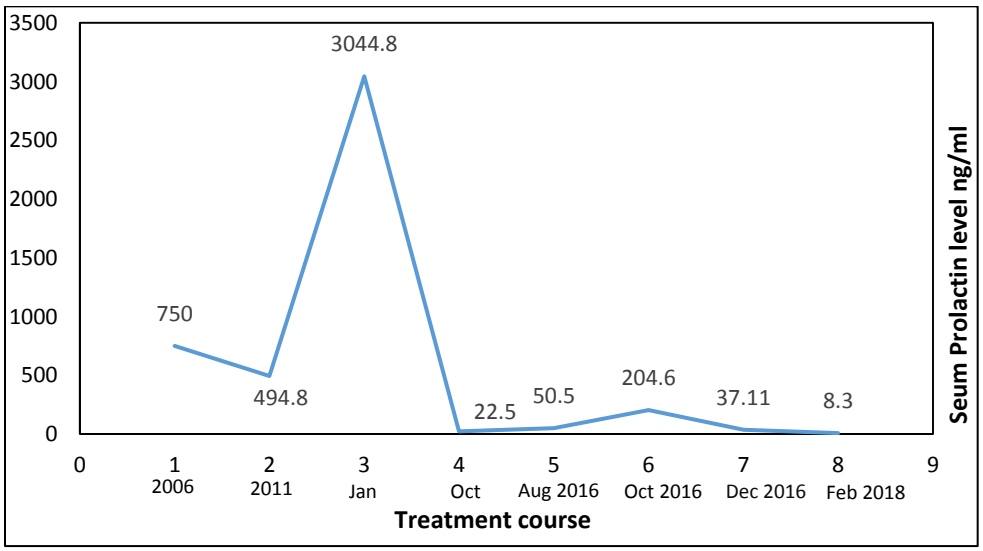

Figure 2 Graph showing SPRL for patient 1 over time since diagnosis. 1. SPRL after DA treatment; 2. Failed surgery and Cyber Knife; 3. SPRL prior to starting TMZ; 4. Completion of 18 cycles of TMZ; 5. SPRL on surveillance; 6. Radiographic recurrence; 7. After 2 cycles of TMZ retreatment; 8. Completion of 21 cycles of TMZ. Note: SPRL from 1996 is unavailable. Normal SPRL in non-pregnant females: 5-40 ng/ml or 106-850 mIU/L.

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Author Contributions

All authors contributed equally to the conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be published.

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