Temozolomide treatment induces a rapid clinical, biochemical and radiological response in an aggressive prolactinoma despite an unmethylated MGMT promoter.

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Background
Pituitary tumours occasionally follow a highly aggressive course and can even become frankly malignant. Temozolomide is an oral cytotoxic agent which has recently been used to treat aggressive pituitary tumours. A positive clinical response to temozolomide is associated with inactivation of the DNA repair enzyme O-methylguanine-deoxyribonucleic acid methyl transferase (MGMT). MGMT inactivation can be demonstrated either by reduced immunohistochemical expression of MGMT or by methylation of the MGMT promoter.

Case History
A 34 year old man initially presented in India in 2003 with a bitemporal hemianopia and was found to have a suprasellar pituitary adenoma. Prolactin was 148,751 mU/L. Trans-sphenoidal surgery was performed resulting in a significant improvement in visual fields. Bromocriptine was commenced and later switched to cabergoline. Despite dopamine agonist therapy there was radiological and biochemical progression of the tumour and he underwent a right fronto-temporal craniotomy in August 2005. Prolactin fell to 71,333 mU/L. Fractionated radiotherapy was performed in early 2006 and cabergoline was continued. By May 2008 prolactin had fallen to 9050 mU/l with a 10mm suprasellar residual tumour.

In 2008 he moved to the UK. Over the following year MRI showed radiological progression with prolactin rising to 90,000 mU/L. Cabergoline was increased to 4mg/week with no change in prolactin level. In May 2009 the patient had worsening headaches and bitemporal visual field loss extending across the midline. A further craniotomy and tumour decompression was performed in May 2009 without significant improvement in visual fields. Histology demonstrated a prolactinoma with Ki67 of 15%. Methylation specific PCR analysis demonstrated an unmethylated status of the MGMT promoter. He developed further visual field loss, near blindness in the left eye, bilateral sixth nerve palsies and proptosis. MRI scan showed further rapid tumour progression, now 6cm in maximal diameter, with orbital canal invasion. In July 2009 the patient was commenced on temozolomide (200mg/m², 5 days every 4 weeks).

After two weeks there was significant improvement in the visual fields. After two cycles the MRI scan showed dramatic radiological regression of the tumour. Visual fields showed objective improvement and the sixth nerve palsies resolved. Prolactin reached a plateau of 8000 mU/L. The patient continues to improve and has presently completed 5 cycles of temozolomide therapy.

Discussion
There are currently 20 patients with pituitary tumours in the literature who have been treated with temozolomide, in whom a response of 85% is described with a variety of endpoints. We report an excellent objective clinical, biochemical and radiological response in a patient with a highly aggressive prolactinoma. In gliomas the MGMT promoter methylation status may be a better indicator of both MGMT expression and clinical response compared to MGMT immunostaining. Where MGMT status has been examined in previous reports amongst pituitary tumours, a positive clinical
response to temozolomide therapy has been associated with MGMT inactivation. This is the first case report of a sustained response to temozolomide in a patient with an unmethylated MGMT promoter.

In individuals with pituitary tumours refractory to treatment an unmethylated promoter should not be a deterrent to temozolomide therapy.