

## Prolonged and severe myelosuppression in two patients after low-dose temozolomide treatment- case study and review of literature

Nimit Singhal · Sudarshan Selva-Nayagam ·  
Michael P Brown

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**Abstract** Temozolomide is an alkylating agent used frequently in the management of gliomas. Although temozolomide is generally safe, rarely it can cause life threatening complications. Here we report the cases of two patients who developed prolonged and severe pancytopenia after low dose continuous temozolomide concurrently with cranial radiotherapy. The pancytopenia lasted two to six months. Both the patients were young, treatment naïve, and had temozolomide treatment for only approximately four weeks.

**Keywords** Pancytopenia · Febrile neutropenia · Bone marrow suppression

### To the editor

Temozolomide (TMZ) is an orally administered alkylating agent indicated for the management of newly diagnosed high grade gliomas at a continuous daily dose of 75 mg/m<sup>2</sup> in combination with external beam radiotherapy (RT) for the duration of RT. It is a well tolerated treatment with fatigue, thrombo-embolic events and lymphopenia being the most common side effects. Grade III or IV myelosuppression is a relatively uncommon side effect that is reported in 4% of patients[1].

Here we report two cases in which TMZ resulted in prolonged and severe pancytopenia.

Patient A, a 49 year-old female non-smoker was diagnosed with glioblastoma multiforme (GBM) when she underwent craniotomy and resection on 19th March 2006. She had no significant co-morbidities and did not report use of any regular medications. She started concomitant brain RT and TMZ at a dose of 75 mg/m<sup>2</sup>/day on 5th May 2006. Two weeks after initiation of treatment, she reported nausea as the only side effect and hematology and serum biochemistry results at that time were normal. She presented on 6th June (day 31) of treatment with fever, easy bruising and vaginal bleeding. Full blood examination showed hemoglobin (Hb) 96 g/l, platelet count (PLT)  $9 \times 10^9/l$  and total leucocyte count (TLC)  $0.28 \times 10^9/l$ . TMZ was ceased and she was started on intravenous antibiotics and supported with blood products. She was discharged two weeks later in a clinically stable state with Hb 106 g/l, PLT  $14 \times 10^9/l$ , TLC  $1.69 \times 10^9/l$  and neutrophil count  $0.88 \times 10^9/l$ .

She re-presented five weeks later with febrile neutropenia and external bleeding. Her Hb was 57 g/l, PLT  $8 \times 10^9/l$ , TLC  $1.83 \times 10^9/l$  and neutrophil count  $0.95 \times 10^9/l$ . Again, she was treated with antibiotics and blood product support and discharged after ten days. Although she never recommenced TMZ treatment, she remained pancytopenic for more than six months after her last dose of TMZ with Hb of 109 g/l, PLT  $54 \times 10^9/l$ , TLC  $3.69 \times 10^9/l$  and neutrophil count of  $2.2 \times 10^9/l$ . She did not receive growth factor support and refused further investigations including bone marrow examination. She had never received cotrimoxazole (trimethoprim and sulphamethoxazole) prophylaxis with TMZ and her vitamin B12 and folic acid levels were also normal.

Patient B, a 55 year-old female smoker was diagnosed with GBM when she underwent craniotomy and resection on 26th April 2006. She had no major co-morbidities and

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N. Singhal (✉) · S. Selva-Nayagam ·  
M. P. Brown  
Department of Medical Oncology, Royal Adelaide Hospital,  
Adelaide, SA 5000, Australia  
e-mail: nsinghal@mail.rah.sa.gov.au

was not receiving any regular medications. She commenced concomitant brain RT and TMZ at a dose of 75 mg/m<sup>2</sup>/day on 5th July 2006. She did not receive cotrimoxazole prophylaxis. She was reviewed 2 weeks after starting treatment with normal blood counts. After a further two weeks treatment on 8th August, routine blood examination showed pancytopenia with Hb 108 g/l, PLT  $6 \times 10^9$ /l, TLC  $2.1 \times 10^9$ /l and neutrophil count  $1.47 \times 10^9$ /l. There was no fever or external bleeding. TMZ was stopped and she received prophylactic platelet transfusion. Ten days later, she presented with febrile neutropenia and bruising. Blood tests showed Hb 71 g/l, PLT  $0 \times 10^9$ /l, and TLC of  $0.27 \times 10^9$ /l. She received treatment with antibiotics, antifungal agents, blood product support and daily G-CSF for one week. Her vitamin B12 and folic acid levels were normal. On discharge two weeks later, her Hb was 114 g/l, PLT  $13 \times 10^9$ /l, TLC  $2.24 \times 10^9$ /l and neutrophil count  $1.66 \times 10^9$ /l. A bone marrow examination performed approximately two months after stopping TMZ was normal. She recovered slowly but remained mildly pancytopenic ten weeks after stopping TMZ with Hb 106 g/l, PLT  $110 \times 10^9$ /l, TLC  $2.96 \times 10^9$ /l and neutrophil count  $2.14 \times 10^9$ /l.

Low-dose continuous TMZ is considered safe with a low incidence of side effects, especially myelosuppression. Prolonged and severe myelosuppression requiring multiple admissions has not been reported previously after use of low-dose continuous TMZ. Not surprisingly, inadvertent high-dose TMZ administration for the treatment of GBM produced profound but reversible pancytopenia [2]. There has been a report of three patients who developed severe neutrophil function impairment after one cycle of TMZ [3]. In addition, two cases of TMZ related myelodysplasia and acute myeloid leukemia (MDS/AML) occurred after prolonged treatment lasting 6 months to 2 years [4, 5]. Both the cases had previous treatment with other alkylating agents, which might have contributed.

Doyle et al [6] described three patients who developed severe myelosuppression after low dose TMZ and RT. In fact two patients had aplastic anemia. Concurrent cotrimoxazole was given that might have contributed to toxicity. Another case report describes a case of aplastic anemia after the 4th cycle of adjuvant TMZ [7]. The patient was on concomitant anticonvulsants.

In contrast, the two patients described above did not receive any concurrent bone marrow toxic drugs such as anticonvulsants or cotrimoxazole. Other common causes of pancytopenia such as vitamin B12 or folate deficiency were ruled out with appropriate testing. While low levels of

these haematonic factors may predispose to the myelotoxic effects of drugs such as TMZ, a persisting influence of these factors on the protracted myelosuppression described here is considered less likely.

The protracted effect of low-dose continuous TMZ on bone marrow function together with reports of the association of prolonged cyclical TMZ treatment with MDS/AML suggest that TMZ may impair the self-renewal capacity of haematopoietic stem cells. Perhaps, certain genetic polymorphisms of the DNA mismatch repair (MMR) enzyme system, which is required for the full effects of TMZ-induced DNA damage [8], may predispose particular individuals to TMZ-related myelotoxicity.

The case report described above is notable for the young age of the patients, short treatment period, absence of confounding concomitant medications and lack of prior cytotoxic drug exposure.

These cases highlight the importance of regular monitoring especially of blood counts, while patients receive continuous TMZ treatment.

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