CASE REPORT

Persistent bone marrow depression following short-term treatment with temozolomide

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Accepted 17 April 2016

SUMMARY

Temozolomide (TMZ) is, in combination with radiotherapy (RT), the treatment of choice for glioblastoma multiforme. Although generally well tolerated, haematological side effects are observed in approximately 1–10% of patients receiving TMZ. We report a case of a patient who developed severe bone marrow failure (BMF) after only 3 weeks of concomitant TMZ. The BMF was grave with no signs of improvement for 12 months, resulting in more than 100 transfusions of blood cells.

BACKGROUND

Glioblastoma is the most common solid high-grade brain tumour, with an age-adjusted incidence of just above 3/100 000 inhabitants in the USA and with about 200 new cases per year in Norway.^{1–4} Despite state-of-the-art treatment, the prognosis is poor with a median survival of approximately 15 months. Since Stupp *et al*¹ published their landmark paper in 2005, the treatment of choice following maximal safe surgery has been concomitant radiotherapy (RT) and temozolomide (TMZ) with six subsequent cycles of TMZ monotherapy. Nationwide Norwegian data have reproduced the beneficial effect of TMZ observed in that randomised controlled trial.⁵

TMZ is an oral alkylating agent causing DNA methylation, subsequent DNA breakage and apoptosis of tumour cells.⁶ TMZ is generally well tolerated with mild side effects such as nausea or fatigue occurring in more than 10% of patients. Thrombocytopenia, leukopenia and anaemia are observed in 1–10% of patients, in varying severity.² Bone marrow failure (BMF) usually occurs after repeated cycles of TMZ, as a dose-dependent effect, most often self-limiting with spontaneous normalisation within 4 weeks. Permanent BMF (>4 weeks) is rare.⁷ Secondary malignancies such as myelodysplastic syndrome and leukaemia, as well as prolonged pancytopenia resulting in aplastic anaemia, are listed as side effects affecting less than 0.001% of patients.² The present case highlights the risk of persistent and severe BMF, which should be taken into account for all patients receiving TMZ.

inhibitor and diuretic (enalapril and hydrochlorothiazide) and a proton-pump inhibitor (lansoprazole), respectively, he had been otherwise healthy. A cerebral MRI scan revealed a tumour with largest dimension 63 mm, located in the temporoparietal area of the right hemisphere, compressing the right lateral ventricle and shifting the midline about 8 mm to the left (figure 1). The patient underwent an open craniotomy and the pathohistological evaluation confirmed the preoperative radiological diagnosis of glioblastoma multiforme. A postoperative MRI scan showed that most contrast-enhancing tissue was removed, however, with a residual contrast-enhancing tumour component medial to the resection cavity (figure 2). As thrombotic prophylaxis, he received low-molecular weight heparin (LMWH) postoperatively; the LMWH was discontinued after 4 weeks.

One month postoperatively, he started RT with a concomitant daily TMZ dose of 160 mg based on a body surface area of 2.1 m². At that time, he had a haemoglobin level of 13.1 g/dL and a thrombocyte (trc) count of 239×10⁹/L. The first 2 weeks of treatment were uneventful. During the third week, however, the trc count fell to 52×10⁹/L and TMZ was discontinued after 24 days of treatment. A week later, the trc count was 24×10⁹/L. The following day the patient reported an incident of self-limiting nose bleeds, the trc count was below 10×10⁹/L and he received his first transfusion of thrombocytes.

Shortly after, the patient was admitted to the hospital ward due to febrile neutropaenia. He

Figure 1 Contrast-enhanced T1-weighted MRI at the time of primary diagnosis.

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To cite: Vandraas K, Tjønnfjord GE, Johannesen TB, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-215797

CASE PRESENTATION

A 69-year-old man sought medical attention in late 2014 due to frontal headache and gradual personality changes over the preceding months. Besides hypertension and gastro-oesophageal reflux disease, treated with a combined angiotensin-converting-enzyme-

Figure 2 Contrast-enhanced T1-weighted MRI following tumour resective surgery.

recovered on antibiotic treatment, but during the admission and during the following weeks it became clear that the patient was suffering from severe and protracted pancytopenia. His neutrophil granulocyte count during the next 10 months was rarely above $1.0 \times 10^9/\text{L}$ (figure 3). His haemoglobin fell from 13 g/dL to 7.0 g/dL in 1 month (figure 3). The patient began receiving weekly outpatient transfusions of trc and erythrocytes. He was lethargic, and suffered from poor appetite and weight loss, but was otherwise in an acceptable general health condition. Since this time his trc count has rarely been above $10 \times 10^9/\text{L}$ for more than 1 week following trc transfusions (figure 3).

INVESTIGATIONS

To investigate whether the BMF was caused by a myelodysplastic disorder, a trephine biopsy and a bone marrow smear were performed. No dysplastic features were identified, however, a hypocellular environment primarily consisting of small mature lymphocytes, plasma cells and macrophages, was noted. Serum protein electrophoresis showed no signs of a monoclonal component. Fluorescence in situ hybridisation (FISH) analyses were normal with no signs of genetic aberrations suggestive of acute leukaemia: neither 5q-deletion, 7q-deletion, 20q-deletion, trisomy 8, *MLL*-split nor findings suggestive of *PML/RARA*, *AHL1/ETO* or *CBFB/MYH11*-fusions were found. Cytogenetic analysis revealed a normal male karyotype (46,XY).

TREATMENT

Treatment with filgrastim and romiplostim was started 4 months after TMZ was discontinued, in an attempt to stimulate granulocytopenia and thrombopoiesis. Filgrastim resulted in a transient increase in granulocyte level before it fell again. It was therefore discontinued after 1 month. Romiplostim had little effect on the trc level despite an increasing dosage regimen, and the medication was discontinued after 2 months of treatment. Because of underlying incurable malignancy and reduced general health, the patient was not considered eligible for a bone marrow transplant and/or treatment with antithymocyte globulin in combination with cyclosporine.

OUTCOME AND FOLLOW-UP

Following a chemotherapy-free interval of 7 months, an MRI scan of the brain revealed progressive T2/fluid attenuated inversion recovery high-intensity changes suggestive of increasing oedema and/or low-grade tumour components, as well as contrast enhancement, indicating tumour progression (figure 4).

Figure 3 Platelet counts (A), neutrophil granulocyte counts (B) and haemoglobin (C) values. Temozolomide was initiated on 5 January. Filgrastim was initiated on 22 April and used on and off until 27 May, initiated again on 16 September (for 1 week) and for the third time on 7 October (for 1 week). Romiplostim was initiated on 29 April and discontinued on 24 June without effect.

Figure 4 Contrast-enhanced T1-weighted MRI at the time of neoplastic regrowth.

Due to the patient's BMF and the lack of adjuvant postoperative antineoplastic treatment alternatives, surgery was not considered an option. The patient was at this point experiencing increasing motor function disabilities, epileptic seizures and lethargy. He began treatment with oral corticosteroids and antiepileptic drugs, and achieved satisfactory symptom control.

At about 12 months after the primary diagnosis of glioblastoma, the patient had received a total of more than 50 transfusions of erythrocyte concentrate and trc, given at almost weekly intervals. During this period, he was in a surprisingly good general health condition. Unfortunately, his illness progressed (figure 5) and the patient subsequently passed away.

DISCUSSION

This patient experienced a life-threatening side effect from a cytostatic drug considered to be safe and relatively well

Figure 5 Contrast-enhanced T1-weighted MRI (5 months later than the image shown in figure 4) showing further neoplastic progression.

tolerated. The effect was not dose-dependent, but idiosyncratic and was observed surprisingly early during the TMZ treatment.

We cannot rule out that the BMD may have been caused by a factor other than TMZ, but it seems unlikely. The patient had not started any other drugs at the time of the glioblastoma diagnosis, except LMWH, taken only postoperatively, and the drugs he had been taking before he fell sick with glioblastoma had been well tolerated for several years. The possibility of BMF resulting from RT to a partial brain field is considered very unlikely. No other apparent cause for the BMF was observed, and the haematologist as well as the pathologist concluded that the patient had aplastic anaemia likely due to TMZ use.

There are several reports of TMZ-related BMD in the literature.^{8–12} These are, however, primarily reports of BMD following longer periods of TMZ treatment. In 2011, Villano *et al* analysed more than 3490 patient reports of haematological adverse events following TMZ, including 76 cases of anaplastic anaemia. The median duration of TMZ treatment was 6 weeks, but the authors underlined that the duration of TMZ exposure may be short prior to developing aplastic anaemia.⁸

Armstrong *et al*¹³ proposed a model to predict the likelihood of myelosuppression following TMZ treatment. Male gender and not being on corticosteroids or laxatives were both favourable characteristics. Polymorphisms in the methylguanine methyltransferase (MGMT) gene have been suggested to predispose to TMZ-BMF, as silencing of the MGMT promoter has been associated with increased TMZ toxicity.^{14 15} Previous reports are, however, conflicting, and bone marrow precursor cells are reported to have low levels of MGMT.¹⁵ In general, it seems difficult to predict who will experience these side effects. There might be a genetic susceptibility that is so far unknown.

Learning points

- ▶ Although temozolomide (TMZ) is generally well tolerated, clinicians need to be aware of the potentially life-threatening adverse events that may develop following such treatment, and that these effects may manifest very early.
- ▶ The risk of persistent bone marrow failure and other severe side effects is especially important to be aware of as the use of TMZ for metastatic disease in other tumour entities has been seen to have increased.
- ▶ The potential serious adverse effects should also be taken into consideration when treating patients with gliomas with prognostically more favourable tumour histology.

Acknowledgements The authors wish to thank the radiologist, Dr Saxhaug, for helping to prepare the MRI.

Contributors All the authors have participated in the care of the patient and agreed, based on the signed patient consent form, that the case should be published. The manuscript was drafted by the first author, KV, and critically reviewed by all the authors before being submitted by PB.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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