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Severe and Prolonged Myelosuppression during Concomitant Temozolomide and Radiotherapy Treatment in a Patient with Glioblastoma Multiforme

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: We describe the case of a patient with glioblastoma (GBM) who developed severe and prolonged myelosuppression during concomitant daily temozolomide (TMZ) and radiotherapy (RT)

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treatment. Analysis of polymorphisms in genes correlated with TMZ-induced myelotoxicity was also performed.

Presentation of the Case: A 67–year-old man with diagnosis of GBM undergoing concomitant RT-TMZ treatment developed severe and prolonged pancytopenia that led to discontinuation of TMZ and required frequent platelet and red cells transfusions. Analysis of single nucleotide polymorphisms (SNPs) in the genes NAD(P)H dehydrogenase, quinone 1 (NQO1) and glutathione S-transferase pi 1 (GSTP1) was carried out. Both SNPs were found to be wild-type.

Discussion: TMZ is an oral alkylating agent used for the treatment of glioblastoma. TMZ is usually considered well tolerated and safe, with nausea and mild myelosuppression being the most common side effects. However, severe haematologic adverse events have been also reported. Recently, there has been growing interest in gene polymorphisms that might be associated with an increased risk of hematologic toxicity.

Conclusion: Myelosuppression is a side effect that can occur relatively early during concomitant TMZ treatment and can negatively impact on patient's quality of life. Further studies are warranted to find out a correlation between genetic factors and the occurrence of severe hematologic toxicity.

Keywords: Temozolomide; glioblastoma; myelosuppression.

ABBREVIATIONS

GBM: Glioblastoma multiforme, TMZ: Temozolomide, RT: radiotherapy.

1. INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. The standard treatment for newly diagnosed glioblastoma consists of maximum safe surgical resection followed by radiotherapy (RT) with concomitant and adjuvant chemotherapy with Temozolomide (TMZ) [1]. The use of TMZ, an oral alkylating agent, in association with RT can improve overall survival of patients with GBM [1-2]. TMZ is relatively safe and generally well-tolerated. However, severe haematologic adverse events have been reported in several case reports and small series [3-11]. Recently, there has been growing interest in the analysis of gene polymorphisms that might be associated with an increased risk of hematologic toxicity [12-15].

We describe the case of a patient with GBM who developed severe and prolonged myelosuppression during concomitant daily TMZ and radiotherapy treatment. Analysis of polymorphisms in genes correlated with TMZ-induced myelotoxicity was also performed.

2. PRESENTATION OF THE CASE

A 67–year-old man with a history of arterial hypertension was admitted to the emergency department with paresthesias of the left upper extremity.Magnetic resonance imaging of the brain showed an enhancing solid mass (20 mm) in the right parietal lobe and diffuse signal hyperintensity on T2-weighted images in the right hemisphere suggestive of gliomatosis cerebri (Fig. 1). The patient subsequently underwent a right temporal craniotomy and subtotal excision of the mass. The histopathological findings of the tumor were consistent with the diagnosis of GBM. Molecular analysis revealed methylation of the O^6-methylguanine-DNA-methyltransferase (MGMT) gene promoter in the tumor sample.

The patient was put on antiepileptic medication with levetiracetam and referred to us for adjuvant treatment. He began treatment with RT and concomitant daily TMZ at a dose of 140 mg/die (75 mg/m^2). The planned RT dose was of 59.4 Gy to be given in 33 fractions of 1.8 Gy. Prior to treatment the patient had a white blood cell (WBC) and platelet (PLT) count of 8.8 x 10^3/uL and 197 x 10^3/uL, respectively. He did not receive co-Trimoxazole prophylaxis. During treatment, complete blood count (CBC) was carried out regularly once a week. He tolerated the combined therapy quite well, being mild fatigue the main side effect. After 21 of 33 planned fractions of radiation therapy and 30 of 47 days of TMZ, a platelet count of 11 x 10^3/uL was found. TMZ and RT were immediately stopped. One week later, when the platelet count dropped to 8 x 10^3/uL and multiple petechiae appeared on the trunk and arms, he was hospitalized in the medical oncology department. During hospitalization he became pancytopenic and required repeated platelet and red cell transfusions. He was treated with growth factors,

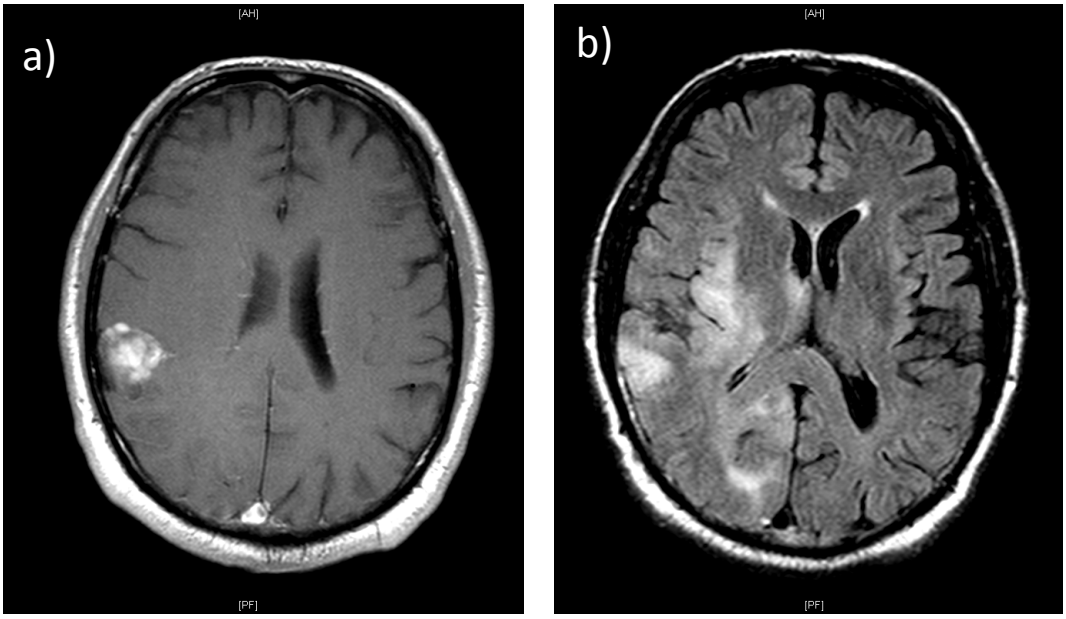

Fig. 1. Brain MRI of the patient at diagnosis

a) Enhanced lesion in the right parietal lobe on axial T1-weighted contrast image. b) Diffuse signal hyperintensity on axial T2-weighted image.

Table 1. Haematologic parameters over time

	Platelets (x 10^3/uL)	WBC (x 10^3/uL)	Hemoglobin (g/dl)
Baseline values at the beginning of RT/TMZ	197	8.8	13.5
Day 13 of RT/TMZ	140	7.8	14.4
TMZ discontinuation (day 21 of RT/TMZ)	11	2.28	11.3
Day 6 from TMZ discontinuation	12	0.16	9.4
Day 9 from TMZ discontinuation	29	0.09	9.2
Day 15 from TMZ discontinuation	16	0.26	8.0
Day 22 from TMZ discontinuation	7	1.61	7.8
Day 29 from TMZ discontinuation	11	2.14	7.9
Day 41 from TMZ discontinuation	23	2.20	7.0
Day 65 from TMZ discontinuation	34	4.3	9.8
Day 125 from TMZ discontinuation	16	2.99	7.6
Day 163 from TMZ discontinuation	16	2.77	8.4
Day 206 from TMZ discontinuation	16	3.29	9.1
Day 305 from TMZ discontinuation	34	4.03	9.8
Day 402 from TMZ discontinuation	72	4.35	13.5
Day 590 from TMZ discontinuation	130	3.60	9.3

RT, radiotherapy; TMZ, temozolomide; WBC, white blood cell

erythropoietin and antibiotics. Serum Epstein Barr virus and cytomegalovirus IgMtiters were undetectable. Vitamin B12 and folic acid levels were normal. The values of white blood cells, platelets and hemoglobin (Hb) during the whole period are shown in Table 1.

The patient was discharged from the hospital after one month with partial recovery of blood values. He completed his course of RT without concomitant TMZ. No adjuvant treatment with TMZ was started. Because of persistent pancytopenia a bone marrow aspirate and biopsy were performed one month after the end of treatment. The marrow was hypocellular (5-10%) and the erytroid series was hyperplastic with marked signs of dysplasia. The granulopoietic and megakaryopoietic lineages were hypo-

represented but without dysplasia. Several plasma cells with reactive features were observed in the marrow interstitium. Cytogenetic analysis showed a normal karyotype. Analysis of single nucleotide polymorphisms (SNPs) in the genes NAD(P)H dehydrogenase, quinone 1 (NQO1; rs1800566) and glutathione S-transferase pi 1 (GSTP1; rs1695) was carried out as previously described by Sylvester et al. [16]. Both SNPs were found to be wild-type (Table 2).

Table 2. Genotyping results

SNPs		Increased risk	Global frequencies [19]
GSTP1 (rs1695)	AG	AA	AA: 0.33, AG: 0.55, GG: 0.12
NQO1 (rs1800566)	AA	GG	GG: 0.60, AG: 0.37, AA: 0.03

SNPs, single nucleotide polymorphisms; GSTP1, glutathione S-transferases pi 1; NQO1, NAD(P)H dehydrogenase (quinone) family.

No further treatment was administered until 20 months from GBM diagnosis when, following disease progression, the patient underwent a second course of RT (37.5 Gy in 15 fractions of 2.5 Gy) without TMZ. MRI of the brain performed one month after the end of RT showed further tumor progression and the patient died two years after the initial diagnosis of GBM. The values of the last CBC were: WBC: 3.6 x 10^3/uL; PLT: 130 x 10^3/uL; Hb: 9.3 g/dl.

3. DISCUSSION

TMZ is an oral alkylating agent with activity against brain tumors. TMZ is usually considered well tolerated and has a good toxicity profile. The cytotoxic effect of TMZ is caused by the generation of O^6-methylguanine DNA adducts; when the enzymes of the mismatch repair system attempt to repair this alteration, the mechanism of apoptosis is activated. Myelosuppression is the most common haematologic adverse event of TMZ but it is a non-cumulative and reversible effect, and bone marrow recovery usually occurs within 28 days [17]. However, severe myelosuppression has been also reported. In the phase III trial of the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC) of RT with concomitant and adjuvant TMZ in patients with newly diagnosed GBM, Stupp et al. [1] reported a 16% rate of grade 3-4 myelosuppression. Grade 3-4 thrombocytopenia was observed in 3% and 11% of patients during concomitant and adjuvant treatment, respectively. Higher rates of myelotoxicity were reported by other authors. Doyle et al. [3] observed a 19% rate of severe myelosuppression in 16 patients with GBM treated with concomitant daily TMZ and RT. In a series of 52 patients with newly diagnosed high-grade gliomas receiving RT with concomitant and adjuvant TMZ, Gerber et al. [4] reported a 25% rate of grade 3-4 myelosuppression and 19% of grade 3-4 thrombocytopenia that caused discontinuation of treatment in 17% of patients. More recently, Villano et al. [18] reviewed all the TMZ-associated haematologic adverse events reported in the FDA Med-Watch database between 1997 and 2008, and they identified 228 cases of pancytopenia. Death occurred in 56 patients because of pancytopenia or its complications. The median duration of TMZ treatment was less than 3 weeks. Most of the cases were diagnosed within a week from the end of combined RT-TMZ treatment and, in 59 patients, during concomitant TMZ treatment, as in our case.

The association between genetic alterations in genes involved in DNA repair and drug metabolism and the risk of severe myelosuppression has been addressed in several studies [12-15]. Armstrong et al. [13] observed that the presence of the A allele of NQO1 and of the G allele of GSTP1 decreased the risk of toxicity. Reduced levels of NQO1 could lead to reduced activation of TMZ, while the relationship between GSTP1 and myelotoxicity is not explained. Moreover, the presence of the G allele of MGMT in peripheral blood cells resulted in a significant increase in risk of toxicity, as a result of lower DNA repair and increased DNA damage. In our case, it was possible to perform only analysis of NQO1 and GSTP1 polymorphisms but not of MGMT. Both SNPs were found to be wild-type and no conclusions can be drawn from these findings. Data from a greater number of patients could help in treatment decision. However, currently genetic analysis is not routinely performed at our institution.

4. CONCLUSION

In conclusion, our case shows that severe and prolonged myelosuppression is a side effect that can occur relatively early during concomitant TMZ treatment and can negatively impact on patient's quality of life. Physicians should be

aware of this potential long-term complication and should carefully evaluate hematopoietic function during TMZ treatment in order to eventually detect early bone marrow failure. Further studies are warranted to find out a correlation between genetic factors and the occurrence of severe hematologic toxicity.

CONSENT

Written consent for publication of case details was obtained from the patient's next of kin.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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