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The use of temozolomide in a patient with chronic thrombocytopenia: A case report

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Abstract

Thrombocytopenia is commonly experienced with Temozolomide (TMZ) during treatment for Glioblastoma (GBM). With the increasing prevalence of obesity and associated Non-Alcoholic Steatohepatitis (NASH) worldwide, chronic thrombocytopenia is becoming increasingly common, and necessitates modifications in the standard of care treatment regimen for GBM. To date, no guidelines are present addressing this dilemma. We present a case of a patient with newly diagnosed GBM and NASH-associated cirrhosis with chronic thrombocytopenia and baseline platelet count of approximately 70,000/ µL. She received brain radiation alone followed by 6 cycles of adjuvant TMZ, initially with a 50% dose reduction and subsequent dose increase based on tolerability and stability of platelet counts. This case demonstrates the relative safety of TMZ in a patient whose platelets are affected by liver disease as opposed to bone marrow insufficiency.

Keywords: Thrombocytopenia; Temozolomide; Glioblastoma; Case report.

Abbreviations: ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; CBC: Complete Blood Count; DNA: Deoxyribonucleic Acid; GBM: Glioblastoma Multiforme; IMRT: Intensity Modulated Radiation Therapy; Lfts: Liver Function Tests; MGMT: Methylated Methylguanine Methyltransferase; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; OS: Overall-Survival; RT: Radiation Therapy; TMZ: Temozolomide.

Background

The recommended treatment for glioblastoma (GBM) includes temozolomide (TMZ) with concurrent radiation therapy for 6 weeks, followed by at least 6 cycles of adjuvant TMZ. The addition of TMZ to standard radiation therapy improved median overall survival (OS) [1] for this deadly cancer by approximately 2.5 months, but more importantly improved 2-year survival from 10% to 26%. Furthermore, the improvements were most marked in those patients with methylated methylguanine methyltransferase (MGMT) [2]. While this regimen is the current standard of care, temozolomide can cause thrombocytopenia (Grade 3-4 incidence 12%) [1] and, rarely, life-threatening hepatotoxicity [3].

TMZ demonstrates similar pharmacokinetics in patients with mild to moderate hepatic impairment (Child-Pugh I-II) compared to patients with normal liver function, though our review of the literature did not find any studies on this medication's pharmacokinetics in severe hepatic impairment. While FDA la-

beling for TMZ advises caution and interval liver function tests when treating a patient with known liver disease and/or hematologic abnormalities [4], our review of the literature did not find any guidance regarding dose adjustments or adjustments to TMZ regimens.

The rising prevalence of obesity and associated non-alcoholic steatohepatitis (NASH) liver disease in the United States [5,6], patients presenting with chronic thrombocytopenia from severe hepatic impairment are likely to become more common. Given that patients who receive the TMZ + RT regimen have significantly improved outcomes compared to RT alone, there is a need to evaluate the use of TMZ in patients with liver-disease-associated thrombocytopenia.

Case presentation

Our patient is a 74-year-old female with a past medical history of cirrhosis due to NASH with associated portal hypertension, esophageal varices, and chronic thrombocytopenia who presented following a ground level fall. During her initial evaluation, she underwent brain imaging that demonstrated a right front parietal contrast-enhancing lesion. Shortly after, she underwent a right parietal craniotomy for gross total resection. Pathology was consistent with GBM and MGMT was methylated.

She presented to neuro-oncology clinic the following month to discuss treatment, which would typically consist of concurrent TMZ and radiation therapy. Unfortunately, due to her persistent thrombocytopenia (baseline platelet count ~70,000/μL) and cirrhosis, the decision was made to forgo concurrent TMZ due to the adverse effects of myelosuppression and hepatotoxicity. She received standard Intensity Modulated Radiation Therapy (IMRT) to 6000 cGy in 30 fractions. She tolerated this well and post-radiation MRI showed stable disease.

After a discussion regarding the risks and benefits of taking TMZ, she elected to proceed with cycle 1 of adjuvant TMZ at a 50% dose reduction at 75 mg/m^2 for five days. Prior to starting TMZ, her labs were notable for a platelet count of 67,000/μL, aspartate aminotransferase (AST) of 75 U/L, alanine transaminase (ALT) of 51 U/L, alkaline phosphatase (ALP) of 124 U/L, and total bilirubin of 1.1 mg/dL. This decision was made after an interdisciplinary discussion with her gastroenterologist, with plans to monitor liver function tests (LFTs) and complete blood counts (CBC) weekly. She tolerated the first cycle well and the dose was subsequently increased to 125 mg/m^2 for the remainder of 6 cycles.

Throughout treatment, she remained asymptomatic and specifically denied neurologic deficits, headaches, or seizures. She never had adverse sequelae of thrombocytopenia or required transfusions. Weekly CBCs and LFTs were obtained with platelet count ranging from 54,000/ μL to 74,000/ μL and LFTs remained stable. Table 1 depicts lab trends throughout treatment. After completion of 6 cycles, she went on to surveillance.

Discussion

We present an interesting case of a patient with chronic thrombocytopenia due to NASH cirrhosis who was diagnosed with GBM and the subsequent dilemma in treatment. In a thorough literature review, there has yet to be research conducted or guidelines given about the treatment of GBM in this patient population, despite TMZ being first-line therapy especially in MGMT-methylated GBM.

GBM confers a poor prognosis with population-based studies reporting a median survival of 42.4% at 6 months, 17.7% at one year, and 3.3% at two years [7]. Despite being the highest funded intracranial malignancy by the NIH over the past 40 years, treatment options remain limited and survival rates have not improved significantly [8]. Currently, standard treatment consists of performing surgical resection followed by concurrent chemoradiotherapy and 6 cycles of TMZ. This protocol has led to modest improvements in overall survival of 27.2% at 2 years, 16.0% at 3 years, 12.1% at 4 years, and 9.8% at 5 years [9]. MGMT methylation is the strongest predictor of a patient's response to TMZ. This is thought to be due to direct DNA repair by MGMT leading to resistance to alkylating agents like TMZ, with promoter methylation subsequently silencing expression [9].

Hematologic adverse events associated with TMZ have been widely documented in the literature. In Stupp el al. trial in 2005, severe thrombocytopenia (grade 3-4) was reported in 3% of patients who received concomitant radiation and TMZ and 11% during adjuvant TMZ therapy [1]. Other studies such as Gerber et al. suggest that the incidence of severe thrombocytopenia may be even higher, reporting that 19.2% of patients had grade 3-4 thrombocytopenia with a median duration of 32 days, with subsequent need for platelet transfusions (10%) and discontinuation of therapy (17%) [10].

Several studies have looked to identify predictors associated with severe hematologic toxicity. Fontanilles et al. noted a decrease in platelet count by ≥35% after 6 weeks of concurrent radiation and TMZ was a strong predictor of clinically significant (≤100,000/ μL) TMZ-induced thrombocytopenia [11]. Lomabardi et al. found that pretreatment platelet count of ≤300,000/ μL and certain polymorphic variants in the cytochrome P450 oxidoreductase and methionine adenosyltransferase 1A genes predicted grade 3-4 myelotoxicity [12]. Furthermore, Sabharwal et al. found that inactivation of MGMT expression in peripheral blood mononuclear cells was associated with more severe myelotoxicity [13]. Multiple studies discovered a higher risk of myelotoxicity in female [10,12,14], which is thought to be due to sex differences in pharmacokinetics and pharmacodynamics. Furthermore, females on average have a higher percentage of body fat which affects volume of distribution along with lower glomerular filtration rates affecting the clearance of the drug, ultimately leading to more adverse effects [15]. In this case, our patient had some of these predictive factors including female sex, elevated BMI, and pretreatment platelet count of ≤300,000/ μL, placing her at risk for more severe myelosuppression, therefore leading to a tailored treatment plan. As the options for treatment of GBM are limited, it is important to take early prognostic indicators into account when determining management. Future studies may look at incorporating these predictive indices into a tool that can be used to anticipate potential hematologic adverse effects prior to treatment initiation and guide increased frequency of blood testing.

If a patient is at high risk for severe toxicity, an option for treatment could be changing the scheduling and dosing of TMZ.

Table 1: Lab trends throughout treatment.

	Prior to treatment with adjuvant TMZ	After 1st cycle	After 2nd cycle	After 3rd cycle	After 4th cycle	After 5th cycle	After 6th cycle	Normal range for lab values
Platelet (x10^3/ µL)	71	62	74	58	66	65	62	**150-400**
Hemoglobin (g/dL)	11.4	11.8	11.9	11.4	11.8	11.9	11.8	**11.0-15.1**
White Blood Cell (x10^3 /µL)	2.3	2.6	2.5	2.7	2.6	2.5	2.1	**4.0-11.0**
ANC (x10^3 /µL)	1.2	1.3	1.5	1.6	1.4	1.4	1.1	**1.3-7.5**
ALC (x10^3 /µL)	0.7	0.9	0.6	0.8	0.7	0.7	0.6	**0.7-3.9**
AST (U/L)	75	54	54	49	62	47	60	**15-41**
ALT (U/L)	51	39	43	44	54	44	52	**7-52**
Alkaline Phosphatase(U/L)	124	123	128	126	148	148	168	**32-91**
Total bilirubin (mg/dL)	1.1	1.4	1.5	1.3	1.2	1.4	1.3	**0.3-1.0**

The RESCUE trial included 120 patients with recurrent high-grade glioma, not all GBM and aimed to assess the efficacy and safety profile of continuous dose intense TMZ 50 mg/m^2/day. One year survival in the GBM cohort ranged from 14.8% to 28.6%. This protocol was well tolerated with 15.8% having grade 3 lymphopenia but other hematologic toxicities being very uncommon with no significant effect on platelet count [16]. As already noted, thrombocytopenia is less frequent in the daily schedule during IMRT than during the standard 5-day every 4 weeks cycling. Wei et al. conducted a systematic review on the efficacy and safety of various dose-dense regimens including the standard 5-day regimen, continuous regimen of 40–50 mg/m^2/d, 21 days on/7 days off regimen, 7 days on/7 days off regimen. They found a significant difference in grade 3 to 4 lymphopenia with higher rates in the standard schedule (76.5%), however no significant difference in other hematologic toxicities [17].

The National Health and Nutrition Examination Survey documented that in the US population, the prevalence of obesity was around 42% in 2017-18, and is only expected to rise moving forward [6]. Given this worsening global epidemic of obesity and metabolic disorder, nonalcoholic fatty liver disease (NAFLD) is becoming one of the most common causes of liver disease, with an estimated prevalence in the US of 24% [5]. With a rapid rise in these conditions and the subsequent effect on platelet counts, more research is needed to address the implications when treating GBM and a risk-benefit analysis of giving concurrent TMZ in patients with chronic thrombocytopenia, with the goal of creating guidelines on how to approach treatment in this situation.

Recently, there has been more interest in investigating methods to prevent TMZ associated thrombocytopenia in newly diagnosed GBM. The PLATUM trial enrolled 20 patients with grade 3 or 4 thrombocytopenia during initial chemoradiation and gave weekly subcutaneous injections of the thrombopoietin receptor agonist romiplostim. With this intervention, 60% of patients were able to complete 6 cycles of TMZ [18]. Another group presented a case of using Carica papaya leaf extract for thrombocytopenia, with report improvement in platelet counts from less than 10,000/ µL to 113,000/ µL [19]. This field of study requires more exploration, with hopes of finding a solution to this growing problem.

Conclusion

We present a case report on a patient with history of chronic thrombocytopenia due to NASH cirrhosis who was treated for GBM with IMRT alone followed by 6 cycles of standard-dose TMZ. As NASH becomes more prevalent, we need to approach each patient individually to best balance the risks of toxicity and benefits of therapy. This case demonstrates the safety of TMZ in a patient with NASH-associated chronic thrombocytopenia and emphasizes the need for further clinical study to create guidelines in this subset of patients with GBM.

Declarations

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Informed consent: Informed consent was obtained.

Author contributions: Rosalyn Marar and Conor Houlihan contributed to literature search and manuscript writing. Nicole shonka contributed to direct patient care, editing, and supervising this entire work.

Data availability: The authors declare that data supporting the findings of this study are available within the article.

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