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Temozolamide-Associated Pancytopenia in a Patient with Glioblastoma Multiforme

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor. GBM treatment is a combined modality approach involving maximum surgical resection, adjuvant post-operative radiation and adjuvant chemotherapy treatment.There is a greater risk of hematological toxicity in concurrent temozolomide and radiation therapy. We reported that pancytopenia has been developed on a 54-year old female patient with GBM after concurrently used temozolomide and radiotherapy treatment. It should be kept in mind that this side effect may develop because the risk of morbidity and mortality may be elevated. Therefore, supportive therapies should be started immediately in patients where this toxicity developed.

Keywords:
Temozolomide , Glioblastoma multiforme , Pancytopenia

Conflict of interest:
The authors report no declarations of interest.

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in all brain tumors. It is a malignant tumor originating from the star-shaped astrocytes in the brain. The survival of patients with glioblastoma is approximately 10 to 12 months (1).

Common clinical presentations are headache, seizures, or rapid progression of a focal neurological deficit.(2).Therefore, brain imaging methods are useful in the initial diagnosis. A histologic diagnosis is required for treatment of patients with brain tumors. This can be accomplished either at the time of surgical resection or with a stereotactic biopsy.

GBM is rapidly progressive tumor that can be best managed with a combined modality approach, incorporating maximal surgical resection, adjuvant postoperative radiation therapy and adjuvant chemotherapy. Adjuvant radiation therapy is a standard component of therapy for GBM that has been shown to improve local control and survival after resection. Combination therapy with radiation plus concurrent daily temozolomide followed by monthly temozolomide is the standard for with newly diagnosed glioblastoma in adults (3).

Temozolomide is an oral alkylating agent. It is the first chemotherapy agent in GBM. Bevacizumab and Carmustine polymer wafers are other chemotherapy agents in GBM (3). Temozolomide improves progression-free and overall survival when given in combination with radiation (5).

Temozolomide can cause hematological (anemia,neutropenia,thrombocytopenia,leukopenia) and non-hematological toxicity (nausea, anorexia,fatigue). There is a greater risk of hematological toxicity in chemoradiotherapy. We aimed to present a case of prolonged pancytopenia in a patient with temozolomide and radiation therapy.

CASE REPORT

A 54-year-old female was admitted to the emergency department with amnesia, headache and speech disorder. She didn't have any chronic diseases. Through magnetic resonance imaging (MRI) of the brain, the mass of 64x50x53 mm in the right frontotemporal lobe and diffuse edema in the brain parenchyma has been detected. After an evaluation by neurosurgery, the patient has been operated. Pathology confirmed the diagnosis of GBM. The treatment plan was oral temozolomide 75 mg/m2 once per day with concurrent radiation therapy.

At the 6th week of treatment, she presented to the emergency department with itching and petechiae. Her complete blood cell count showed pancytopenia with a white blood cell count (WBC) of 0.9 K/µL (normal range.3.7–10.4 K/µL), hemoglobin of 9.9 g/dL (normal range: 10.8–15.1 g/dL), neutrophil count (NEU) of 0.2 (normal range: 1.8-7.8 (K/µL) and platelet count of 13 K/µL (normal range: 149–371 K/µL). Her blood count was normal before treatment and at other weeks of treatment. The side effects were evaluated according to The NCI Common Terminology Criteria for Adverse Events version 5.0. After receiving 6th cycle, it has been detected that she has grade 4 anemia, thrombocytopenia and neutropenia. Therefore , temozomide treatment has been discontinued. Other causes of this pancytopenia were investigated. Her blood count was within normal range for B12, folic acid, thyroid function tests, reticulocyte, direct coombs, infection markers, lactate dehidrogenase (LDH), liver function tests and coagulation tests were in the normal range. In her physical examination, there were no petechiae, purpura and ecchymosis. There were no signs of acute bleeding. In dermatological examination, skin candidiasis has been detected. Peripheral blood smear was consistent with blood count. Atypical cells have not been seen in the peripheral blood smear. We thought that her pancytopenia was associated with chemoradiotherapy toxicity. She was given platelet transfusion to keep platelet counts greater than 20 K/µL owing to no active clinical bleeding and started granulocyte-colony

stimulating factor (G-CSF) injections. She was started on prophylactic treatment with intravenous meropenem and fluconazole. At the same time, she was started topical nystatin cream. There was no other infection focus in the imaging due to prolonged neutropenia. She continued to receive supportive treatment with G-CSF injections, erythrocyte and platelet transfusions during 3 weeks. On day 23th, neutrophils started to increase and platelet count increased at the lastly.

DISCUSSION

GBM accounts for the great majority of primary tumors that arise within the brain parenchyma. GBM is seen in about 5/100 000 people. GBM accounts for approximately 20-30 % of all primary brain tumors. It is generally seen on people 40-60 years .Glioblastoma is more common in males, male-to-female ratio of 1.5 : 1. The survival of patients with GBM is approximately 10 to 12 months. It showed a 37% relative reduction in the risk of death and a clinically meaningful median survival of 14.6 months for patients treated with radiotherapy plus temozolomide as compared with those who received radiotherapy alone (5).

The most common symptoms of glioblastoma are headache (%50-60), seizures (%20-%50) memory loss and behavioral changes (%10-%40). These findings are associated with increased pressure due to rapid growth of the tumor. The deep-seated infiltrative masses can also cause cognitive difficulties or personality change. Our patient had amnesia, headache and speech disorder.

Standard therapy combines irradiation with concomitant and adjuvant temozolomide. Given continuously at low dose (75 mg/m ^{2}/day) during the 6 weeks of radiotherapy, followed by 4-6 weeks cycles (150–200 mg/m ^{2} on days 1–5), median overall survival is increased from 12.1 to 14. 6 months with acceptable toxicity (5).

Patients receiving temozolomide chemotherapy are at risk for hematologic toxicity and should be monitored with weekly complete blood counts during radiation therapy. There is a greater risk of hematological toxicity in chemoradiotherapy (6) . During the treatment, the susceptibility to opportunistic infections increases. In addition, pneumocystis pneumonia prophylaxis should be initiated. We have detected skin candidiasis in our patient.

During adjuvant temozolomide, a complete blood count should be obtained on days 21 and 28 of each cycle to monitor for toxicity and help guide dose adjustments, if necessary. The incidence of hematologic toxicity is approximately two to three times higher in women than in men for reasons that are not yet clear. Haematological side effects include aplastic anemia, myelodysplasia, and treatment-induced acute myeloid leukemia (t-AML), plasmablastic lymphoma.(7). Cases of secondary t-AML and other hematologic malignancies in association with temozolomide exposure have mostly been in patients with previous exposure to other alkylating agents (8). Our patient had pancytopenia and continued for 3 weeks despite G-CSF injection. Radiation therapy is not known to increase bleeding risk and can be continued safely during periods of mild to moderate thrombocytopenia.(9). Therefore, early diagnosis of temozolomide-induced pancytopenia is important since it is associated with high morbidity and mortality (10).

When pancytopenia due to temozolomide is detected, the agent firstly should be stopped . Empiric broad-spectrum antibiotic therapy should be initiated to prevent sepsis or opportunistic infection. In our patient, there was no opportunistic infection except skin candidiasis.

The current treatment of temazolide-induced pancytopenia includes transfusion, growth factors; rarely eltrombopag, immunosuppressive therapy (IST), and supportive treatment with allogeneic hematopoietic stem cell transplantation (alloHSCT). Hematopoietic growth factors have been shown to shorten the duration of antibiotic therapy and complete blood counts recovery. Rarely, ATG and cyclosporine

which are used to treat aplastic anemia can be used if pancytopenia persists (11-12) . At the end of 3 weeks, we oberserved that neutrophil and erythrocyte counts has been recovered with supportive transfusions and G-CSF injections on our patient. Bone marrow biopsy would be planned if there was no increase in blood count. It has been reported to be effective in the spontaneous recovery of drug-induced aplastic anemia, usually one to two months after stopping the drug (13).

As a result, chemoradiation increases survival in GBM, but may cause hematological side effects. Aplastic anemia may progress in prolonged pancytopenia in patients given temozolomide. This possibility should not be forgotten because the risk of mortality. When pancytopenia is detected, first-line chemoradiotherapy should be stopped. G-CSF and supportive treatment (such as empiric broad-spectrum antibiotic, platelets and erythrocyte transfusions) immediately should be started. Aplastic anemia or pancytopenia can be resolved spontaneously, or rarely treat with IST or bone marrow transplantation.

REFERENCES

1. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. Neuro Oncol 2016; 18:v1.
2. Chang SM, Parney IF, Huang W, et al. Patterns of care for adults with newly diagnosed malignant glioma. JAMA 2005; 293:557.
3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352:987.
4. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA 2015; 314:2535.
5. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. Stupp R, Mason WP, van den Bent MJ, et al. N Engl J Med. 2005;352:987–996
6. Oh J, Kutas GJ, Davey P, et al. Aplastic anemia with concurrent temozolomide treatment in a patient with glioblastoma multiforme. Curr Oncol 2010; 17:124.
7. Clark SW, Taylor J, Wang DL, et al. Plasmablastic lymphoma after standard-dose temozolomide for newly diagnosed glioblastoma. Neurology 2013; 81:93.)
8. Neyns B, Cordera S, Joosens E, Pouratian N. Non-Hodgkin's lymphoma in patients with glioma treated with temozolomide. J Clin Oncol 2008; 26:4518
9. Karremann M, Krämer N, Hoffmann M, et al. Haematological malignancies following temozolomide treatment for paediatric high-grade glioma. Eur J Cancer 2017; 81:1.
10. Gerber DE, Grossman SA, Zeltzman M, et al. The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. Neuro Oncol 2007; 9:47
11. Temozolomide induced bone marrow suppression-A single institution outcome analysis and review of the literature. Kourelis TV, Buckner JC, Gangat N, Patnaik MM. Am J Hematol. 2015;90:0. 11. Temozolomide-induced Aplastic Anemia Treated with Eltrombopag and Granulocyte Colony Stimulating Factor: A Report of a Rare Complication, Shauna L Newton, Kadra Kalamaha, and Hermina D Fernandes, Cureus. 2018; 18;10(9):e3329.
12. Temozolomide induced bone marrow suppression-A single institution outcome analysis and review of the literature. Kourelis TV, Buckner JC, Gangat N, Patnaik MM. Am J Hematol. 2015;90:0.
13. Scheinberg P, DeZern AE, Steensma DP. The American Society of Hematology Self-Assessment Program (ASH-SAP) Vol. 6. Washington, DC: American Society of Hematology; 2016. Acquired marrow failure syndromes: aplastic anemia, paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndromes; pp. 489–520.