Another Cause of Pancytopenia in a Patient Receiving Temozolomide

Yavuz Pehlivan^a Alper Sevinc^b Ibrahim Halil Turkbeyler^a Ahmet Dirier^c
Mehmet Emin Kalender^b Celalettin Camci^b

Departments of ^aInternal Medicine, ^bMedical Oncology and ^cRadiation Oncology, School of Medicine, Gaziantep University, Gaziantep, Turkey

Key Words

Temozolomide · Myelosuppression · Pancytopenia · Vitamin B₁₂ deficiency · Glioblastoma multiforme

Abstract

Objective: To report pancytopenia caused by temozolomide, a second-generation alkylating agent. **Clinical Presentation and Intervention:** A 22-year-old patient presenting with seizures and confusion was seen in the emergency room. Cranial magnetic resonance imaging revealed a mass. After surgery, the patient was diagnosed with glioblastoma multiforme and was given temozolomide at 150 mg/m² on days 1 through 5 every 4 weeks. During the last cycle of temozolomide, grade 3 thrombocytopenia persisted. Possible causes of pancytopenia including vitamin B₁₂ deficiency were investigated. **Conclusion:** This case report shows that vitamin B₁₂ deficiency can be a potential cause of pancytopenia and it should be kept in mind for patients receiving chemotherapy.

Copyright © 2011 S. Karger AG, Basel

Introduction

Temozolomide is a second-generation alkylating agent. With nearly 100% bioavailability, temozolomide is administered orally, most commonly once a day for 5

days in a 28-day cycle. It has been approved by the Food and Drug Administration for the treatment of refractory anaplastic astrocytoma and newly diagnosed glioblastoma multiforme. Clinical efficacy of temozolomide has also been demonstrated in melanoma, and a variety of other solid tumors [1]. Used as a single agent, temozolomide has also been shown to have activity against brain metastases from melanoma [2]. Three phase II trials have been reported using temozolomide in patients with brain metastases from solid tumors [3–5]. We are reporting this case in order to direct the attention of researchers to another possible cause of pancytopenia in patients receiving chemotherapy.

Case Report

A 22-year-old female patient was admitted to our University Hospital with complaints of seizure and confusion. Neurological examination revealed disorientation of time and place, agitation, mild nuchal rigidity, and mild bilateral papilledema. Cranial magnetic resonance imaging revealed a 5 × 6 × 6 cm irregularly shaped mass with cystic components on the left temporal lobe that was causing peripheral edema and midline shifting. Dexamethasone (16 mg/day) and valproic acid as antiepileptic therapy were started. Total excision of the mass from the temporal lobe was performed. Histopathological examination of the specimens showed a high-grade malignant glioma. After surgery, maximum-dose radiotherapy was delivered to the left temporal lobe. Residual mass was detected upon follow-up cranial MRI

Table 1. Complete blood counts before and after chemotherapy

Cycles	Before treatment						After treatment					
	WBC/ μl	Neu/ μl	Hb g/dl	MCV fl	MCHC g/dl	Plt/ μl	WBC/ μl	Neu/ μl	Hb g/dl	MCV fl	MCHC g/dl	Plt/ μl
1	5,500	3,650	12	90	34.4	200,000	4,600	3,220	11.5	91.5	34.2	179,000
2	5,000	3,250	11.8	88.9	34	185,000	4,500	3,100	11	89.3	34.5	150,000
3	4,700	2,910	11.3	94.5	34	160,000	3,700	2,100	10.5	97.8	34.4	135,000
4	4,750	2,945	11.5	94.5	35.1	150,000	4,250	2,550	10.2	94.8	35.8	120,000
5	4,500	3,050	11	95.2	34.8	140,000	4,100	2,150	10.5	99	34.5	95,000
6	4,200	2,750	11.5	101	32.7	120,000	3,120	1,820	11.2	100	31.9	48,000

Normal range: white blood cells (WBC) 4,300–10,300; neutrophils (Neu) 1,800–6,400; hemoglobin (Hb) 12.3–15.3; mean corpuscular volume (MCV) 80–96; mean corpuscular hemoglobin concentration (MCHC) 32–36; platelets (Plt) 150,000–400,000.

4 months after surgery. A second surgery was not planned. Subsequently, the patient was informed about the possible use of temozolomide, to which she assented. The patient was initially given temozolomide at 150 mg/m² on days 1 through 5 every 4 weeks. The dosage was increased to 200 mg/m² at the second cycle. After the 6th cycle, due to an abscess she was seen by a dentist who inquired about the treatment plan and laboratory findings, which were as follows: hemoglobin level: 11.2 g/dl (13.6–17.2), MCV: 100 fl (80–95), WBC: 3,120/mm³ (4,300–10,300), platelet count: 48,000/mm³ (156,000–373,000), reticulocytes: 1.4%. Grade 3 thrombocytopenia was thought to be due to temozolomide-induced myelosuppression because of the known primary toxicity associated with temozolomide treatment. Temozolomide was discontinued for 2 weeks but no improvement regarding the complete blood count values was observed. The detailed examination of the complete blood counts before and after chemotherapy is shown in table 1. Peripheral smear revealed oval macrocytosis and hypersegmented granulocytes. Serum vitamin B₁₂ level was observed to be 100 pg/ml (243–894). Bone marrow examination was compatible with megaloblastic changes. A detailed medical history revealed that the patient was on a strictly vegetarian diet. Daily intramuscular vitamin B₁₂ injection therapy was applied for 5 days. Five days after vitamin B₁₂ treatment, the patient's reticulocyte count increased to 5.3% and monthly vitamin B₁₂ injections were recommended. Her control complete blood count levels were as follows: hemoglobin: 12.5 g/dl, WBC: 5,320/mm³, and platelets: 194,000/mm³. The patient's final control vitamin B₁₂ level was 986 pg/ml.

Temozolomide is a well-known cytotoxic agent known to cause myelosuppression. However, in this case, vitamin B₁₂ deficiency was the triggering etiological agent causing pancytopenia. After the diagnosis of vitamin B₁₂ deficiency, 5-day vitamin B₁₂ injection therapy was applied and the blood count levels were improved. Under these circumstances vitamin B₁₂ deficiency can be another potential cause of pancytopenia.

Discussion

Patients treated with temozolomide may experience myelosuppression, which tends to occur late in the treatment cycle and return to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21–40) and 28 days for neutrophils (range 1–44). In the present case, although temozolomide was discontinued for 2 weeks, pancytopenia persisted. Possible causes of pancytopenia were investigated and vitamin B₁₂ deficiency was identified.

Adverse effects of temozolomide are typical of traditional cytotoxic chemotherapy. The adverse events associated with temozolomide are mild to moderate and generally predictable; the most serious are noncumulative and reversible myelosuppression and, in particular, thrombocytopenia, which occurs in less than 5% of patients. Grade 3 and 4 hematological toxicity was documented in only 7% of patients for concurrent therapy treated prospectively in the European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada landmark study [6].

Myelosuppression is the dose-limiting toxicity for temozolomide in adults and children in the postchemotherapy period. Specific guidelines regarding dose reductions based on neutrophil and platelet counts are available in the manufacturer's package insert. Geriatric patients and women, who may clear the drug more slowly than men, are at greater risk for myelosuppression [7].

Doyle et al. [8] described 3 patients who developed severe myelosuppression after low-dose temozolomide and radiotherapy. In fact 2 patients had aplastic anemia. Concurrent co-trimoxazole was given that might have con-

tributed to toxicity. Another case report describes a case of aplastic anemia after the 4th cycle of adjuvant temozolomide [9]. The patient was on concomitant anticonvulsants. Moreover, Singhal et al. [10] described 2 patients who developed prolonged and severe myelosuppression after low-dose continuous temozolomide given concurrently with cranial radiotherapy. These patients did not receive any concurrent bone marrow toxic drugs such as anticonvulsants or co-trimoxazole, and vitamin B₁₂ and folate deficiency were also ruled out. Another case report described a patient with prolonged and severe thrombocytopenia with pancytopenia induced by radiation-combined temozolomide therapy. The case was investigated for a possible relationship between methylguanine-DNA methyltransferase status and pancytopenia. However, Nagane et al. [11] found out that there is not a remarkable relationship between methylguanine-DNA methyltransferase status and pancytopenia.

The principal hematologic manifestations of vitamin B₁₂ deficiency are macrocytic anemia, leukopenia, and thrombocytopenia with oval macrocytosis, anisocytosis,

poikilocytosis, and hypersegmented granulocytes on blood smear. Chemotherapeutics may not be the only reason to be blamed for cytopenia in cancer patients. It should also be kept in mind that other etiological factors such as dietary factors may also cause pancytopenia in patients receiving chemotherapy.

In this case report pancytopenia was found to be associated with vitamin B₁₂ deficiency. For that reason, considering other factors can play a vital role in the treatment of pancytopenia in patients receiving chemotherapy.

Conclusion

Insufficient improvement in pancytopenia during the postchemotherapy period leads to the investigation of other etiologic factors. This case report showed that vitamin B₁₂ deficiency can be another potential cause of pancytopenia and it should be kept in mind for patients receiving chemotherapy.

References

- 1 Aoki T, Hashimoto N, Matsutani M: Management of glioblastoma. *Expert Opin Pharmacother* 2007;8:3133–3146.
- 2 Biasco G, Panteleo M, Casadei S: Treatment of brain metastases of malignant melanoma with temozolomide. *N Engl J Med* 2001;345:621–622.
- 3 Addeo R, De Rosa C, Faiola V, Leo L, Cennamo G, Montella L, Guarrasi R, Vincenzi B, Caraglia M, Del Prete S: Phase II trial of temozolomide using protracted low-dose and whole-brain radiotherapy for nonsmall cell lung cancer and breast cancer patients with brain metastases. *Cancer* 2008;113:2524–2531.
- 4 Christodoulou C, Bafaloukos D, Kosmidis P, Samantas E, Bamias A, Papakostas P: Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. *Ann Oncol* 2001;12:249–254.
- 5 Antonadou D, Paraskevaidis M, Sarris G, Coliarakis N, Economou I, Karageorgis P: Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol* 2002;20:3644–3650.
- 6 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–996.
- 7 Birner A: Pharmacology of oral chemotherapy agents. *Clin J Oncol Nurs* 2003;7(6 suppl):11–19.
- 8 Doyle TJ, Mikkelsen T, Croteau D: Fatal hematologic toxicity with prolonged continuous administration of temozolomide during radiation therapy in the treatment of newly-diagnosed glioblastoma multiforme: report of a phase II trial. *J Clin Oncol, ASCO Annu Meet Proc* 2005;23:1546.
- 9 Villano JL, Collins CA, Manasanch EE, Ramaprasad C, van Besien K: Aplastic anemia in patient with glioblastoma multiforme treated with temozolomide. *Lancet Oncol* 2006;7:436–438.
- 10 Singhal N, Selva-Nayagam S, Brown MP: Prolonged and severe myelosuppression in two patients after low-dose temozolomide treatment: case study and review of literature. *J Neurooncol* 2007;85:229–230.
- 11 Nagane M, Nozue K, Shimizu S, Waha A, Miyazaki H, Kurita H, Homori M, Fujioka Y, Shiokawa Y: Prolonged and severe thrombocytopenia with pancytopenia induced by radiation-combined temozolomide therapy in a patient with newly diagnosed glioblastoma – analysis of O6-methylguanine-DNA methyltransferase status. *J Neurooncol* 2009;92:227–232.