Emergence of Cytomegalovirus Disease in Patients Receiving Temozolomide: Report of Two Cases and Literature Review

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Temozolomide chemotherapy has become part of the therapy used to treat glioblastoma multiforme and refractory anaplastic astrocytoma. Temozolomide frequently produces profound lymphopenia. We report 2 cases of cytomegalovirus disease that occurred in patients receiving temozolomide therapy and review 4 additional cases reported in the literature. Narrow monitoring with cytomegalovirus antigenemia assay should be considered for recommendation.

Temozolomide is an oral alkylating agent with antitumor activity that has been approved by the Food and Drug Administration for newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma [1, 2]. The use of temozolomide together with radiotherapy after surgical resection, followed by temozolomide monotherapy, resulted in a statistically significant survival benefit for up to 5 years of follow-up, compared with the use of only radiotherapy for the treatment of glioblastoma after surgical resection [3, 4]. Postoperative adjuvant radiation therapy and temozolomide chemotherapy have become the standard treatment for these malignant diseases. Several trials investigating different future uses of temozolomide are currently being performed by the European Organization for Research and Treatment of Cancer and other groups. These temozolomide uses include the treatment of metastatic melanoma, brain metastasis, and low-grade glioma.

Temozolomide produces myelotoxic effects [5] and frequently produces profound lymphopenia [1, 6]. Importantly, several cases of Pneumocystis jiroveci pneumonia in patients receiving temozolomide have been reported [7–9]. In this regard, prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole) or pentamidine has been advised by the Food and Drug Administration and the European Organization for Research and Treatment of Cancer for patients receiving temozolomide therapy. Prophylaxis should be administered during temozolomide treatment and continued until recovery from lymphopenia has been achieved (ideally determined by measuring the CD4+ T-lymphocyte count).

Thus far, information regarding other opportunistic infections involving patients treated with temozolomide is scarce [10, 11]. We report 2 cases of cytomegalovirus (CMV) disease that have occurred in patients receiving temozolomide and review 4 additional cases previously reported in the literature [12–15].

Case reports. The first case was that of a 57-year-old woman with a diagnosis of glioblastoma multiforme. The patient was treated with radiotherapy, corticosteroids, and temozolomide after surgery. The temozolomide dosage was 75 mg/m2/day during the first radiotherapy concomitant phase of the therapy. She underwent prophylactic cotrimoxazole treatment. After 45 days of introduction of temozolomide treatment and before the beginning of the maintenance phase of the therapy, the patient developed gastrointestinal CMV disease. She had colitis with diarrhea, rectal bleeding, colonic ulcers, CMV-positive immunohistochemical findings in intestinal tissue, and pp65 antigenemia (less than 10 cells per 200,000 leukocytes). The patient developed lymphopenia (lymphocyte count, 703/μL), and her CD4+ T-lymphocyte count was 260/μL. After treatment with valganciclovir, symptoms improved, but 3 days later the patient was hospitalized because of an episode of meningitis due to extended-spectrum β-lactamase–producing Escherichia coli, which was probably related to a ventriculoperitoneal shunt (placed because of previous hydrocephalus during radiotherapy). The patient also had a new episode of rectal bleeding. Valganciclovir treatment was replaced with ganciclovir administered intravenously, meropenem was added, and the shunt was removed. After this treatment regimen was completed, the patient tested negative for CMV antigenemia and recovered well with no further symptoms, although she finally died as a result of malignant disease.

The second patient was a 59-year-old man with a diagnosis of primary high-grade B-cell lymphoma of the central nervous system. After the administration of different treatment protocols, he received temozolomide as a compassionate use treat-
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**Note.** CMV, cytomegalovirus; PCR, polymerase chain reaction.

a On an every other week schedule.

b First concomitant radiotherapy phase therapy.

c Dosage explained in the text.
ment. The temozolomide dosage was 150 mg/m²/day during a 5-month period (days 1–7 and 15–21 during the first 2 months and days 1–5 during the last 3 months). The patient also received prophylactic cotrimoxazole treatment. He had a CD4⁺ T-lymphocyte count of 168/µL and lymphopenia (lymphocyte count, 600/µL). Ten days after the last temozolomide cycle, he developed alveolo-interstitial pneumonitis and tested positive for pp65 antigenemia (150 cells per 200,000 leukocytes). Other opportunistic infections, such as those due to *P. jiroveci, Mycobacterium*, or fungi, were ruled out. *Pseudomonas aeruginosa* resistant to carbapenem was isolated from a sample obtained during bronchoalveolar lavage. After receiving treatment with ganciclovir, piperacillin-tazobactam, and colistin, the patient tested negative for antigenemia, showed improvement in clinical and radiological findings, and was ultimately discharged without symptoms. The final diagnosis was CMV alveolo-interstitial pneumonitis with *P. aeruginosa* superinfection. The patient finally died of his underlying disease.

Characteristics of 4 additional cases reported in the literature and these 2 new cases are shown in Table 1. In all these cases, temozolomide was used to treat patients with malignant central nervous system tumors. There were 4 women and 2 men; mean age was 62 years (range, 55–70 years). Temozolomide was administered for at least 1 month before the onset of infection. All patients were receiving temozolomide or had just finished temozolomide therapy some days before, except 1 patient who had completed temozolomide therapy 3 months previously. This patient developed CMV colitis and transverse myelitis and finally died of this opportunistic infection [12]. Five of the 6 patients were receiving concomitant treatment with corticosteroids, with daily doses not exceeding 12 mg of dexamethasone. All patients developed lymphopenia. Among the 3 patients for whom a CD4⁺ T-lymphocyte count was recorded, the measurement was less than 300/µL in 2 patients and less than 100/µL in 1 patient. One patient with 6-phosphate dehydrogenase enzyme deficiency who did not receive prophylaxis with cotrimoxazole developed *P. jiroveci* pneumonia [15]. Two of the 6 patients died of the CMV disease.

**Discussion.** Patients treated with temozolomide have an increased risk of infection. Opportunistic infections associated with the use of temozolomide have been related to underlying cellular immunosuppression. The majority of these opportunistic infections have occurred while patients were concurrently receiving steroids. Corticosteroids are used to prevent peritumoral edema in the majority of patients with these malignant gliomas. We cannot eliminate the possibility that the associated use of steroids might have played a role in the infection. The simultaneous use of temozolomide and corticosteroids in the treatment of the majority of this population makes it difficult to differentiate the roles of temozolomide and steroids, but the results of recent studies suggest that selective CD4⁺ lymphopenia is itself associated with temozolomide use [8, 12, 16]. Moreover, opportunistic infections, such as *P. jiroveci* pneumonia, have also been described in patients receiving temozolomide for treatment of melanoma, a group that seldom receive steroids [8]. Temozolomide probably induces immunosuppression, with profound T-cell lymphopenia, which is exacerbated by corticosteroids.

Prophylaxis with cotrimoxazole has been advised since the first research studies were performed with temozolomide [7], when the first *P. jiroveci* infections were reported. However, there is no recommendation for prophylaxis against other opportunistic infections, such as viral or fungal infections. In this case series it is shown that CMV reactivation is associated with temozolomide treatment. Surveillance for CMV antigenemia is recommended for patients who are receiving other types of cellular immunosuppression therapy, such as alemtuzumab. For these patients, preemptive therapy with ganciclovir or valganciclovir is advised, and perhaps such preemptive therapy should also be administered to patients receiving temozolomide. Because of the small number of cases and the different dosages of temozolomide used in our patient series, it is difficult to give a firmer recommendation regarding screening and preemptive therapy for the global management of CMV disease. Lymphopenia and CMV disease appeared after at least 1 month of temozolomide treatment with a dosage of greater than 75 mg/m²/day in all these patients. It seems reasonable that patients’ lymphopenia should be closely monitored and that if profound lymphopenia appears, screening for CMV infection by means of antigenemia or CMV polymerase chain reaction assay should be carried out. In any case, it is recommended that a high index of clinical suspicion for CMV disease be maintained.

In summary, we would like to draw attention to the emergence of CMV disease in patients receiving temozolomide treatment. A total of 6 cases, including these 2 new cases, have been described (Table 1). Narrow monitoring with CD4⁺ T-lymphocyte count and CMV antigenemia or CMV polymerase chain reaction assay should be considered for recommendation in patients receiving temozolomide. If new cases of CMV disease appear, preemptive therapeutic administration of valganciclovir or ganciclovir in patients who are receiving temozolomide treatment could be considered.

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