Bortezomib-induced Posterior Reversible Encephalopathy Syndrome in a Patient with Newly Diagnosed Multiple Myeloma

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a known but extremely rare side effect of bortezomib therapy. An unusual case of PRES possibly caused by bortezomib during induction treatment in a patient with multiple myeloma is reported. The patient experienced neither hypertensive crisis nor uremic encephalopathy at the onset of PRES, which are both well-known etiologies of PRES. The patient’s PRES-related symptoms resolved completely after discontinuation of bortezomib and administration of a bulk dose of corticosteroids. The importance of early recognition of this potential neurological complication must be emphasized because this new drug is being increasingly prescribed.

Key words: PRES, bortezomib, multiple myeloma

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Introduction

Bortezomib, a proteasome inhibitor that targets myeloma cells and their bone marrow microenvironment, is highly effective and generally well tolerated in patients with not only newly diagnosed, but also relapsed or refractory multiple myeloma (1, 2). The most frequent toxicities associated with bortezomib are gastrointestinal symptoms, anemia, thrombocytopenia, asthenia (fatigue, malaise and weakness), elevated calcium levels and peripheral neuropathy (3). Peripheral neuropathy in particular can become severe, which presents serious difficulties for many patients and represents a major clinical problem (4), while the central nervous system is not considered a main target organ for toxicity. Reports of posterior reversible encephalopathy syndrome (PRES) occurring in patients receiving a variety of antineoplastic therapies such as molecular targeting agents are increasing; however, bortezomib has rarely been reported to be associated with PRES, and only three cases of bortezomib-induced PRES have been reported thus far (5-7). A case of PRES possibly induced by bortezomib is herein described, the existing literature regarding bortezomib-induced PRES is reviewed and the underlying pathophysiology of this rare complication is explored.

Case Report

A 54-year-old woman was diagnosed with multiple myeloma (IgA-κ) in February 2012. The serum IgA level at symptom onset was 6,408 mg/dL. The patient participated in a phase II multicenter clinical trial with sequential VAD (vincristine, adriamycin and dexamethasone) and BD (bortezomib and dexamethasone) induction followed by autologous stem cell transplantation for newly diagnosed multiple myeloma patients (UMIN000002611). After the administration of VAD therapy, the serum IgA level decreased to 2,640 mg/dL. The patient then received BD therapy consisting of bortezomib at a dose of 1.3 mg/m² on days 1, 4, 8 and 11 and dexamethasone at a dose of 20 mg on days 1-2, 4-5, 8-
9 and 11-12 on an every 21-day cycle. However, the patient complained of drowsiness on day 8, which did not improve following dose reduction of oxycodone for bone pain control. Moreover, the patient suddenly developed generalized clonic-tonic convulsions and an altered mental status early in the morning on day 11. Emergency laboratory tests performed at that time showed no serious abnormalities in the liver or renal functions, and the levels of blood glucose, NH₃ and electrolytes were all within the normal limits. A cerebrospinal fluid (CSF) examination revealed protein-cytological dissociation (cells: 3/mm³, total protein: 95 mg/dL); however, molecular examinations for HSV, VZV and HHV-6 were all negative. The CSF findings were consistent with those of previously reported cases of drug-induced PRES. Although the patient’s blood pressure remained in the slightly high range (mean: 140/85 mmHg) after the first administration of bortezomib, no clinical signs of hypertensive crisis were observed. Computed tomography of the brain showed a slight low-density area in the subcortical white matter of the occipital lobes, indicating the possibility of PRES (Fig. 1). Moreover, magnetic resonance imaging (MRI) of the brain demonstrated extensive asymmetrical high intensity signals in the subcortical white matter of the occipital lobes and thalamus (Fig. 2A). The constellation of neurological symptoms along with the typical MRI image were highly suggestive of bortezomib-induced PRES; therefore, further administration of bortezomib was withheld and steroid pulse therapy (methylprednisolone: 1 g/day for three days) was administered. Since the patient developed no obvious neurological symptoms during the preceding VAD therapy, we assumed that high-dose steroids would not exacerbate the PRES, but rather could be administered as a precautionary approach for possible acute disseminated encephalomyelitis. Although progressive multifocal leukoencephalopathy (PML) could also be raised as a differential diagnosis based on the initial MRI findings, the drastic clinical courses observed in our case did not support a diagnosis of PML. The patient’s consciousness then improved dramatically and returned to normal within two days. No recurrent convulsions were observed even after discontinuation of the anticonvulsant agent. Moreover, subsequent MRI images, obtained one week and one month later revealed prominent improvements in the cerebral lesions (Fig. 2B, 2C). Although the patient received only three doses of bortezomib, the serum IgA level decreased to the normal range and, surprisingly, immunofixation tests of both the serum and urine became negative. The rapid resolution of the patient’s symptoms after drug discontinuation might substantiate suspicion of a causal relationship between bortezomib and PRES in the present case, although no other explicit evidence exists to justify this notion. Although we had planned to administer either thalidomide or lenalidomide as an alternative key agent, the patient was transferred to another hospital soon after these clinical events.

**Discussion**

PRES is characterized by typical neurological symptoms, including headaches, altered mental functioning, visual disturbances and convulsions, along with bilateral posterior cerebral white matter lesions (8). A variety of clinical conditions, including toxemia of pregnancy, uremia, accelerated hypertension and immunological conditions, as well as certain immunosuppressive agents, might be responsible for the development of PRES (9). In the present case, there seemed to be no evidence of any such causative conditions, except for bortezomib. Moreover, the close correlation between the discontinuation of bortezomib and the complete resolution of the symptoms of PRES pointed to bortezomib as being responsible. Although dexamethasone treatment can also be associated with PRES (10), considering that there were no obvious neurological symptoms during the preceding VAD treatment, dexamethasone-induced PRES seems unlikely. No other medical agents had been added during BD induction therapy, so bortezomib was the most likely causative agent for PRES. However, bortezomib has been previously described to be associated with PRES in only three cases (Table). Examining the four cases of bortezomib-induced PRES, including the present case, the following were found to be common features. First, the condition appears to be prevalent in women, as previously suggested for other molecular targeting agents, such as anti-vascular endothelial growth factor (VEGF) (11, 12). Second, PRES occurred at a relatively early phase; in fact, two patients developed PRES within the first cycle of administration of bortezomib, which is in contrast to that observed in cases related to anti-VEGF or RAF kinase inhibitor. Third, a full recovery of neurological symptoms was observed in most patients, and no patients experienced seizure recurrence even after discontinuation of anticonvulsant medications.

Although controversy remains concerning the pathophysiological trigger, the mechanism of this disorder ultimately depends on failure of the blood-brain barrier (BBB) to maintain compartmentalization of intravascular fluid (13). Anti-VEGF agents such as bevacizumab or tyrosine kinase inhibi-
Table. Cases of Posterior Reversible Encephalopathy Syndrome Induced by Bortezomib

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Patient (age, sex)</th>
<th>disease</th>
<th>Onset/treatment</th>
<th>Symptoms</th>
<th>CT/MRI findings</th>
<th>Outcome</th>
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<td>1</td>
<td>Kelly, et al. (2008)</td>
<td>66, M</td>
<td>Waldenström macroglobulinemia</td>
<td>2 cycle / BD*</td>
<td>Seizures, altered mental status</td>
<td>Asymmetrical high intense lesions in the subcortical white matter of the occipital lobes (FLAIR)</td>
<td>Full recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache, visual disturbance, confusion, speech disability</td>
<td>Hypodense lesions on bilateral subcortical and parieto-occipital white matter (CT)</td>
<td></td>
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<td>2</td>
<td>Kager, et al. (2009)</td>
<td>62, F</td>
<td>Multiple myeloma</td>
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<td>Hyperintense lesions on bilateral occipital grey and white matter (FLAIR)</td>
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</tr>
<tr>
<td>3</td>
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<td>58, F</td>
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<td>Asymmetrical high signal in the subcortical white matter of the occipital lobes and thalamus (FLAIR)</td>
<td>Full recovery</td>
</tr>
<tr>
<td>4</td>
<td>Present case (2012)</td>
<td>54, F</td>
<td>Multiple myeloma</td>
<td>1 cycle / BD</td>
<td>Seizures, altered mental status</td>
<td></td>
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</tbody>
</table>

Abbreviations: M: male; F: female; B: bortezomib; D: dexamethasone; CT: computed tomography; MRI: magnetic resonance imaging; FLAIR: fluid attenuated inversion recovery.

* Details of chemotherapy were not provided except for usage of bortezomib.

Tors can alter the integrity of the vascular endothelium, which might induce a loose compartmentalization of intravascular fluid and eventually result in a failure of the BBB. There have been 26 cases of anti-VEGF agent-induced PRES reported thus far (11). Bortezomib blocks protein degradation by proteasomes and then inhibits activation of nuclear factor-kappa B (NF-κB), which leads to decreased transcription of cellular growth factors, including VEGF. Therefore, bortezomib might indirectly alter the integrity of the vascular endothelium through the NF-κB pathway. In addition, the present patient developed other symptoms, including bladder disturbance and brief syncope after the administration of bortezomib. These symptoms could be due to bortezomib-induced autonomic nervous system dysfunction. This patient might also have had cerebral vasospasm caused by autonomic dysfunction. Therefore, cerebral vasospasm and subsequent ischemia and edema may also play a role in the development of PRES.

In summary, this single case of bortezomib-induced PRES suggests that a larger study involving a series of patients is...
needed. Physicians, as well as pharmacists, should be alert to this potential neurological complication, given the use of bortezomib for treating newly diagnosed multiple myeloma.

The authors state that they have no Conflict of Interest (COI).

References