LETTER TO THE EDITOR

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Severe Orthostatic Hypotension and Weight Loss After Bortezomib, Lenalidomide, and Dexamethasone Therapy

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To the Editor,

Peripheral neuropathy is common in patients with multiple myeloma (MM), whereas severe treatment-related orthostatic hypotension, syncope, and weight loss are rarely reported. We describe a patient who developed severe orthostatic hypotension and marked weight loss during VRD therapy (bortezomib, lenalidomide, dexamethasone).

A 55-year-old man presented with dizziness, blurred vision, and shortness of breath for 1-2 weeks. He had a history of coronary artery disease and hypertension, and he was diagnosed with immunoglobulin G lambda MM. The disease was stage II according to both the International Staging System (ISS) and the revised ISS. Because of findings of hyperviscosity, three sessions of plasmapheresis were performed, and VRD therapy (bortezomib 1.3 mg/m^2, lenalidomide 25 mg/day, dexamethasone 40 mg/week) was initiated.

On day 8 of the second treatment cycle, the patient developed anorexia, nausea, and dizziness upon standing. Laboratory tests showed: Na 133 mmol/L, creatinine 1.5 mg/dL, Hb 10 g/dL, platelets 350,000/mm^3, and white blood cells 5,000/mm^3. Blood pressure was monitored. Within 1 minute of standing, a 30 mmHg drop in systolic blood pressure and a 20 bpm increase in heart rate confirm orthostatic hypotension. Intravenous saline replacement was administered. Doxazosin was discontinued, and the lercanidipine dose was reduced.

After the third cycle, the patient developed persistent anorexia, presyncope, orthostatic hypotension, and marked weight loss (approximately 30% of body weight). Lercanidipine was discontinued. Echocardiography showed a normal ejection fraction without valvular pathology. Endoscopy and colonoscopy with biopsy revealed no evidence of amyloidosis.

Following the fourth cycle, the patient experienced recurrent presyncope upon standing. A brain magnetic resonance imaging was performed to rule out neurological disorders, but no pathological findings were observed. Echocardiography was repeated and rhythm and blood pressure were monitored with a Holter monitor. Carotid Doppler ultrasonography was performed. No stenosis was observed. VRD therapy was discontinued. Response evaluation after the fourth cycle demonstrated a complete response, and the patient subsequently underwent

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autologous hematopoietic stem cell transplantation with high-dose melphalan (200 mg).

During hospitalization, he received intensive hydration until engraftment and experienced no syncope. However, two days after discharge, he was readmitted due to recurrent syncope when standing. He was unable to perform daily activities and reported severe dizziness even while sitting, along with persistent anorexia. Neurology and cardiology evaluations revealed no pathology other than orthostatic hypotension.

Compression stockings, increased oral hydration, and midodrine (5 mg twice daily) were initiated. Because recurrent syncope caused anxiety, escitalopram was started and oral nutritional support was provided. After initiation of midodrine, syncope did not recur, and the patient gradually returned to normal physical activity. Midodrine was tapered during follow-up. Weight loss stabilized after discontinuation of VRD therapy.

Peripheral neuropathy occurs in approximately 35% of MM patients and is more common in those who have previously received neurotoxic treatment or have pre-existing neuropathy (1). Bortezomib-associated neuropathy is predominantly sensory, and postural hypotension has been reported in approximately 10% of patients; this condition is likely related to dehydration, concomitant antihypertensive treatment, or autonomic dysfunction (2). A clear association between lenalidomide and orthostatic hypotension has not been reported. In our case, VRD treatment was associated with progressive orthostatic hypotension, leading to syncope and significant impairment of daily activities. Discontinuation of antihypertensive drugs and administration of intravenous hydration initially improved symptoms, but the improvement was insufficient in subsequent treatment cycles. It was controlled with compression stockings and midodrine. Pregabalin (3) improved bortezomib-associated orthostatic hypotension in a previously reported case. Shishkina et al. (4) reported postural hypotension and weight loss in a case series of patients receiving VRD treatment. Patients were treated with fludrocortisone or midodrine, and appetite stimulants were used to control weight loss. In this case, tests necessary to differentiate neurogenic orthostatic hypotension, such as the tilt-table test and Valsalva maneuver, could not be performed. Bortezomib-associated autonomic dysfunction was considered the most likely cause given the significant neuropathic effects; however, the contribution of lenalidomide could not be ruled out. We believe that classifying orthostatic hypotension in this patient group will guide drug selection.

Clinicians should be aware that severe orthostatic hypotension, accompanied by syncope and weight loss, may occur during VRD therapy. Management may include hydration, compression stockings, discontinuation of antihypertensive medications, and pharmacological agents such as midodrine.

Ethics

Informed Consent: Written informed consent for publication of this case was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.T.T., E.K., Concept: B.T.T., Design: B.T.T., Data Collection or Processing: B.T.T., E.K., Analysis or Interpretation: B.T.T., Literature Search: B.T.T., Writing: B.T.T.

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