Letter to the Editor

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Hyponatremia Is Not a Rare Adverse Event in Bortezomib-Treated Patients

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Hyponatremia is not a rare event in patients with cancer, and the cause may be due to the cancer itself or drugs used to treat cancer. A case of hyponatremia probably related to bortezomib use is reported here, and the available literature was reviewed.

A 69-year-old man was admitted to hospital with fatigue and left knee pain. Physical exam showed pallor and limited left knee movements. Abnormal laboratory findings were as follows: hemoglobin 10.7 g/dl, erythrocyte sedimentation rate 77 mm/h, total protein/albumin 9.2/3.9 g/dl, blood urea nitrogen/creatinine 39/1.05 mg/dl, calcium 9.8 mg/dl and alkaline phosphatase 166 IU (normal range 30–120). Protein electrophoresis showed a monoclonal peak (β_2-microglobulin: 3.02 mg/l, normal range 0.56–2.74). Bone marrow biopsy was compatible with plasma cell neoplasia. CD38 and lambda were found to be positive in the biopsy sample.

The patient was diagnosed with multiple myeloma stage I disease (International Staging System staging), and he had symptomatic disease. The patient was not a candidate for high-dose chemotherapy with stem cell support due to his age. A melphalan, prednisolone and thalidomide combination and zoledronic acid were started. Response to this combination was good, but disease progression was detected 22 months later. A bortezomib (1.3 mg/m^2 on days 1, 4, 8 and 11) and dexamethasone regimen was given for relapsed disease. The patient received the 4th course of bortezomib and dexamethasone on 9 August 2010. He was admitted to the outpatient clinic with a sleep tendency on 13 August 2010. Physical examination showed a temperature of 37°C, blood pressure of 90/60 mm Hg and pulse rate of 68/min. There was mild pallor. Neurologic examination was found to be negative except for the sleep tendency, and there was no evidence of focal neurologic findings. There was no evidence of peripheral edema. The patient was hospitalized. Complete blood counts were as follows: hemoglobin 10.5 g/dl, white blood cells 7.8 × 10^9/l, platelets 92 × 10^9/l and erythrocyte sedimentation rate 27 mm/h. The results of biochemical tests were as follows: blood urea nitrogen/creatinine 20.2/1.1 mg/dl, sodium 123 mEq/l, potassium 3.2 mEq/l, aspartate aminotransferase/alanine aminotransferase 19/17 ■■■, γ-glutamyltransferase 34 ■■■, calcium 8.2 mg/dl, C-reactive protein (CRP) 6.5 mg/l (normal range 0–8.2), thyroid-stimulating hormone 1.13 mIU/l, free T3 and T4 ~~3.91/1.43~~ ■■■. Urine analysis revealed a density of 1,011 ■■■ and was negative for protein; there was no evidence of urine infection. Urine sodium was found to be 76 mEq/l. Repeated urine sodium was 87 mEq/l. Thyroid function and surrenal function tests were within normal limits. There was no evidence of adrenal insufficiency either clinically or biochemically. The patient did not receive additional medication, including diuretics. He was receiving dexamethasone in addition to the bortezomib, and the hyponatremia could have been related to dexamethasone use, but this is a less probable cause of hyponatremia. Although we cannot exclude the hyponatremic effect of dexamethasone, we would like to stress the possible role of bortezomib in the development of hyponatremia. CRP was within normal limits (although CRP is not a good marker for infection in patients with multiple myeloma because it may reflect the tumor burden in these cases). There was no evidence of an infectious process such as pulmonary or central nervous system infections. The patient was considered to have inappropriate antidiuretic hormone (ADH) secretion probably related to bortezomib. Fluid restriction was only imposed with close follow-up in the clinic. His sleep tendency improved within 3 days, and on the 4th day in hospital, serum sodium was 133 mEq/l and urine sodium was less than 20 mEq/l. Hypertonic saline

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infusion was not given due to the danger of worsening of neurologic complications with the rapid correction of serum sodium. The serum sodium level was corrected solely by means of fluid restriction. The patient was discharged in a good clinical condition. When he was admitted to hospital 2 weeks later, his condition was very good. However, he complained from numbness in his hands and feet. Bortezomib-related peripheral neuropathy was diagnosed and bortezomib was stopped.

Our patient presented with mild neurologic findings, and laboratory examinations showed hyponatremia. Restriction of water intake was effective for the correction of serum sodium. His clinical condition improved rapidly. Bortezomib was stopped due to peripheral neuropathy.

Hyponatremia is a severe problem in clinical practice. The first step is to rule out pseudohyponatremia, and the second step is to find the cause of this problem. In cancer patients, hyponatremia may be related to inappropriate secretion of ADH by the tumor or paraneoplastic hyponatremia but may also be due to drugs used for cancer treatment. In clinical practice, antineoplastic drugs or their combinations may cause various electrolyte disturbances including hyponatremia, but generally clinicians may not notice these complications among the other severe problems. Some of these toxic effects are related to sensitivity of the patients, and some are seen in the majority of patients [1, 2]. Our patient was receiving bortezomib and dexamethasone. Although dexamethasone could have been the cause of hyponatremia in our case and it may not be strictly legitimate to rule out the effect of dexamethasone, he had been treated with prednisolone for 22 months and there was no evidence of hyponatremia during this period. Our patient was also receiving bortezomib, and bortezomib may have been the cause of hyponatremia in our case. When we looked at the literature we found some reports about hyponatremia in cases treated with bortezomib. Now we can review these studies one by one according to the year in which they were published. Takamatsu et al. [3] reported a phase I study of a doxorubicin-, bortezomib- and dexamethasone-containing regimen in cases with relapsed/refractory multiple myeloma. When we looked at the toxicity profile, there was an interesting nonhematologic toxicity. In cohort 1, in which 28 cycles were administered, hyponatremia was reported as grade I in 14 cycles, grade III in 1 cycle and grade IV in 1. In cohort 2, in which 23 cycles were administered, hyponatremia was reported as grade I in 19 cycles, and grade IV hyponatremia was found to be a dose-limiting toxicity. Hyponatremia in this study was attributed to the intermediate-dose dexamethasone. However, it is not possible to exclude an effect of bortezomib on the hyponatremia. Orlowski et al. [4] reported a phase I study of 27 patients with hemopoietic neoplasias; single-agent bortezomib was used, and grade III hyponatremia was reported in 7 cases (26%). Hyponatremia was found to be a dose-dependent side effect in this study. This finding provides important evidence for the hyponatremic effect of bortezomib [4]. Jagannath et al. [5] reported a phase II study including 54 cases of relapsed/resistant multiple myeloma. Patients were treated by single-agent bortezomib, and grade III hyponatremia was detected in 3 cases treated with a dose of 1 mg/m^2 (3/28; 11%) and in 2 cases treated with 1.3 mg/m^2 (2/26; 8%) [5]. O'Connor et al. [6] reported a phase I study including 24 cases of non-Hodgkin's lymphoma in which bortezomib was used as a single agent. Two incidences of grade III and 1 of grade IV hyponatremia were reported, and hyponatremia was found to be a dose-limiting toxicity [6]. In the Assessment of Proteasome Inhibition for Extending Remissions trial (669 cases), hyponatremia was reported in bortezomib-treated cases, but this complication was not reported in cases treated with dexamethasone only. However, the number of patients who developed hyponatremia was not published [7]. Brodmann et al. [8] reported a case of mantle cell lymphoma treated by single-agent bortezomib. Hyponatremia developed in this patient 11 days after the 8th injection of bortezomib [8]. Belch et al. [9] reported a phase II study including 30 cases of mantle cell lymphoma treated by single-agent bortezomib, and grade III hyponatremia was reported in 1 case (3%). These reports are strong evidence for the development of hyponatremia secondary to a syndrome of inappropriate secretion of ADH related to bortezomib because in these studies and case reports, bortezomib was used as a single agent. On the other hand, Davies et al. [10] reported a study of 26 patients with lung cancer treated by gemcitabine plus carboplatin and bortezomib, and grade III hyponatremia was reported in 1 case. Lastly, Richardson et al. [11] reported a phase I study including 38 cases with relapsed/refractory multiple myeloma. A lenalidomide-, bortezomib- and dexamethasone-containing regimen was used in this study, and grade III hyponatremia was reported in 1 case [11].

Among these 8 reports, bortezomib was used as a single agent in 6 of them and in combination with other drugs in 2. These results suggest that hyponatremia is not a rare side effect of bortezomib. The time point at which bortezomib-related hyponatremia generally occurs is not clear, but in some cases hyponatremia has been reported as late as during the 8th cycle of bortezomib treatment [6]. For this reason, the development of hyponatremia in our case after 3 cycles of bortezomib treatment is not clear evidence that the hyponatremia was unrelated to bortezomib. It is likely that hyponatremia associated with bortezomib is underreported or clinicians are not aware of this important complication. Hyponatremia may be asymptomatic or it may be attributed to the other drugs used in these cases. Hyponatremia is a relatively frequent clinical condition in patients with cancer receiving cancer drugs and concomitant medications. For this reason, hyponatremia requires detailed clinical and biochemical evaluation.

In conclusion, hyponatremia is a frequent adverse event in patients with neoplastic disorders; this may be due to the malignancy itself or related to drugs used in these cases. This event may be life threatening in some cases due to the complicated clinical presentations of the malignant disorders. For this reason, careful monitoring of serum sodium levels and appropriate treatment are critical points. Otherwise, this side effect may cause a fatal outcome. Serum sodium levels must be monitored strictly in patients treated by bortezomib, and hyponatremia should be considered in bortezomib-treated patients with cognitive dysfunction.

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