

CASE REPORT

Bortezomib Induced Tumor Lysis Syndrome in Multiple Myeloma

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The tumor lysis syndrome (TLS) commonly occurs in the lymphoproliferative disorder, either spontaneously or in response to therapy. TLS is uncommon in multiple myeloma. However, with the use of bortezomib in the treatment of multiple myeloma, cases of TLS have been reported. We report here three patients who presented with TLS after the administration of bortezomib. Two of them presented mild symptoms and recovered with hydration only. However, death of the other patient was associated with TLS. We should monitor patients who had high tumor burden, especially in early phase of bortezomib therapy and appropriate prophylaxis for high risk patient is also needed.

Keywords: Bortezomib; Multiple myeloma; Tumor lysis syndrome

INTRODUCTION

The tumor lysis syndrome (TLS) commonly occurs in lymphoproliferative disorders, either spontaneously or in response to therapy. But TLS is uncommon in multiple myeloma. However, after use of bortezomib in the treatment of multiple myeloma, cases of TLS have been reported. Here we describe three patients who presented with TLS after treatment of bortezomib in two university hospitals (case 1 in Soonchunhyang University Hospital, Seoul, and case 2/case 3 is in Soonchunhyang University Hospital, Bucheon, Korea).

CASE REPORTS

1. Case 1

A 61-year-old man presented with a week history of back pain. He was diagnosed of Immunoglobulin G κ multiple myeloma. M protein was 6.0 g/dL in serum protein electrophoresis. Bone marrow examination showed 56.1% plasma cell infiltration. β_2 -microglobulin was 4.7 mg/L and serum lactate dehydrogenase (LDH) was 150 U/L (normal: 106-211 U/L).

The patient was treated with bortezomib (1.3 mg/m² on days 1,

4, 8, and 11), thalidomide 200 mg once daily and dexamethasone 40 mg on days 1-4 and 9-12). After the fourth dose of bortezomib (day 11 of cycle 1), he presented with general weakness. Serum chemistry showed elevated LDH to 1,550 U/L and calcium decreased to 7.3 mmol/L (normal: 8.4-10.2 mmol/L). Potassium was 4.2 mmol/L (normal: 3.5-5.3 mmol/L), phosphate was 2.7 mmol/L (normal: 2.5-4.5 mg/L), uric acid was 3.1 mg/dL (normal: 2.5-6.3 mg/L), blood urea nitrogen was 19.8 mmol/dL (normal: 8-20 mg/dL), and creatinine was 0.61 mmol/dL (normal: 0.6-1.3 mg/dL). Because there was no other cause of increased LDH, we started intravenous hydration with sodium bicarbonate for alkalization to him. A week later LDH was back to normal.

2. Case 2

A 61-year-old woman had a diagnosis of immunoglobulin G λ multiple myeloma. Bone marrow examination showed 67% plasma cell infiltration. After three cycles of thalidomide and dexamethasone, she presented with severe asthenia that she could not receive chemotherapy anymore. But after one month later, she presented with both leg weakness due to aggravated back pain, she received local radiotherapy for lumbar spine and again one month later, percutaneous vertebroplasty.

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She was treated with bortezomib (1.3 mg/m² on days 1, 4, 8, and 11) and dexamethasone 40 mg (on days 1, 4, 8, and 11) as a second line therapy. M protein before administration of bortezomib and dexamethasone was 0.6 g/dL in serum protein electrophoresis. At day 15, after the fourth dose of bortezomib (day 11 of cycle 1), serum chemistry showed elevated LDH from 483 U/L before the fourth dose of bortezomib to 2,582 U/L. Potassium was 5.6 mmol/L, phosphate was 3.6 mmol/L, calcium was 8.8 mmol/L, and uric acid 10.1 mmol/L. Creatinine increased to 1.4 mg/dL from 1.0 mg/dL. She received massive intravenous hydration with sodium bicarbonated alkalization with allopurinol. A week later, serum LDH decreased to 746 U/L. After 1st cycle of VD, M protein decreased to 0.25 g/dL, but because of peripheral neuropathy and recurrent infection, she didn't receive chemotherapy anymore.

3. Case 3

A 60-year-old woman had a diagnosis of immunoglobulin G κ multiple myeloma. M protein was 6.0 g/dL in serum protein electrophoresis. She was treated with 4th cycle of vincristin, adriamycin, and methylprednisolone regimen, followed by autologous peripheral blood stem cell transplantation. Two years later, she developed swelling in her left side gum with mass. The mass was plasmacytoma. She received radiotherapy for mass and started bortezomib (1.3 mg/m² on days 1, 4, 8, and 11) monotherapy. After administration of first dose of 2nd cycle, she was discharged from hospital. However, three days later, she presented with dyspnea and serum chemistry showed elevated LDH from 582 U/L before the fourth dose of bortezomib to 807 U/L. Potassium was 6 mmol/L, phosphate was 5.1 mmol/L, calcium was 8.6 mmol/L, and uric acid 9.3 mmol/L. Creatinine increased to 1.8 mg/dL from 1.5 mg/dL. There is no evidence of infection. Since metabolic acidosis wasn't corrected despite aggressive medical management lead to patient's death.

DISCUSSION

The TLS is an oncological emergency occurring when tumor cells release their contents into the bloodstream. It commonly occurs in the lymphoproliferative disorders, either spontaneously or in response to therapy. But TLS is uncommon in multiple myeloma, since it is a slowly proliferative disease of plasma cell with only a small fraction of cells in S phase at a given time.

TLS is diagnosed as any three or more abnormal serum values:

1) ≥ 2 -fold increase in LDH, 2) $\geq 50\%$ increase in phosphate, uric acid, or creatinine, 3) $\geq 30\%$ increase in potassium in the absence of supplementation, and 4) $\geq 20\%$ decrease in calcium in the absence of concomitant bisphosphonate therapy. If every parameter is not available, the combination of hyperphosphatemia, hyperkalemia, hypocalcemia, and increased LDH after chemotherapy, which returned to normal rapidly, are considered obvious evidence [1].

The three patients in this report presented with rapid elevation of LDH and change of other laboratory test during treatment of multiple myeloma and it fit to criteria of TLS. Two of them presented mild symptoms and hence recovered with hydration only, however, the other one died associated with TLS. The direct cause of death of case 3 was TLS. We routinely monitor for TLS in induction therapy for acute leukemia, Burkitt lymphoma, and other rapidly proliferative lymphomas with standard prevention with aggressive hydration and allopurinol. However, for the treatment of multiple myeloma, we usually don't do specific treatments for prevention of TLS.

Fassas et al. [2] reported 7 cases of TLS in the patient with multiple myeloma treated high dose chemotherapy. It is a side effect of high dose chemotherapy and autologous stem cell transplantation. It is suggested that TLS can occur in multiple myeloma, slow growing tumor, with intensive therapy like autologous hematopoietic stem cell transplant.

Bortezomib is a reversible inhibitor of the 26S proteasome approved for the treatment of multiple myeloma. Bortezomib is a highly active drug in multiple myeloma treatments and its effect was rapid [3]. The most serious side effect of bortezomib is peripheral peripheral neuropathy (range, 37% to 44%) [4]. Although concern about TLS is low because of its low incidence, TLS reported more commonly as increased use of bortezomib containing regimen including first line treatment for patients with high tumor burden. One phase 1/2 study reported 1 episode of TLS among 10 patients who treated bortezomib and melphalan combination in patients with the relapsed multiple myeloma [5]. Other phase II multicenter studies reported 8 episodes of TLS among 497 patients in bortezomib therapy, with or without dexamethasone [1]. Clinically, because of almost treatment of multiple myeloma taken in the outpatient clinic and LDH is not routinely tested, the incidence of TLS related with bortezomib could be underestimated.

In one series, patients with rapidly proliferative disease and a high tumor burden appear to be at greatest risk for TLS [6]. One

case report reported TLS with bortezomib on the patient had a high tumor burden and carried an unfavorable karyotype [7]. Hence, we could presume the amount of M protein that reflect tumor burden is related with risk of TLS, but has not been adequately evaluated. In our case, case 2 and 3 has TLS although low M protein. Other previous case reports also revealed tumor lysis occurring within the first cycle of treatment of bortezomib due to rapidity of bortezomib action [8-10]. In our cases, 2 of them experienced TLS after fourth dose of first cycle, but, the other one, it occurred after first dose of second cycle. Therefore we need more studies about risk factor and time of development.

Bortezomib associated TLS is usually mild form and almost of cases treated just symptomatic management including appropriate hydration, allopurinol administration. But some cases were required intermittent dialysis due to renal deterioration. Also, it is potentially life-threatening complication.

As the bortezomib widely used in multiple myeloma, TLS occurs more frequently. It seems the patient with TLS in Korea is also increasing by expanding of health assurance coverage as the first-line treatment for patients with multiple myeloma. We should monitor patient who had high tumor burden, especially in early phase of bortezomib therapy and appropriate prophylaxis for high risk patient is also need. And more studies about risk factors are needed.

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