

Thrombotic microangiopathy associated with bortezomib treatment in a patient with relapsed multiple myeloma

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Abstract

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) describe microvascular occlusive disorders characterized by thrombocytopenia due to increased platelet aggregation and fragmentation hemolysis. We report here what to our knowledge is the second case of TTP/HUS associated with bortezomib treatment.

Introduction

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) describe microvascular occlusive disorders characterized by thrombocytopenia due to increased platelet aggregation and fragmentation hemolysis.¹ Clinical distinction between the two entities is rarely clear and, therefore, the term TTP/HUS has also been used. In rare cases, TTP/HUS may occur secondary to identifiable causes, such as drugs, infections and malignancies.^{1,2} We read with great interest the case report by Alonso *et al.* of a patient with disseminated adenocarcinoma presenting as TTP.³ We report here a patient in whom bortezomib treatment was an apparent cause of TTP/HUS.

Case Report

A 52-year old woman was diagnosed with lambda-light chain multiple myeloma in 1994. Upfront autologous stem cell transplantation was performed leading to complete response (CR). In December 2008, the disease relapsed with bone pains, hypercalcemia and renal failure. Laboratory results at presentation were: Hb 86 g/L, WBC $5.1 \times 10^9/L$, platelets $148 \times 10^9/L$, creatinine 188 $\mu\text{mol/L}$ (reference range 60-100), ionized calcium 2.07 mmol/L. Bone marrow aspiration showed 50-100% plasma cells, serum free lambda chain concentration was 1580.0 mg/L and 24-h urine lambda chain secretion was 1176 mg. There were new lytic lesions identifiable on plain X-rays and mag-

netic resonance imaging revealed a plasmacytoma causing LIII nerve root compression. After conventional treatment of hypercalcemia and urgent radiotherapy to low back, systemic treatment with bortezomib (1.3 mg/m² days 1, 4, 8, 11, for a 21-day cycle) and dexamethasone (20 mg days 1-2, 4-5, 8-9, 11-12) at 3-week intervals was started. CR was obtained after three cycles. Details of blood counts, plasma creatinine concentration, lactate dehydrogenase (LDH) levels and dose modifications due to thrombocytopenia during the treatment are shown in Table 1.

During the fifth treatment cycle (day 11) the patient was admitted to hospital with diarrhea and severe orthostatic hypotension. She needed red blood cell and platelet transfusions but response was minimal. Laboratory tests showed: hemoglobin 78 g/L, erythrocytes $2.84 \times 10^{12}/L$, hematocrit 0.23, LDH 3001 U/L (reference range 105-205), reticulocytes 2.2% (reference range 0.6-2.0), direct Coombs test negative, APTT 26.9 seconds (s) (reference range 23-33), D-dimer 8.3 mg/L (reference range <0.5), fibrinogen 3.5 g/L (reference range 2-4), and serum creatinine 421 $\mu\text{mol/L}$. Peripheral blood smear demonstrated a significant increase of schistocytes (25% of 500 red cells) and thrombocytopenia. Findings were consistent with thrombotic microangiopathic hemolysis. TTP/HUS was suspected and plasma exchange therapy was started. Bone marrow aspirate and negative u-immunofixation confirmed the remission of myeloma, and subcutaneous fat staining for amyloid was negative. Gingival biopsy stained positive for fibrin consistent with HUS. Stool sample for *Enterohaemorrhagic E. coli* (cause of typical HUS in children) was negative. At that time, analytical tests for plasma ADAMTS13 activity was not yet available in our institution. A total of 14 daily plasma exchanges were performed and at the end of treatment blood hemoglobin level was 90 g/L, platelet count $58 \times 10^9/L$ and 14% of schistocytes were found in the peripheral blood smear. Serum LDH had dropped to 272 U/L and plasma creatinine level to 298 $\mu\text{mol/L}$. No dialysis was required. After bortezomib discontinuation no recurrence occurred. The patient was never rechallenged with bortezomib.

Discussion

Bortezomib is one of the novel myeloma drugs with significant efficacy in new and relapsed diseases. It reversibly inhibits the action of proteasome and degradation of multiple intracellular proteins involved in the pathogenesis of the disease. Common adverse effects are gastrointestinal and hematologic toxicities, peripheral neuropathy and orthostatic hypotension. Transient thrombocytopenia is

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typical with the mean platelet nadir of approximately 40% of baseline that usually recovers until the next cycle. In our patient, both orthostatic hypotension and diarrhea were timely related to bortezomib administration. The drop in platelet count was more prominent than expected but recovered before the next cycle. It is evident that fragmentation hemolysis had insidiously commenced already at the beginning of the treatment and propagated during each bortezomib cycle. There were no signs of other causes of fragmentation. The fact that discontinuation of bortezomib resolved fragmentation further supports its causative role. Most cases of acquired idiopathic TTP are caused by severe deficiency of von Willebrand factor-cleaving metalloprotease, ADAMTS13, caused by autoantibody and leading to accumulation of ultra large VWF multimers that propagate platelet aggregation.¹ The microvascular thrombi in TTP are platelet-rich and stain negative for fibrin in contrast to HUS. Plasma exchange removes the circulating autoantibody and the ultra large VWF multimers and replaces the missing ADAMTS13 protease activity. Thrombotic microangiopathy and severe renal failure are the predominant features of HUS. In the classic form of HUS, ADAMTS13 activity is normal and plasma exchange is not effective.

TTP or HUS like thrombotic microangiopathy may also occur in some distinct clinical settings, including allogeneic hematopoietic stem cell transplantation and use of antineoplastic agents (mitomycin, cisplatin, bleomycin).^{1,2} In these, microangiopathy is believed to be caused by direct microvascular toxicity initiated by endothelial injury. Interestingly, HUS-like thrombotic microangiopathy has been described with use of anti-vascular endothelial growth fac-

Table 1. Laboratory values during velcade treatment.

	Hb	Plt	Creat	LDH
<i>Cycle 1</i>				
D1	116	72	99	202
D8	108	13	70	
<i>Cycle 2</i>				
D1	90	171	53	
D16	90	15	74	687
<i>Cycle 3</i>				
D1	101	84	62	508
D11	88	25		
<i>Cycle 4</i>				
D1	88	104		
D7	121	10	200	
<i>Cycle 5</i>				
D1	84	150	126	855
D11	78	13	268	

D, day; Hb, haemoglobin; Plt, platelet count; Creat, serum creatinine; LDH, serum lactate dehydrogenase (reference range 105-205). Cycle 1: Velcade was not given days 8 and 11; Cycle 3: Velcade dose was reduced to 1.0 mg/m²; Cycle 4: Velcade was not given days 8 and 11.

tor (VEGF) agents, *i.e.* bevalizumab and sunitinib.⁴ In mouse models, ablation of VEGF production in the kidney was sufficient to recapitulate the glomerular injury seen in patients.⁵ This may be the most probable mechanism by which also bortezomib can cause thrombotic microangiopathy since bortezomib is known to decrease transcription of VEGF and other pro-angiogenic molecules by NF- κ B inhibition.⁶

Conclusions

In summary, we describe what to our knowledge is the second case of TTP/HUS associated with bortezomib treatment.⁷ Bortezomib is increasingly used in the treatment of multiple myeloma and clinicians should be aware of this association in patients with anemia and unexpectedly severe thrombocytopenia.

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