

Bortezomib induced reversible left ventricular systolic dysfunction: A case report and review of literature

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Abstract

Bortezomib is a reversible proteasome inhibitor, currently approved by US FDA for use in multiple myeloma and mantle cell lymphoma. Bortezomib has been shown to cause new onset and exacerbation of underlying congestive cardiac failure (CHF) in some case reports. Studies on human tissue have shown dysregulation of ubiquitin proteasome system (UPS) in cardiac tissues in end stage heart failure. Recently, an animal study has shown reduced left ventricular contractility after bortezomib administration, which was attributed to reduced ATP synthesis in mitochondria of cardiac myocytes.

Our case demonstrates development of new onset severe reversible left ventricular systolic dysfunction after 4 cycles of bortezomib in a 58 year old female with multiple myeloma. Her only medical condition was well controlled hypertension and she did not have any other risk factor for coronary artery disease. We also present a review of all case reports of CHF associated with bortezomib administration published till date and occurrence of CHF with bortezomib administration in major clinical trials of multiple myeloma.

Our manuscript highlights the importance of maintaining a high level of suspicion for development of CHF after therapy with bortezomib. Currently, there is no guideline for routine evaluation and monitoring of cardiac function in all patients during the course of bortezomib therapy. Further studies are required in future to address this issue.

Keywords: Bortezomib, Congestive heart failure, Ubiquitin proteasome system.

Introduction

Bortezomib is a reversible proteasome inhibitor, currently approved by US FDA for use in multiple myeloma and mantle cell lymphoma. It has been shown to cause new onset and exacerbation of underlying congestive cardiac failure (CHF) in some case reports. Although the exact mechanism of bortezomib induced congestive cardiac failure is unknown, studies have shown dysregulation of ubiquitin proteasome system (UPS) in human cardiac tissues in end stage heart failure¹⁻³. Furthermore, a study in rats has shown reduced left ventricular contractility after bortezomib administration, which was attributed to reduced ATP synthesis in mitochondria of cardiac myocytes⁴. Our case demonstrates new onset severe reversible left ventricular systolic dysfunction after 4 cycles of bortezomib in a 58 year old female with multiple myeloma. It highlights the importance of monitoring cardiac function in patients receiving bortezomib.

Case Report

A 58 year old female with past medical history of well controlled hypertension presented with severe low back pain, anorexia and unintentional weight loss of around 20 pounds over a period of 3 months in medical clinic. On evaluation of her routine laboratory tests, she was found to have haemoglobin of 6.5 g/dl, haematocrit of 19.9%, white blood cell (WBC) count of $3.9 \times 10^3/\text{cc}$, red blood cell (RBC) count of $2.18 \times 10^6/\text{cc}$ and platelet count of $1.52 \times 10^5/\text{cc}$. Her blood urea nitrogen and creatinine was 10 mg/dl and 0.7 mg/dl respectively and corrected calcium level was 10g/dl. On liver

function test, her total protein was 12.4 g/dl and albumin level was 2.8 g/dl. X-ray of lumbosacral spine revealed a compression fracture at the level of T12 and L2 vertebra. Bone survey confirmed diffuse osteopenia, severe collapse of the body of T12 and partial collapse of L2 and L3. Due to the presence of severe anaemia and compression fractures, multiple myeloma was suspected. Urine protein electrophoresis showed two monoclonal protein bands with concentration of 46.8% and 4.8% and urine immunofixation showed two intact monoclonal IgA-Kappa immunoglobulin bands. Beta-2 microglobulin level was 5.49. Bone marrow aspiration and biopsy confirmed the diagnosis of multiple myeloma. Patient was staged as IIIA according to Durie-Salmon staging system.

Subsequently, patient was planned to be treated with eight cycles of bortezomib and dexamethasone, with bortezomib being given on day 1, 4, 8 and 11 of each cycle at a dose of 1.3 mg/m² body surface area. Prior to initiation of chemotherapy, she received radiotherapy to spine as well. However, after completing the fourth cycle of bortezomib/dexamethasone, she was admitted to the hospital with generalized weakness, nausea and vomiting. Chest X ray revealed possible right lower lobe infiltrate or effusion along with increased bronchovascular markings and she was treated with antibiotics for suspected community acquired pneumonia. However, an echocardiogram was obtained due to bilateral crackles on physical exam and increased bronchovascular markings on chest X ray, which revealed dilation of left ventricle with left ventricular ejection fraction of 30-35%, diffuse hypokinesis of left ventricle, mild mitral and tricuspid regurgitation and diastolic dysfunction

with abnormal relaxation (Tajik grade I). Left ventricular septal and posterior wall thickness was 0.8 cm. Infiltrative Cardiomyopathy in the setting of multiple myeloma was unlikely due to the absence of bi-atrial enlargement, pericardial effusion and thick bright myocardium on echocardiogram. Cardiology consultation was sought and their impression was new onset left ventricular dysfunction due to bortezomib therapy.

Patient did not receive any further cycles of chemotherapy due to cardiotoxicity and was on optimal medical management for heart failure with lisinopril, carvedilol and isosorbide dinitrate. An echocardiogram was repeated four months after discontinuation of bortezomib, which revealed normal left ventricular contractility with global left ventricular ejection fraction of 55% and trace mitral regurgitation.

Currently, at 2 year follow up, her echocardiogram shows global left ventricular ejection fraction of 65%, trace mitral and tricuspid regurgitation and diastolic dysfunction with abnormal relaxation (Tajik grade I).

Discussion and Review of Literature

Bortezomib is a novel proteasome inhibitor which acts by inducing bcl-2 phosphorylation and cleavage, resulting in G2-M cell cycle phase arrest and apoptosis⁵. US Food and Drug Administration (FDA) have approved bortezomib for use in multiple myeloma and mantle cell lymphoma. The common adverse effects of bortezomib observed in clinical trials and post marketing surveillance include thrombocytopenia, neutropenia, hypotension, asthenia, peripheral neuropathy and nausea. US package insert for bortezomib states that acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction and it is recommended to closely monitor patients with risk factor for, or existing heart disease.

The role of ubiquitin proteasome system (UPS) in heart failure has been studied extensively in recent years. Two studies by Hein et al and Weekes et al in 2003 have shown presence of increased amount of ubiquitinated proteins and substrates in cardiac tissues of heart failure patients, indicating reduced activity of UPS in end stage heart failure¹⁻³. Another study has shown impaired proteasome activity in hypertrophic and dilated cardiomyopathy likely secondary to post translational modification of proteasome⁶. However, in early stage heart failure, there is increased activity of UPS, resulting in remodelling and high cardiac output². Bortezomib, by inhibiting UPS, would lead to accumulation of ubiquitinated proteins in cardiac myocytes, similar to that seen in end stage heart failure. A study in rats exposed to bortezomib alone showed development of left ventricular systolic dysfunction by echocardiography and reduced synthesis of ATP was observed

in the mitochondria of cardiac myocytes⁴. However, the exact mechanism of bortezomib induced systolic dysfunction in humans is not clear.

There have been a few reported cases of bortezomib induced congestive cardiac failure in literature (Table 1). The amount of bortezomib administered before development of symptoms of heart failure was 20.8 mg/m² in four patients, 3 mg/m² in one patient and 10.4mg/m² in one patient. Three of them have received prior anthracycline based chemotherapy. Complete reversibility of heart failure after discontinuation of bortezomib was documented only in two cases by follow up echocardiograms and brain natriuretic peptide levels^{7, 8}. The patient described in our index case had well controlled hypertension and no additional cardiac risk factors at baseline. She developed non-specific symptoms, including weakness, nausea and vomiting after the fourth cycle of chemotherapy and was admitted to the hospital for community acquired pneumonia. However, an echocardiogram was obtained due to pulmonary congestion, which uncovered the diagnosis of left ventricular systolic failure. The two echocardiograms obtained at a follow up of 4 months and 2 years showed gradual improvement in ejection fraction to 55% and 65% respectively from 15% after chemotherapy with bortezomib.

We did a review of major clinical trials of bortezomib in patients with multiple myeloma, Waldenstrom's macroglobulinemia and plasma cell leukaemia (Table 2) to investigate the incidence of congestive cardiac failure reported after administration of bortezomib. In APEX trial, the incidence of congestive cardiac failure was 2% in both bortezomib and high dose dexamethasone group¹¹. In a study on melphalan refractory multiple myeloma by Hjorth et al, 3 cases of congestive cardiac failure was reported in bortezomib-dexamethasone group and 2 cases were reported in thalidomide-dexamethasone group¹². Another study evaluating the safety of prolonged therapy with bortezomib by Berenson et al reported 1 case of cardiomegaly and 1 case of pulmonary edema¹³. However, further studies are needed to specifically evaluate the incidence of congestive cardiac failure with bortezomib therapy.

In summary, our case and review highlights the importance of maintaining a high level of suspicion for development of congestive cardiac failure after therapy with bortezomib. Given the widespread use of bortezomib and new generation proteasome inhibitors in multiple myeloma, there might be increased incidence of new onset and exacerbation of underlying congestive cardiac failure in future. Currently, there is no guideline for routine evaluation and monitoring of cardiac function in all patients during the course of bortezomib therapy. Furthermore, it is unclear whether the severity of congestive cardiac failure is proportional to the cumulative dosage of bortezomib administration and also, if there is any correlation between onsets of congestive cardiac failure with the timing of bortezomib therapy. Further studies are required in future to address these issues.

Table 1: Review of cases of bortezomib induced congestive cardiac failure reported so far.

Author	Age/sex	Prior cardiac history and risk factors	Baseline cardiac function	Number of Bortezomib containing cycles	Exposure to other cardiotoxic medications	Amount of Bortezomib received before onset of cardiac symptoms	Lowest EF** after Bortezomib administration	EF on follow up visits
Voortman et al ⁷	53/M	36 pack years of smoking and COPD	Echo not available; NT-Pro BNP 1389 ng/l	4	Gemcitabine	3 mg/m ²	10-15% on Echo after 4 cycles	45% on MUGA scan at 6 months
Orciuolo et al ⁹	73/M	NK*	NK	6	1 Anthracycline containing regimen	20.8 mg/m ²	EF 25%	NK
Orciuolo et al ⁹	61/F	NK	NK	4	2 Anthracycline containing regimens	20.8 mg/m ²	EF 20%	NK
Orciuolo et al ⁹	80/F	NK	NK	4	1 prior non anthracycline chemotherapy regimen received	20.8 mg/m ²	EF 35%	NK
Hasihaneftoglu et al ¹⁰	47/M	None	EF 70% and normal coronary angiogram	2	1 cycle of Vincristine, Doxorubicin and Dexamethasone	10.4 mg/m ²	EF 10%	EF 20% at 6 month follow up
Bockorny et al ⁸	56/F	Hypertension, well controlled	NK	4	None	20.8 mg/m ²	EF 20-25%	EF 55-60%
INDEX CASE	58/F	Hypertension, well controlled	NK	4	None	20.8 mg/m ²	EF 30-35%	EF 55% at 4 month and 65% at 2 year follow up.

*NK: Not Known; **EF: Ejection Fraction

Table 2: Review of cases of congestive cardiac failure reported in clinical trials with bortezomib in multiple myeloma, Waldenström's Macroglobulinemia and plasma cell leukaemia.

Authors (ref)	Study	Study population	Significant Cardiac events (n)
Berenson, J.R. et al. 2005 ¹³	Safety of prolonged therapy with bortezomib in relapsed or refractory multiple myeloma	63 patients with relapsed and/or refractory MM	Cardiomegaly (1) MI, SVT, Pulmonary oedema (1) Complete AV block (1)
Chen, C.I. et al. 2007 ¹⁴	Bortezomib in Waldenström's Macroglobulinemia	27 patients with untreated or relapsed WM	Congestive Heart Failure (1)
D'Arena, G. et al. 2012 ¹⁵	Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukaemia	29 patients with untreated PPCL	None reported
Hjorth, M. et al. 2012 ¹²	Thal-Dex vs. Bort-Dex in refractory myeloma	131 patients with Melphalan refractory MM	2 cases of cardiac failure in Thal-Dex group and 3 in Bort-dex group

Jagannath, S. et al 2009 ¹⁶	Bortezomib for Relapsed or Refractory Multiple Myeloma	54 patients with relapsed or refractory MM	None reported
Jagannath, S. et al 2010 ¹⁷	Extended follow-up of Frontline Bortezomib ± Dexamethasone for MM	49 patients with untreated MM	None reported
Kobayashi, T. et al. 2010 ¹⁸	Bortezomib plus dexamethasone for relapsed or treatment refractory multiple myeloma	88 patients with relapse/refractory MM	None reported
Mikhael, J.R. et al. 2009 ¹⁹	High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma	638 patients with refractory or relapsed MM	None reported
Richardson, P.G. et al. 2003 ²⁰	A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma	202 patients with relapsed MM	None reported
Richardson, P.G. et al. 2005 ¹¹	Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma(APEX trial)	669 patients with relapsed MM	Congestive cardiac failure in 2% of each arm.
Rosino, L. et al. 2007 ²¹	Phase II PETHEMA Trial of Alternating Bortezomib and Dexamethasone As Induction Regimen Before Autologous Stem-Cell Transplantation in Younger Patients With Multiple Myeloma	40 patients with newly diagnosed MM	None reported
Sonneveld, P. et al. 2012 ²²	Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma	827 patients with newly diagnosed MM	Cardiac Disorders in 5% of patient in VAD group vs. 8% of patients in PAD group.
Yuan, Z.G. et al. 2011 ²³	Different dose combinations of bortezomib and dexamethasone in the treatment of relapsed or refractory myeloma	168 patients with relapsed MM	None reported
Suvannasankha et al 2006 ²⁴	Weekly bortezomib/methylprednisolone in relapsed multiple myeloma	29 patients with relapsed multiple myeloma	1 case of congestive cardiac failure

Conclusion

CHF is an infrequent but serious adverse effect of bortezomib. Cardiac function should be closely monitored in patients receiving bortezomib, as case reports have shown that these patients might present with non-specific symptoms like weakness and fatigue. Further studies are required to establish the frequency and mode of monitoring of cardiac function during and after bortezomib therapy.

Competing Interests

None.

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