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Bortezomib-induced Dilated cardiomyopathy – Myth or Reality

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Introduction:

Bortezomib (Velcade) is a novel chemotherapeutic agent which has been approved since May 2003 by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression during the previous treatment. It acts through reversible inhibition of intracellular proteasomes resulting in the accumulation of polyubiquitinated proteins involved in triggering apoptosis, with a relative selectivity for malignant cells. It has been hypothesized that accumulation of damaged proteins in myocytes may impair cardiac function. Prominent adverse effects of this drug include thrombocytopenia and peripheral neuropathy. We report a lesser known side effect associated with bortezomib treatment in a patient with multiple myeloma-systolic heart failure.

Case:

A 64 year old African American woman with no prior cardiac history was referred to our institution for further management of stage IIB kappa light chain multiple myeloma. She was initially diagnosed with multiple myeloma in September 2008 when she had a work up for renal failure. She has no preexisting coronary artery disease, hypertension, dyslipidemia, congestive heart failure, smoking, alcohol or drug abuse

Chest radiograph showed a baseline cardiothoracic ratio of 50%. A baseline echocardiogram performed prior to initiation of treatment revealed an ejection fraction (EF) of 55-60% with normal sized left ventricle and normal valve function.

She completed six cycles with bortezomib and dexamethasone with each cycle lasting for 21 days.

She was then re-admitted for autologous bone marrow transplantation in April 2009. The patient was asymptomatic at the time of admission except for occasional fatigue. She had no history of alcohol abuse, recent upper respiratory illness or previous history of heart disease. Home medications included pantoprazole and acetaminophen- hydrocodone. Shortly after admission, patient complained of vague left sided chest pain which was worse on deep inspiration. Physical examination was remarkable for tachycardia. There was no evidence of peripheral edema, pulmonary congestion or cardiomegaly on exam. Her bloodwork showed a brain natriuretic peptide level (BNP) of 192 pg/ml and serial troponins were within normal limits. Electrocardiogram (EKG) showed sinus tachycardia with a rate of 120 without any evidence of ischemic changes. A ventilation perfusion scan done in view of suspected pulmonary embolism revealed low probability of pulmonary embolism.

Chest radiograph showed an increase in cardiothoracic ratio to 66% from a baseline of 50%. The echocardiographic study showed a globally dilated hypokinetic left ventricle with normal thickness and stable trivial pericardial effusion. The estimated left ventricular ejection fraction was 20-25%.

Discussion:

Bortezomib is a novel dipeptide boronic acid which leads to downregulation of transcripts that are associated with important growth and survival pathways and upregulation of transcripts involved in pro-apoptotic pathways (1, 2).

Proteasomes are bulky protein complexes that break down the unwanted proteins in the cell, with the help of ubiquitin to maintain cellular integrity. The ubiquitin–proteasome system (UPS) is the main route of cellular protein degradation. In addition to its role in the removal of damaged proteins, the UPS is involved in a number of biological processes including inflammation, proliferation, and apoptosis (3).

Bortezomib is known to act on UPS blocking the activity of the proteasomes leading to cell death. Inhibition of proteasomes results in accumulation of the ubiquitin complexes, preventing the breakdown of apoptotic factors leading to programmed cell death in neoplastic cells. UPS through regulation of apoptosis and structural remodeling of heart plays a key role in maintaining normal cardiac size and structure (4). However, this effect can have impact on various organs including the myocardium.

Cardiac myocytes are highly vulnerable to disturbances in UPS (5). Acccumulation of ubiquinated proteins has been implicated in cardiac myopathies (6). Dysfunction of the proteasome has been related to various cardiac pathologies including myocardial ischemia, congestive heart failure and idiopathic cardiomyopathy. Proteasomal dysfunction has also been demonstrated in animal models prior to and during development of heart failure (7). Studies using experimental animals have suggested that proteasome inhibition can suppress cardiac

hypertrophy and reduce myocardial injury possibly through preventing NFκB activation (7, 8) but clinical reports suggest that bortezomib is associated with cardiac toxicity.

The most frequent moderate to serious adverse events observed with the use of bortezomib in humans have been thrombocytopenia, fatigue, peripheral neuropathy and neutropenia. But recent case reports have linked bortezomib to development of congestive heart failure (9, 10).

Cardiac effects of bortezomib have been only reported in case reports. No major study has shown any association. APEX trial was a phase 3 trial comparing bortezomib with high-dose dexamethasone in heavily pretreated patients with relapsed multiple myeloma. The incidence of cardiac disorders during treatment with bortezomib and dexamethasone was 15 percent and 13 percent, respectively. Only 2 percent of patients receiving bortezomib developed CHF (11). In a study looking into 69 patients treated with bortezomib, either alone or as combination therapy, 8 of the 69 patients developed serious cardiac side effects including 4 who developed LV heart failure (12). Two open-label, phase II trials (SUMMIT [n = 202] and CREST [n = 54]) established the efficacy of bortezomib administered by intravenous bolus on days in heavily pretreated patients with relapsed/refractory multiple myeloma. With this regimen, the percentages of patients with at least a minimal was 50% in CREST and 35% in SUMMIT (13). In a study by Enrico et al, 8 of 69 patients developed serious cardiac side effects (9).

Interestingly though, there was no difference in the incidence of congestive heart failure between patients treated with bortezomib versus dexamethasone in the APEX study (2% in both groups) involving 669 patients. However, three of the four drug related deaths in the bortezomib group were from cardiac causes as compared to none in the dexamethasone group.

Clinical experience with Bortezomib so far indicates that the incidence of cardiac failure is rare. Nevertheless, development of new onset systolic dysfunction/heart failure or exacerbation of congestive heart failure has been reported with the use of bortezomib with reversible cardiac impairment after discontinuation of the drug. Presence of a subclinical cardiac failure may explain the susceptibility of patients to bortezomib but our patient had normal LVEF. Genetic susceptibility of certain patients to bortezomib needs to be considered and further research is required on it.

Considering the sequence of events, the absence of signs and symptoms of other evident causes for dilated cardiomyopathy (including viral cardiomyositis and cardiac amyloidosis) and normal pre-treatment echocardiogram, we hypothesize that the severe reduction in EF was most probably related to bortezomib therapy.

Conclusion:

The chronology of events in this patient's management of myeloma points toward an unexplored and potentially life-threatening adverse effect of bortezomib. As the therapeutic spectrum of bortezomib continues to expand, physicians need to be aware of the hitherto uncommon side-effects. The good part is that the heart failure caused by Bortezomib is reversible. There are no

screening criteria established for the Bortezomib- induced heart failure. The chances of exacerbation of congestive heart failure are more if there is preexisting heart failure. We strongly recommend that patients be told about the warning signs and symptoms of congestive heart failure while being treated with Bortezomib and a baseline echocardiogram be obtained.

Key points

1. Novel chemotherapeutic drugs including Bortezomib and Lenalidomide have largely replaced the conventional regimen improving the survival of patients with multiple myeloma.

2. Bortezomib acts through intracellular proteasomal inhibition resulting in cell degradation.

3. The proteasomal inhibition effect can also extend to myocardial cells resulting in significant

myocardial damage leading to dilated cardiomyopathy.

4. Bortezomib must be used with caution in patients with pre-existing heart disease.

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