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CASE REPORT

Partially reversible bortezomib-induced cardiotoxicity: an unusual cause of acute cardiomyopathy

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Chemotherapy-associated cardiotoxicity can present as a spectrum from arrhythmia to acute congestive heart failure. Unlike anthracyclines, proteasome inhibitors – for example, bortezomib – are not notorious for causing cardiotoxicity in absence of pre-existing cardiac dysfunction or without concomitant use of other cardiotoxic agents. We describe a 66-year-old woman with end-stage renal disease who developed acute dyspnea hours after a third treatment with bortezomib for IgG kappa myeloma. The Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 5) between bortezomib and acute left ventricular dysfunction. Patients receiving proteasome inhibitors should be closely monitored for evidence of cardiac dysfunction during treatment.

Keywords: *bortezomib*; *proteasome inhibitors*; *cardiotoxicity*; *multiple myeloma*; *heart failure*

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In spite of the progress that has been made in therapeutic modalities of neoplastic diseases, life-threatening toxicities (especially cardiotoxicity) resulting from chemotherapy protocols remain a problem. Detection of cardiac injury after chemotherapy is essential in order to start treatment as early as possible. We report a probable case based on the Naranjo probability scale (1) of bortezomib-induced cardiotoxicity.

Case report

A 66-year-old woman with recently diagnosed Durie and Salmon stage IIIB IgG kappa myeloma was started on CyBorD chemotherapy including cyclophosphamide 500 mg orally weekly, bortezomib (given weekly after hemodialysis, at a dose of 2.5 mg subcutaneously), and dexamethasone 20–40 mg orally weekly, having failed plasmapheresis. She was also on antiviral prophylaxis (acyclovir 200 mg orally twice a day) and double-strength trimethoprim–sulfamethoxazole once daily on Mondays, Wednesdays, and Fridays. She tolerated the first two weekly doses of chemotherapy well. However, 6 h after the initiation of her third dose, she was brought to the emergency room due to acute-onset shortness of breath that was progressive and associated with palpitations without chest pain, dizziness, or lightheadedness. She had no fever, chills, cough, sputum production, orthopnea, pain, or change in bladder or bowel habits. Her medical history included renal failure attributed to myeloma, hypertension, diabetes mellitus type 2, stage I ovarian cancer treated with surgery, as well as carboplatin and paclitaxel 5 years prior, and left bundle branch block (LBBB) first noted 2.5 months prior but associated with normal echocardiography (ECHO). She had started hemodialysis the day before commencement of chemotherapy, and had not missed any scheduled dialysis sessions. The patient never smoked and used alcohol socially. Her family history was non-contributory.

At the time of this presentation, she weighed 64 kg and had tachypnea and tachycardia; her oxygen saturation was 76% on room air. She was in distress but alert and oriented; examination revealed increased jugular venous pressure, diffuse bilateral crackles, and normal heart sounds with no murmurs, gallops, or rubs. She had neither focal neurologic deficit nor edema of the lower extremities. Her troponin was 0.323, with rise to 0.916 in 17 h; hemoglobin was 7.5, hematocrit 22, sodium 128, chloride 91, creatinine 5.9, and glucose 410. Electrocardiography revealed normal sinus rhythm and LBBB; chest radiography showed increased interstitial markings suggestive of pulmonary venous congestion, which was confirmed by contrast-enhanced computerized tomography of the chest done to rule out pulmonary embolism. ECHO revealed dilated cardiomyopathy with ejection fraction (EF) of 15%,

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worse than 55% obtained 2 months prior (Table 1). Extensive workup – including viral serologies – failed to detect the cause for decline in cardiac function. Cardiac catheterization showed insignificant coronary artery disease with minimal myocardial bridging of the posterolateral branch of the right coronary artery; this was thought not to be responsible for the heart failure. Bortezomib-induced cardiotoxicity was entertained; the Naranjo adverse drug reaction probability scale (1) indicated a probable relationship (score of 5) between bortezomib and acute left ventricular dysfunction. She was treated for acute heart failure and her dyspnea gradually improved. Her EF improved, but did not reach her prior baseline (Table 1); N-terminal pro-B-type natriuretic peptide (BNP) was 11,000 three weeks after presentation. In place of CyBorD, she received lenalidomide and dexamethasone chemotherapy, which was expanded to bendamustine/lenalidomide/dexamethasone. She, however, developed infection of her vascular access catheter, as well as atrial fibrillation, and ultimately expired in home hospice care 3 months after presenting in heart failure.

Discussion

Recent recommendations for treatment of multiple myeloma include induction with bortezomib and dexamethasone-based regimens in patients with myeloma kidney (2). Bortezomib is a boron-containing molecule and proteasome inhibitor; the ubiquitin-proteasome system – the major pathway for intracellular protein degradation – plays a role in cell survival. Thus, proteasome inhibition induces cell apoptosis (3). Pig data suggest that chronic (over 12 weeks) proteasome inhibition is associated with increased propensity to atherosclerosis (4); other animal studies have associated proteasome inhibition with control of cardiac hypertrophy (5) or reversible systolic dysfunction in rat hearts (6).

In a study comparing bortezomib to high-dose dexamethasone for treatment of relapsed myeloma, 2% in each group had congestive heart failure (CHF) (7). A meta-analysis of that and 24 other trials found a statistically insignificant increase in cardiotoxicity associated with bortezomib compared with control – but only patients with 'adequate' renal function were included (8).

Nevertheless, acute development of heart failure has been associated with bortezomib treatment. In one instance, this was after four 3-week cycles of bortezomib on days 1 and 8 of each cycle; pretreatment BNP was elevated to 1,389 (9). However, cotreatment with anthracyclines – which are better known for association with cardiotoxicity – occurred in two of seven cases in one review (10).

LBBB predisposes to heart failure (11); the role of LBBB or other features of asynchrony in bortezomib cardiotoxicity is unclear. Chronic hemodialysis has also been associated with incidence of CHF (12). Cyclophosphamide is known to induce diastolic dysfunction via direct endothelial damage, but cardiotoxicity has not been reported in association with cumulative doses less than 100 mg/kg (13). Fortunately, most patients with bortezomib-associated heart failure respond to standard therapy for heart failure and cessation of bortezomib – but it has taken 6 or more months to document this (9, 10).

Table 1. Systolic ejection fraction by months before (denoted by negative numbers), at (time 0) and after presentation

Time in months	Ejection fraction (%)
−22	60
−2.5	55
0	15
0.1	30
0.6	30
2.4	30
3	30

Conclusion

In light of the above, cardiac function should be assessed at baseline with echocardiogram, BNP, and EKG, even in asymptomatic patients, as part of a routine workup before starting proteasome inhibitor therapy. We also recommend that BNP be monitored serially during therapy or at the first hint of symptoms referable to cardiac failure. Repeat cardiac assessments after treatment should also be strongly considered. Further research is required to inform guidelines for cardiac assessment of patients on proteasome inhibitor therapy.

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