

Bortezomib-Induced Cardiac Tamponade in a 49-Year-Old Man

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Proteasome inhibitors such as bortezomib and carfilzomib have been used effectively to treat patients who have certain hematologic malignancies. Proteasome activity is elevated in the heart, and potent inhibition results in accumulation of misfolded intracellular protein aggregates and apoptosis. Heart failure, conduction disturbances, and premature atherosclerosis have been associated with bortezomib therapy. We describe the case of a 49-year-old man who was taking bortezomib for graft-versus-host disease, when he developed cardiac tamponade and needed emergency pericardiocentesis. At that time, there was no evidence of graft-versus-host disease. To our knowledge, this is the first time that a pericardial effusion without underlying cardiac dysfunction has been reported in relation to bortezomib therapy. The diagnosis of pericardial effusion during bortezomib therapy, the absence of other causative agents—including graft-versus-host disease—and no recurrence of pericardial effusion after discontinuing bortezomib therapy suggest that bortezomib caused our patient's tamponade. (Tex Heart Inst J 2018;45(4):260-3)

Key words: Bortezomib; cardiotoxicity/complications; heart/drug effects; heart diseases/chemically induced; proteasome inhibitors/ adverse effects/therapeutic use/toxicity; risk

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Proteasome inhibitors (PIs) belong to a new class of chemotherapeutic agents that are being used more often to treat relapsed or refractory multiple myeloma.¹ These agents have recently come under scrutiny because they have been linked to cardiotoxicity. Although the mechanisms of PIs are not well understood, the ubiquitin–proteasome system (UPS) regulates protein turnover and activates cell signaling pathways crucial for cell growth and survival.² Cancer therapies targeting the proteasome pathway have been associated with cardiac dysfunction, including heart failure due to off-target effects in normal cells.^{2,5} Carfilzomib, an irreversible inhibitor of the chymotryptic site of the proteasome,⁶ has been associated with heart failure, with a reported incidence of 7% in 526 clinical trial patients.⁷ Bortezomib and ixazomib have also been associated with systolic heart failure.⁸ In this report, we describe the diagnosis of pericardial effusion without concomitant cardiac dysfunction in a patient who was taking bortezomib for graft-versus-host disease (GVHD).

Case Report

In February 2016, a 49-year-old man with a history of hypertension and chronic myelogenous leukemia (CML) presented at the emergency department with acute onset of diffuse chest pain and dyspnea. The CML had been diagnosed in 2008, and he had undergone therapy with several drugs, all of which had been discontinued: imatinib had failed to cure the disease, dasatinib had caused thrombocytopenia, and nilotinib had caused cytopenia. In September 2013, bone marrow biopsy results obtained after nilotinib had been discontinued showed myelodysplastic syndrome, so the patient underwent peripheral blood stem cell transplantation. Because of concerns about recurrent disease in January 2015, a repeat bone marrow biopsy was performed and revealed myelofibrosis. Two months later, the patient underwent hematopoietic stem cell transplantation, which was complicated by systemic GVHD. Repeat testing by use of a peripheral blood reverse transcription-polymerase chain reaction (rt-PCR) assay showed 100% chimerism of bone marrow cellularity and the absence of breakpoint cluster region-Abelson murine leukemia (BCR-ABL) fusion messenger RNA. In August 2015, the patient was started on subcutaneous bortezomib (dose, 1.3 mg/m²) to treat GVHD, which was evidenced by worsening skin disease and liver function abnormalities. He had completed 4 cycles of bortezomib before presentation. Treatment had stabilized his liver function, and there was no new progression of skin disease.

Upon arrival at the emergency department, the patient's vital signs were as follows: heart rate, 103 beats/min; blood pressure, 87/68 mmHg; respiration rate, 18 breaths/min; and oxygen saturation, 95% on room air. An electrocardiogram showed diffuse ST-segment elevation with low voltage in all leads. His initial cardiac troponin levels were within normal range. A computed tomographic angiogram of the chest revealed a large circumferential pericardial effusion. A 2-dimensional transthoracic echocardiogram (TTE) showed normal biventricular systolic function, a large pericardial effusion, a dilated noncompressible inferior vena cava, and invagination of the right atrial and right ventricular free walls during diastole (Fig. 1). Transthoracic Doppler echocardiograms showed increased respiratory variation in mitral and tricuspid inflow, consistent with increased intrapericardial pressure. These features supported the clinical diagnosis of cardiac tamponade.

The patient underwent emergency fluoroscopic-assisted pericardiocentesis and pericardial drain placement, which initially yielded 550 mL of cloudy, dark yellow fluid, followed by an additional liter of fluid over 48 hours with tapering output. The pericardial fluid was sent for serologic and cytologic analyses (Table I). The drain was then closed for 24 hours, and limited TTE revealed no accumulation of the effusion.

A review of the patient's records from 6 months before he started bortezomib therapy revealed normal TTE results without pericardial effusion. Although no other echocardiograms had been obtained until the current presentation, the close timing between events and the lack of any other changes to the patient's therapeutic regimen led the oncologist to conclude that the pericardial effusion was caused by bortezomib therapy, so it was discontinued. One month later, a TTE showed normal biventricular systolic function and no reaccumulation of pericardial fluid. Subsequent rt-PCR assays for BCR-ABL were negative for recurrent CML. However, in March 2016, the patient had recurrent GVHD, evidenced by worsening liver function, and it was managed with tacrolimus. Therapy was eventually discontinued after the patient's GVHD became stable. His liver function and skin disease have remained stable as of July 2018.

Discussion

Bortezomib, a dipeptidyl boronic acid, is a potent, specific, reversible PI currently approved by the U.S. Food and Drug Administration (FDA) for use in multiple myeloma and other hematologic malignancies. Bortezomib has shown positive clinical benefit, either alone or in combination therapy, to induce chemo- or radiosensitization and to overcome chemotherapeutic drug resistance.⁹ Multiple molecular mechanisms have been proposed for the antineoplastic effects of PIs such

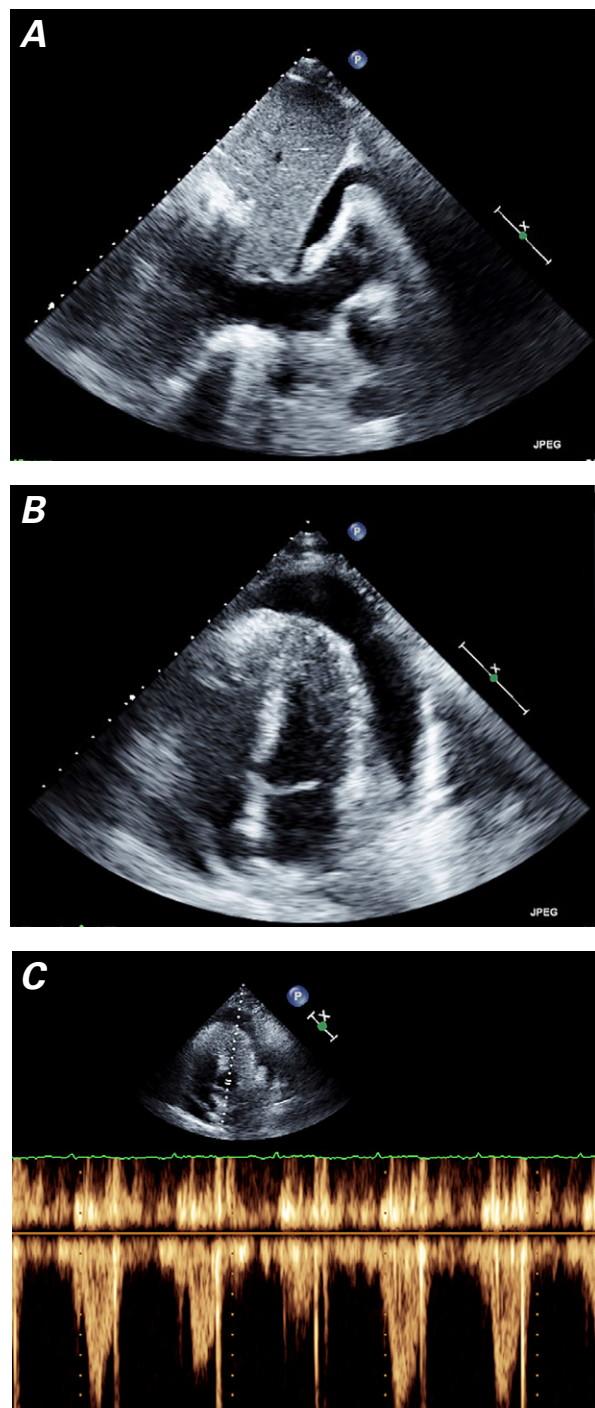


Fig. 1 Transthoracic echocardiograms show **A**) a dilated inferior vena cava, **B**) right ventricular diastolic invagination, and **C**) increased respiratory variation in mitral and tricuspid inflow (pulsed-wave Doppler mode), all of which support the diagnosis of cardiac tamponade.

as bortezomib, all of which may work in potentiating or, at least, complementary fashion.¹ The primary mechanism of action relates to the interruption of the UPS, and thus circuitously affects the well-described cellular process of autophagic flux.²

TABLE I. Laboratory Results

Test	Value (reference range)
Serum and cytologic features	
C-reactive protein (mg/L)	52.9 (≤4.9)
Thyrotropin (mIU/L)	2.8 (0.46–4.68)
Adenosine deaminase (U/L)	29 (<9.2)
Creatinine (mg/dL)	0.73 (0.7–1.4)
Troponin I (ng/mL)	0.015 (0.035–0.12)
Glucose (mg/dL)	100 (65–110)
Total protein (g/dL)	6.2 (6.3–8.2)
Cytomegalovirus (copies/mL)	<200 (<200)
Fas ligand (pg/mL)	112
Pericardial fluid	
Glucose (mg/dL)	88
Total protein (g/dL)	4.3
Neutrophils (cells/μL)	9,623

These test results were negative: acid-fast bacilli stain, adenovirus, coronavirus, coxsackievirus A and B, gram stain, influenza, parainfluenza, tuberculosis, and tumor necrosis factor- α . Bacterial and acid-fast bacilli cultures showed no growth. Pericardial cytologic results showed no malignant cells.

During autophagy, damaged intracellular organelles and proteins are recycled to avoid toxic buildup of non-functional cellular components. Disturbances in intracellular degradation and recycling pathways cause damaged and dysfunctional intracellular proteins to accumulate, ultimately blocking cellular growth and mitotic pathways and indirectly promoting cellular apoptosis.⁹⁻¹² When cellular injury is intentionally induced by chemotherapy, normal autophagy can counteract the therapy by rescuing malignant cells from toxic accumulation and cell death. Thus, agents that interfere with this process may promote chemotherapeutic sensitivity and synergism.

Cellular toxicity resulting from chemotherapeutic agents is not confined to neoplastic cells. Accordingly, disturbance of the UPS and autophagy, along with up- and downstream effectors, may affect normal homeostasis and the function of off-target cell types. Cardiac involvement does not appear to have been reported in the medical literature. However, after phase III trials, such as the Assessment of Proteasome inhibition for EXtending remissions (APEX) trial, and FDA approval, the use of bortezomib to treat some hematologic malignancies has increased, and cases of cardiotoxicity have been described.¹¹

Cardiomyocytes lack, or at least have only limited, mitotic ability.¹³ Therefore, possible cardiotoxicity and

a decrease in cardiac function secondary to bortezomib therapy cannot be explained simply by the interference of cellular growth, mitosis, or both. Cardiotoxicity from bortezomib has been reported to cause decreases in systolic function with reduced ejection fraction and subsequent heart failure,^{3-5,14,15} as well as cardiac conduction disturbances¹⁶ and accelerated atherosclerotic disease.¹⁷ Carfilzomib and ixazomib have also caused cardiotoxicity, so this may represent a drug class effect.^{6,8} Grandin and colleagues⁶ reported that cardiotoxicity associated with carfilzomib may be reversed by discontinuing the drug, as evidenced by improvement of heart failure symptoms and ejection fraction in a group of patients. Bockorny and associates⁴ described pericardial effusion with associated systolic dysfunction in a patient who had multiple myeloma and underwent 4 cycles of chemotherapy with bortezomib. In a meta-analysis of 25 prospective studies, the incidence of cardiotoxic events was 3.8%.¹⁸

Our patient had an isolated, hemodynamically significant pericardial effusion, notable because he had no systolic dysfunction; to our knowledge, this is the first report of this finding after bortezomib treatment. Before starting therapy, he had normal biventricular systolic function and no pericardial effusion. He then underwent 4 cycles of bortezomib therapy. No other changes were made to his therapeutic regimen, so the pericardial effusion and the resultant tamponade physiology were most likely related to bortezomib. Furthermore, after the drug was discontinued, there was no recurrence of pericardial effusion. Although the patient had no evidence of GVHD during the episode of pericardial effusion, it recurred after bortezomib was stopped. On the basis of serologic and cytologic testing, we concluded that our patient had acute inflammation, evidenced by the predominance of neutrophils secondary to bortezomib therapy.

Of note, we did not test the patient for parvovirus B19, autoimmune diseases, or fungal diseases as possible causes of his condition, nor could we absolutely confirm a correlation between the pericardial effusion and bortezomib therapy because no serial images were obtained during treatment. As a result of our patient's case and other reports of cardiotoxicity, we recommend that patients undergo continual cardiac monitoring during bortezomib therapy, as is done with other cardiotoxic chemotherapeutic agents. Further study of the cardiac sequelae of bortezomib is warranted.

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