Ventricular fibrillation after bortezomib therapy in a patient with systemic amyloidosis

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Abstract
A 64-year-old female was diagnosed with systemic amyloidosis associated with multiple myeloma. Bortezomib and dexamethasone-therapy was initiated; however, she developed lethal ventricular fibrillation (VF) and cardiac arrest after 84 hours of therapy. Cardiopulmonary resuscitation using direct current shocks with epinephrine and amiodarone was initiated but failed to receive cardiac function. Although her arterial pulsations recovered immediately after the injection of vasopressin, she died of heart failure 8 hours after the onset of VF. Cardiac amyloidosis was verified by autopsy. Although the direct association of bortezomib with lethal VF remained to be clarified in our patient, the current report emphasizes on bortezomib as a substantial risk factor for cardiomyocyte damage. The potential risk of lethal events associated with cardiac amyloidosis should be carefully considered during bortezomib treatment for patients with AL amyloidosis.

Case Report
A 64-year-old female suffering from general fatigue, appetite loss, and weight loss was referred to our institute for the investigation of M-protein and hypercalcemia. Upon hospital admission, her Eastern Cooperative Oncology Group performance status was 2 and her Karnofsky performance status (KPS) was approximately 50%. She was also found to suffer from class II heart failure according to the functional classification system of New York Heart Association (NYHA). Physical examination revealed a palpable liver edge 15 cm below the costal margin and bilateral pretibial pitting edema.

Results of her blood test revealed the following: aspartate aminotransferase, 81 (normal, 13-33) U/L; alkaline phosphatase, 534 (115-359) U/L; γ-glutamyl transpeptidase, 311 (10-47) U/L; lactate dehydrogenase, 343 (119-229) U/L; calcium, 11.7 (8.7-10.3) mg/dL; creatinine, 1.18 (0.4-0.7) mg/dL; brain natriuretic peptide, 359 (2.5-4.2) U/L; troponin I, 0.242 (0.0-14) ng/mL. Her serum beta-2 microglobulin level was 5.5 (2-5.25) mg/dL and free light chain difference (FLC-diff) was 33.46 mg/dL.

Immunoelectrophoresis demonstrated a monoclonal immunoglobulin light-chain with λ isotype in the urine. A bone marrow aspirate revealed 10% plasma cells with CD38+, CD138+, and cytoplasmic λ+ phenotypes. An iliac biopsy confirmed the infiltration of plasma cells. Diffuse osteoporosis was revealed by radiography, and magnetic resonance imaging showed the absence of focal lesions. Histopathological examination revealed amyloid infiltration in biopsy samples of the gastric mucosa.

Marked cardiomegaly was noted on chest radiography. Electrocardiography (ECG) revealed left-axis deviation, low-voltage QRS complexes, and first degree atrioventricular block (Figure 1A). A 24-h Holter ECG demonstrated 129 beats of ventricular premature contractions (VPCs) and 1268 beats of atrial premature contractions (APCs), including 5 VPC short runs (maximum, 5 runs) and APC short runs (maximum, 8 runs; Figure 1B). Transthoracic echocardiography revealed a left ventricular ejection fraction of 64%, diffuse thickening of the left and right ventricular walls with granular sparking, and pericardial effusion.

She was diagnosed with systemic AL amyloidosis associated with Bence Jones protein type multiple myeloma (MM). After written informed consent was obtained from the patient, administration of dexamethasone and bortezomib (oral dexamethasone, 20 mg/day, days 1-4; bortezomib, 1.3 mg/m²/day, subcutaneous injection on day 4) was initiated under 24-h ECG monitoring (Figure 1C). The incidence of tachycardia was decreased through dexamethasone treatment. Serum calcium levels were corrected by intravenous infusions of normal (0.9%) saline with elcatonin, leading to increased body weight. After adjustment of infusions and diuretic treatment, her body weight returned to that at baseline. The day before the onset of VF, her serum mineral levels were within normal limits as follows: calcium, 9.2 mg/dL; magnesium, 1.8 (1.8-2.7) mg/dL; and potassium, 3.9 (3.6-4.9) mmol/L. The patient no longer complained of insomnia,
constipation, or the stress of hospital admission. However, approximately 84 h after bortezomib administration, in the middle of the night, the patient conversed with nursing staff and walked to the rest room for urination. A few minutes later, her cardiac monitor alarm sounded and showed VF pattern. She was found lying down at her bedside. Cardiopulmonary resuscitation (CPR) using direct current shocks with epinephrine and amiodarone was initiated. Her serum mineral levels were as follows: sodium, 138.1 (138-146) mmol/L; potassium, 3.56 mmol/L; ionized calcium, 1.11 (1.1-1.4) mmol/L; and bicarbonate, 29.9 (22-30) mmol/L. Continuous CPR for approximately 30 min failed to recover the cardiac features required to sustain the general circulation, but just after the injection of vasopressin, her arterial pulsations recovered. However, she died of heart failure 8 h after the onset of VF.

Autopsy revealed congested, hemorrhagic lungs and right and left ventricular hypertrophy (heart weight, >400 g). Gross examination revealed round-to-web-like yellow waxy deposits in the myocardium. Histopathological examination revealed cardiac amyloid deposition, even in the atrioventricular node, and no ischemic lesion was complicated (Figure 1D, E). The amyloidosis had also spread to the tongue, lung, liver, colon, kidney, bone marrow, adrenal gland, thyroid gland, and ovaries.

Discussion

The present patient possessed one of two risk factors (systolic blood pressure <100 mmHg) in stage III cardiac amyloidosis. According to the revised prognostic staging system for AL amyloidosis, the present patient is categorized to stage 3 (NT-ProBNP ≥1800 [page 40] [Hematology Reports 2013; 5:e12]

Figure 1. A) Low-voltage of QRS complexes and the absence of P wave in all leads on electrocardiography (ECG) performed on hospital admission. B) The results of 24-h Holter ECG reveal a long pause (arrow) and short-run of premature contractions (asterisks). C) Results from a continuous bedside monitoring device during 1 week around bortezomib subcutaneous injections. The day when the cardiac arrest occurred is referred to as day 0. DEXA, dexamethasone. D) Histopathological analyses of the region of atrioventricular nodes. Deposits of amorphous materials (arrows) can be seen in a hematoxylin and eosin stained section (x100). E) The amorphous deposits (arrows) are stained positively by Congo-red (x100). The asterisks indicate perivascular amorphous materials that are positively stained with Congo-red.
After 3 cycles of cyclophosphamide, bortezomib, and dexamethasone, 1 patient was complicated with fluid overload while another patient developed decompensated heart failure.\textsuperscript{13} Although the authors did not mention the possibility of accidental cardiac event independent of bortezomib nor the association between bortezomib and heart failure, we cannot deny the cardiac arrest induced by bortezomib.

According to the data \textit{in vitro}, the ubiquitin-proteasome system (UPS) is activated in hypertrrophic cardiomyocytes,\textsuperscript{14} and it protects blood vessels from the formation and rupture of plaques,\textsuperscript{9} and maintains protein quality in cardioamyocytes.\textsuperscript{15} With regard to dilated cardiomyopathy, the genes for UPS are highly expressed in a rat model and human heart specimens.\textsuperscript{16} Age-related activation of the UPS has been proposed to maintain essential cardiac function.\textsuperscript{17} Once proteasome activity is inhibited, atherosclerotic plaques become unstable, smooth muscle cells become apoptotic, and expression of the adrenergic sensitizer GRK2 increases, which can harm cardioamyocytes. The inhibition of nuclear factor-kappa B by bortezomib is responsible for higher incidence of cardiac damage in AL amyloidosis compared to multiple myeloma.\textsuperscript{18} In the future, we should determine the mechanism that could have been associated with lethal VF in our patient.

We should discuss about the use of implantable devices and CPR. Our patient did not have a history of syncope, and then no indication for preventive implantation of a pacemaker. According to a trial, 19 patients associated with syncope and/or ≥2 consecutive VPC beats received an implantable cardioverter-defibrillator (ICD), and 6 of them died from electromechanical dissociation.\textsuperscript{19} In our patient, immediate direct-current shocks were not effective for recovery from cardiac arrest. Accordingly, whether we could have avoided the occurrence of lethal VF in our patient by ICD implantation remains unclear. With regard to CPR, vasopressin has been considered to be a promising alternative to epinephrine and proposed as an initial vasopressor for cardiac arrest.\textsuperscript{20} Vasopressin is associated with a longer duration of action compared with epinephrine. Our patient required frequent injections of epinephrine, one shot of vasopressin could have maintained her blood pressure for a long period, and then this may have been effective in maintaining the systemic circulation.

### Conclusions

We described a form of systemic AL amyloidosis with cardiac involvement that resulted in sudden cardiac death induced by VF following bortezomib therapy. We should not ignore the potential risk of lethal arrhythmia associated with advanced cardiac amyloidosis during bortezomib treatment. Furthermore, vasopressin may be useful for CPR in patients with cardiac amyloidosis requiring frequent injection of epinephrine.

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