CASE REPORT

Acute severe cardiac failure in a myeloma patient due to proteasome inhibitor bortezomib

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Abstract We present here a case of severe congestive cardiac failure, in a 47-year-old patient with myeloma who had no prior cardiac history, after receiving bortezomib. Bortezomib is a boron-containing molecule, which reversibly inhibits the proteasome, an intracellular organelle, which is central to the breakdown of ubiquitinated proteins and consequently crucial for normal cellular homeostasis. Phase II clinical trials demonstrate that it is effective for the treatment of relapsed refractory myeloma. Acute development of congestive cardiac failure associated with bortezomib therapy occurs very rarely or may be underestimated. Inhibition of proteasome activity may impair cardiac function due to accumulation of unfolded, damaged and undegraded proteins in myocytes. Patients with or without cardiac disease or previously received anthracycline-containing regimes should be closely monitored when being subjected to treatment with bortezomib.

Keywords Bortezomib · Proteasome inhibitors · Cardiac failure · Myeloma

1 Introduction

The ubiquitin–proteasome system is responsible for the nonlysosomal degradation of the proteins that regulate cell cycle, apoptosis and angiogenesis. Bortezomib is a new proteasome inhibitor that inhibits the proteosomal degradation of these proteins therefore providing an antiproliferative, proapoptotic, antiangiogenic and antitumor activity [1–3]. In preclinical studies, bortezomib has been shown to increase the antitumor efficiency of the commonly used drugs in myeloma treatment such as doxorubicine, melphalan and dexamethasone, and has even been demonstrated to have an effect on the myeloma cells that were resistant to these drugs [1, 2]. Bortezomib binds to the chymotryptic area of the 20S β subunit of the proteasome and inhibits it. As a result, IκB is not degraded into smaller proteins. It remains bonded to NFκB and inhibits its effects [4]. Moreover, proteasome inhibition gives rise to an increase in the activity of p53 and proapoptotic Bax protein that leads to accumulation of cycline-dependent kinase inhibitors, p27 and p21 [5–8]. The most frequently encountered side effects under bortezomib therapy are lassitude, gastro-intestinal abnormalities and peripheral neuropathy. Common grade 3 toxicities are peripheral neuropathy, thrombocytopenia, neutropenia and anemia [9].

Recently six cases have been reported in four manuscripts to have reversible cardiac failure due to bortezomib usage [10–12]. The latest report on this puts forward cardiac failure in four patients [13] and all four patients were also estimated to have various arrhythmias [13]. In a new manuscript, atrial fibrillation as grade-3 toxicity has been reported only in one patient [12]. As the cardiac side effects of bortezomib were not described in product monograms and in the study that aimed to investigate the side effects profile of the drug, the APEX study, this side effect seems either to be a truly rare one or must have been eluded from observation [14]. In this report, we are presenting a myeloma case in whom severe cardiac failure ensued due to administration of bortezomib.
2 Case report

A 47-year-old patient was under investigation for having epistaxis, gingival bleeding and chest pain when a high sedimentation rate was established (117 mm/h). Protein electrophoresis displayed M spike; immuno-fixation electrophoresis showed IgG and κ-type monoclonality (IgG: 10 g/dL, κ: 3.7 g/dL). Blood analysis of the patient showed the following: Hb 9.1 g/dL, WBC $7 \times 10^9/L$, granulocyte $4.5 \times 10^9/L$, platelet $171 \times 10^9/L$, urea 27 mg/dL, creatinine 1.1 mg/dL, LDH 174 U/L (N: 100–190 U/L), total protein 13.8 g/dL, albumin 2.5 g/dL, calcium 8.4 mg/dL (N: 4.5–5.6 mg/dL), β2-microglobulin 4.68 mg/L (N: 1.2–2.8 mg/L). Urine analysis showed 3+ proteinuria. Urine immunofixation electrophoresis displayed 13 g kappa-type free chain in 24 h. The result of the creatinine clearance test was 85 mL/min. Bone marrow aspiration was done and atypical plasma cells with immature appearance were observed at a rate of 50%. A cranial X-ray was taken that demonstrated many lytic lesions. The radiograph of the spine indicated diffuse osteoporosis. As a result, the patient was diagnosed to have grade IIIA, IgG, κ-type myeloma.

In his medical history, we learned that the patient had undergone an echocardiography and angiography with the suspension of coronary ischemia both of which have turned out to be normal. We re-evaluated the angiography and echocardiography records for reconfirmation and the result was the same.

As HBV-DNA was (+) (416 IU/μL with PCR), the patient was put on lamivudine tablet therapy, 100 mg/day. After 2 weeks, MP (melphalan 10 mg/day, 5 days/month and methylprednisolone 64 mg/day, 5 days/month) and zoledronic acid 4 mg/month was added to the therapy. In the immunofixation electrophoresis performed after of five regiments of MP therapy, the monoclonal IgG content was found to be within normal limits both in the sera and in the urine specimens; hence, they were unable to be measured. κ-free light chain levels in the urine were lowered from 13 g/24 h to 7.8 g/24 h. At the same time, a 50% reduction in the plasma cell ratio in the bone marrow has been estimated (second ratio 28%). When these data are taken into consideration according to the International Myeloma Working Group (IMWG) uniform response criteria, we thought that the patient had a partial response (PR). So the patient was given VAD (infusional vincristine, doxorubicine and pulsed dexamethasone). Following the first regimen of VAD, the patient presented a lobar pneumonia. Unfortunately, the causative agent was not isolated microbiologically. This had been treated well with piperacilin and tazobactam combination. Our patient did not have a prominent hypogammaglobulinemia (IgA 3.3 g/dL, IgM 2.5 g/dL) and neutropenia (1.8 × 10^9/L). The cardiac functions were normal during pneumonia and there were no sign of cardiac failure. It was thought that the patient would not tolerate a high dose of corticosteroid therapy. Therefore, it was decided to give him bortezomib 1.3 mg/m² on the 1st, 4th, 8th and 11th days, in every 21 days. A severe abdominal pain and weakness ensued after the second regimen of bortezomib (9th day of the second regimen of bortezomib administration), which was followed by dispnea 2 weeks after the onset of these symptoms (dyspnea ensued 14 days after the 8th therapeutic day of the second regimen of bortezomib). Auscultation of the lungs revealed crepitation at the bases. A chest X-ray was taken that showed an increase in the cardiothoracic ratio. The reason for intensive abdominal ache was not fully understood, but we thought that it might have been because of mesenteric ischemia that resulted from cardiac failure. A second probability to explain this situation may be a sub-ileus associated with bortezomib neuropathy. With echocardiography, LVEF (left ventricle ejection fraction) calculated with the Simpson method was found to be 10% and RVEF (right ventricular ejection fraction) was found to be 20%. The right and left ventricular diameters were increased. There was left ventricular diastolic dysfunction with grade II SEC (spontaneous echo contrast) in both the left atrium and the left ventricle. BNP (brain natriuretic peptide) level was estimated to be 1170 pg/mL (control <100 pg/mL, at normal control 120 pg/mL). Bortezomib was discontinued as it was thought to be the reason for cardiac failure. Because of SEC (spontaneous echo-contrast) in the left atrium, left ventricle anticoagulant therapy with warfarin, 5 mg/day, was initiated to prevent any thromboembolic complications. After consultation with the Cardiology Department, metoprolol 25 mg/day was also added to the cardiac therapy of the patient. In the first place, the clinical findings and the complaints of the patient were relieved by the cessation of bortezomib. His BNP levels and echocardiographic findings improved slowly but progressively (Figs. 1, 2). Warfarin was discontinued as SEC disappeared.

![BNP Levels vs Date](image-url)

*Fig. 1* BNP (brain natriuretic peptide) levels after bortezomib withdrawal were shown. After bortezomib was withdrawn, BNP level increased up to 4000 pg/mL and then decreased to almost normal level.
The ubiquitin–proteasome system is responsible for the nonlysosomal degradation of the intracytoplasmic proteins. It plays an important role in the maintenance of the protein quality by degradation of the misfolded, unassembled or damaged proteins that otherwise could have been toxic. The ubiquitin–proteasome system has a special importance for the cardiac myocytes. The proteasome’s function is important in keeping the normal size and shape of the heart. When the functions of the proteasome system alter cardiac hypertrophy, insufficiency may ensue [15]. The role of the ubiquitin–proteasome system is therefore especially important in maintaining the protein quality in the heart. The interaction between the cardiac ubiquitin–proteasome system and apoptosis, and preservation of the cellular mass and quality control of the sarcomer is becoming more and more limpid. The suppression of the proteasome activity leads to an increase in the apoptosis of the smooth muscle cells [15, 16]. It has been found out that, in cardiac failure, the ubiquitin–proteasome system is functionally deteriorated and net protein degradation is lessened [16].

MP treatment was applied in this patient according to the present technical facilities of the hematological center, where he was admitted and his personal attitude regarding the ways of further treatment, consequently excluding the possibility of treatment with high-dose therapy followed by the auto PBSCT.

Two months later, the patient was retreated with MP to prevent the progression of myeloma. It has now been 6 months in the follow up of the patient and his myeloma is in partial remission. The LVEF of the heart did not reach to its pretreatment values, but his BNP levels showed a significant decline.

3 Discussion

The results of echocardiography, which was performed on our patient before the therapy, were normal. On the other hand, adriamycin has been applied only once within the VAD regimen; so, it is not likely that the cardiotoxicity can be attributed to anthracycline. This shows that the serious cardiac failure that our patient has experienced was related with bortezomib therapy. The slow but progressive improvement of the LVEF and the progressive decline in BNP levels after the discontinuation of bortezomib support our opinion. Although the clinical findings of cardiac failure have been ameliorated during the 6-month follow-up period, improvement in the LVEF did not reach to a level that was anticipated. We believe that the slow progress in the improvement of LVEF should be monitored for a long time, to be able to decide whether cardiac failure is literally reversible or not.

The left ventricular hypertrophy (increase in the wall thickness), left ventricular diastolic dysfunction in a restrictive manner and the global hypokinesia in cardiac walls, found with echocardiography in our patient, indicates a functional deterioration in the smooth muscles, rather than decrease in the muscle mass itself. Apart from causing cardiac failure as a complication, bortezomib can also lead to various arrhythmias. This property has been attributed to the ischemia induced by the progression of the atherosclerotic plaques due to the proteasome inhibition [13]. It is conceivable to think that, in patients at older ages, the existing atherosclerotic process would accelerate with bortezomib. Bortezomib endangers functional deterioration in the cardiac muscle cells by either accelerating atherosclerosis, increase in the apoptosis of the smooth muscle cells or by some other unknown mechanisms. Although, the reason may not be known very well, it can be said that some patients are more liable to cardiac dysfunction due to proteasome inhibition in comparison with the others. Presence of a subclinical cardiac failure may be explanatory for some patients but as for our case, because the basal LVEF was normal, this can hardly be accepted to be true.

It should also be kept in mind that those complaints such as weakness and dyspnea that are attributed to bortezomib’s side effects can also be related with cardiac failure. As the patient was in a state of profound cardiac failure, we did not think it would be suitable to administer thalidomide, a drug with many potent side effects; hence, we felt obliged to restart the MP therapy once again, at least a method of therapy to which we have observed a partial response.

As a conclusion, with patients using bortezomib, especially the patients with cardiac diseases, basal LVEF values, ECG findings and BNP levels should be monitored closely. This gains more importance in patients with cardiac problems at older ages.
References