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Case Report

Bortezomib-induced multiple organ failure: report of two cases and review of literature

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Abstract: Incidence of bortezomib-induced severe organ damage is low, but once it happened, the prognosis is poor and mortality is extremely high. We present here two cases about bortezomib-induced multiple organ failure. This paper is distinct from the other reports, in that the case is seldom in clinic, especially the pulmonary complication, acute cardiac failure, and gastrointestinal tract bleeding occurred simultaneously on one patient after bortezomib treatment. Secondly, we detected the expression of P65 by RT-PCR, the outcome hinted us that bortezomib possibly reduced NF-κB activity, decreased the tolerance of myocardium to hypoxia, and induced heart failure. We suggested that suspected patients should be given early glucocorticoid therapy, oxygen therapy and positive symptomatic treatment. Strict monitoring, changing the administration route and timely symptomatic treatment, maybe reduce the complications, during the bortezomib treatment.

Keywords: Multiple myeloma, bortezomib, multiple organ failure

Introduction

Bortezomib (Velcade), as the first approved proteasome inhibitor into the clinical therapy, is currently used as the primary treatment for multiple myeloma (MM) and lymphoma worldwide. Compared with ordinary chemotherapy, less side effects of bortezomib have been observed, and controlled easily. Anyway, severe adverse event, such as acute lung injury, has been reported frequently. Here we sent a report about two patients had multiple organ failure after bortezomib treatment, such as pulmonary complication, acute cardiac failure, and gastrointestinal tract bleeding.

Case reports

Case 1

A 52-year-old woman was hospitalized with the chief complain having back pain for one year, and front chest lump for four months. Protein electrophoresis displayed M spike; immuno-fixation electrophoresis showed IgG and κ-type monoclonality (IgG: 101 g/L). A high sedimentation rate was established (117 mm/h). Blood analysis of the patient showed the following: WBC $4.32*10^9$/L, granulocyte $2.19*10^9$/L, Hb 40 g/L, platelet $128*10^9$/L, urea 14.68 mmol/L, creatinine 201 μmol/L, uric acid 802 μmol/L, LDH 126 U/L (N: 109-245 IU/L), total protein 41 g/L, albumin 22.5 g/L, globulin 136 g/L, calcium 2.25 mmol/L (N: 2.02-2.6 mmol/L), b2-microglobulin 6.10 mg/L (N: 0.8-3.2 mg/L). The result of the creatinine clearance test was 35.89 mL/min. Bone marrow aspiration was done and atypical plasma cells with immature appearance were observed at a rate of 70%. A Lung spiral CT examination was taken that demonstrated many lytic lesions at right rib. The whole spine MRI examination indicated the eleventh, the twelfth thoracic vertebra, the second, and the fourth lumbar vertebra flattened, and the fourth lumbar spondylolisthesis (one degree). The cardiac ultrasound examination showed the left atrium and left ventricle enlargement, mitral valve prolapse, mitral valve regurgitation and the three tricuspid regurgitation. The ejection fraction is 64%. As a result, the patient was diagnosed to have IgG-κ type myeloma (DS IIIB, ISS III).

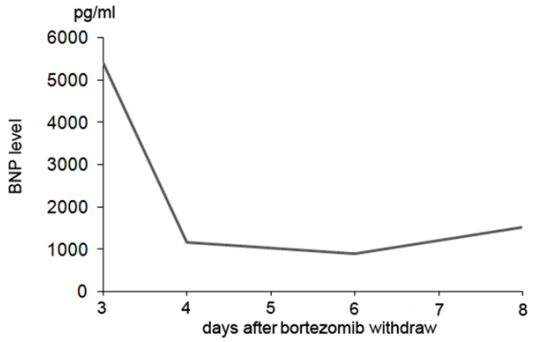

Figure 1. BNP (brain natriuretic peptide) levels after bortezomib withdrawal were shown. After bortezomib was withdrawal, BNP level increased up to 5383 pg/mL and then decreased to 1520 pg/ml, still far above normal level.

The patient was given the chemotherapy VTD (Velcade 2.1 mg d1, 4, 8, 11; Thalidomide 75 mg QN; Dex 10 mg d1-4, d8-11). On the second day after the second time Velcade administration, the patient got fevered; the body temperature was 37.8 degrees Celsius. The blood routine analysis showed WBC $1.98*10^9$/L, granulocyte $1.01*10^9$/L, Hb 63 g/L, platelet $82*10^9$/L. We gave patient broad-spectrum antibiotics treatment empirically and G-CSF subcutaneous injection. The body temperature returned to normal after 3 days' antibiotics treated. We continued to give Velcade treatment. At the 9 am in the third day after the fourth time Velcade administration, the patient suddenly felt palpitation and dyspnea. Physical examination showed the patient orthopnea and the lower right lung can be heard a little wet rales. Given nasal catheter oxygen 5 L/min, the blood pressure was 132/79 mmHg; HR was 86 BPM, and oxygen saturation of 95%. Blood gas analysis showed pO_2 66 mmHg, the oxygenation index was 160. BNP (brain natriuretic peptide) level was estimated to be 5383 pg/mL (control <100 pg/mL, at normal control 120 pg/mL). Compared with the first echocardiography before treatment, the second cardiac ultrasound examination showed generalized cardiac enlargement, mitral valve prolapse, aortic valve thickening and pericardial effusion. The ejection fraction fell to 58%. At the 3 pm of that day, the patient vomited about 250 ml of dark red blood. We diagnosed her respiratory failure, heart failure and upper gastrointestinal bleeding. After 5 days' treatment of oxygen therapy, strong heart, diuresis, anti infection, anti acid, and hemostasis, etc, the symptoms of palpitation, dyspnea and osteodynia significant improved, without any more haematemesis. The Blood test showed the following: Hb 84 g/L, WBC $5.67*10^9$/L, platelet $152*10^9$/L, urea 8.67 mmol/L, creatinine 46 μmol/L, uric acid 203 μmol/L, LDH 467 U/L, total protein 74 g/L, albumin 24.7 g/L, globulin 49.3 g/L, calcium 1.67 mmol/L, Detection of immunoglobulin told us that IgG fell to 61.5 g/L, b2-microglobulin fell to 2.84 mg/L. BNP fell to 1520 pg/ml (**Figure 1**). Bedside chest X-ray showed bilateral pulmonary infection with bilateral pleural effusion, aorta widened and increased heart shadow (**Figure 2**). That means the lung injury and heart failure are not completely recovery. Because of economic difficulties, this patient abandoned further treatment, discharged, and followed up in outpatient department.

Case 2

A 58-year-old man was hospitalized with the chief complain having chest pain for four months. Protein electrophoresis displayed M spike; Immuno-fixation electrophoresis showed IgG monoclonality (IgG: 94 g/L). Blood analysis of the patient showed the following: WBC $8.71*10^9$/L, Hb 70 g/L, platelet $63*10^9$/L, urea 40.73 mmol/L, creatinine 1667 μmol/L, uric acid 1004 μmol/L, globulin 107 g/L, b2-microglobulin 14.46 mg/L. Bone marrow aspiration was done and atypical plasma cells with immature appearance were observed at a rate of 53%. As a result, the patient was diagnosed to have IgG type myeloma (DS IIIB, ISS III).

The patient was given the chemotherapy VTD (Velcade 1.75 mg d1, 4, 8, 11; Thalidomide 75 mg QN; Dex 10 mg d1-4, d8-11) and dialysis treatment. On the second day after the second time Velcade administration, the patient felt palpitation and had orthopnoea. Moist rales can be heard in whole lung. BNP level was estimated to be 1620 pg/ml. ECG hinted atrial fibrillation. Acute left heart failure, pulmonary edema and arrhythmia were diagnosed for this patient. We gave first-aid measures including correct hypoxia, sedation, asthma, cardiac, diuretic. Dexamethasone 10 mg per day was administrated. After 9 days' treatment, those symptoms were significantly improved. During the treatment, we detected the NF-κB/P65 activity by real-time-PCR, and found that expression of P65 decreased when acute left heart failure occurred, but increased when

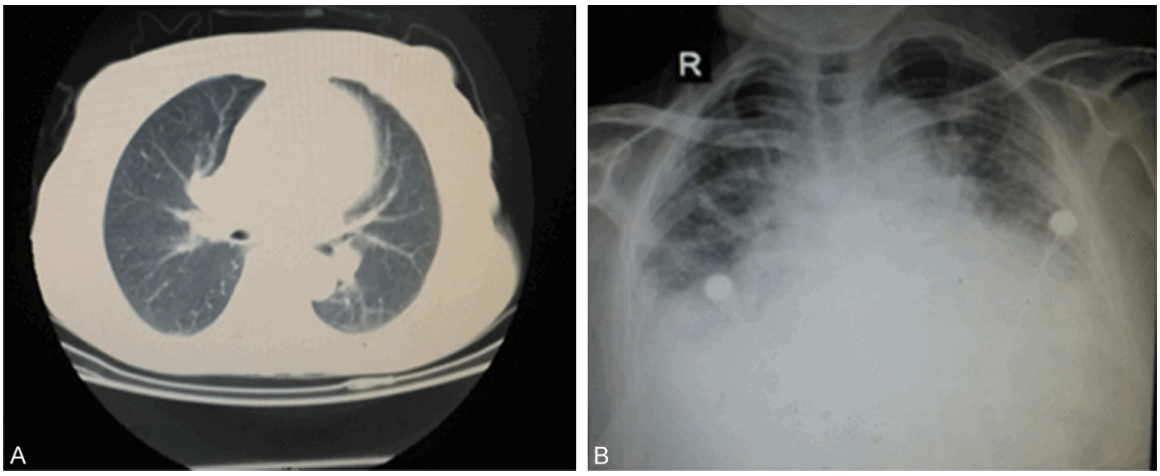

Figure 2. Lung imaging examination before and after bortezomib therapy. A. CT of the chest before bortezomib showed lytic lesions, without obvious pulmonary inflammation. B. X-ray of the chest on day 5 of the first course of bortezomib showed bilateral pulmonary infection with bilateral pleural effusion, aorta widened and increased heart shadow.

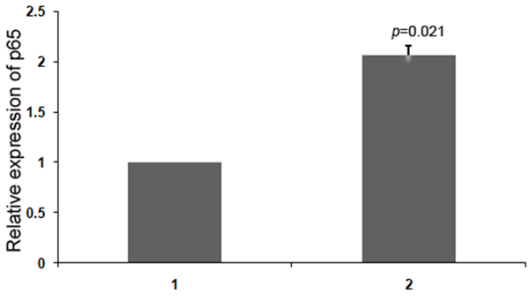

Figure 3. p65 expression of the second patient. 1. When acute left heart failure occurred. 2. When heart failure controlled. The expression of P65 decreased when acute left heart failure occurred, but increased when symptoms improved (the t test was used for parametric testing, $P<0.05$ was considered to be statistically significant). (Primer sequence: human-NF-κB/p65Rf 5'-CGACGTATTGCTGTGCCTTC-3', Ra 5'-TGAGATCTGCCCAGGTGGTAA-3').

symptoms improved (**Figure 3**). Some other blood biochemical indices showed urea 28.45 mmol/L, creatinine 568 μmol/L, uric acid 332 μmol/L and globulin 37.5 g/L. Detection of immunoglobulin told us that IgG fell to 38.4 g/L. BNP fell to 75.8 pg/ml. This patient discharged and followed up in outpatient department.

Discussions

Being a targeted drug for MM, therapeutic effect of bortezomib has been approved widely. Meanwhile, toxic and side-effects have been observed and reported gradually. Some sever adverse reaction might be fatal. These two cases we reported, especially three sever complications occurred simultaneously on one patient, are seldom in clinic.

In 2006, Miyakoshi [1] firstly reported lung injury after bortezomib treated. More and more doctors pay attention to this complication during the bortezomib therapy. From the literatures, acute lung injury (ALI), could take place after the first time bortezomib administration, or multiple cycle of bortezomib treatment [2]. ALI could take place in the course of cycle of bortezomib administration, or in the end of cycle of borezomib usage [3]. ALI happened more frequently in female patients, especially those have basic lung diseases, such as pulmonary infection, pulmonary embolism [4]. Main features of ALI include acute onset, progressive dyspnea, respiratory distress, and hypoxemia, pulmonary infiltrates, accompanied by pleural effusion. This first case we displayed has the above characteristics. According to the literature, hormone and high flow oxygen therapy might be help for ALI [1, 5], but some others say the hormone is invalid [6]. The mechanism of acute lung injury caused by bortezomib is not very clear. At present, most scholars think that the NF-κB system may play an important role [3, 7]. We know the mechanism of anti-tumor effect of bortezomib mainly relies on the inhibition of the signal transduction pathways of NF-κB. When bortezomib administration ended, the NF-κB system was activated again, the

release of numerous inflammatory factors, such as IL-6, TNF-α, play the critical roles in ALI. Some scholars think that bortezomib and (or) the metabolites accumulate in the body, not only affect the activity of NF-κB, but also affect other signaling pathways, lead to lung injury finally [6, 7]. Additionally, Shimazaki et al [5] thought the genetic predisposition to interstitial pneumonitis in the Japanese population maybe the main reason for bortezomib induced ALI.

Bortezomib related cardiotoxicity contains congestive heart failure, ischemic heart disease, arrhythmia, etc, which usually happen after the bortezomib treatment. Risk factors for bortezomib related heart failure could be: the cumulative dose, the number of cycles, pre-existing cardiac disease, exposure to other cardiotoxic drugs [8]. Clinical symptoms of heart failure were dyspnea, sputum and cough with pink frothy sputum. The imaging examination about heart failure showed increased cardiothoracic ratio, increased left ventricle and the right ventricular diameter, ventricular ejection fraction reduction, and increased progressively BNP. In our report, the cardiac ultrasound examination of the second patient is ok before the treatment of bortezomib, and the patient doesn't have any symptoms of heart failure. However, after accepted bortezomib treatment, his symptoms of heart failure suddenly happened, including dyspnea, arrhythmia, and BNP increase. Those symptoms improved after oxygen therapy, hormone therapy, cardiac stimulant application and diuretic therapy.

To this day, mechanisms of bortezomib induced cardiac toxicity remain unclear. Some think it is concerned with the inhibition of the ubiquitin proteasome system (UPS) by bortezomib. UPS is involved in protein degradation in 80%-90% eukaryotic cells, and is very important for maintaining shape, size and function of heart. UPS functions in patients with bortezomib related heart failure decreased and protein degradation decreased [9, 10]. Takamatsu [11] found that bortezomib induced cardiac muscle cell to undergo apoptosis. Bortezomib can lead to vascular endothelial cells apoptosis, intracellular nitric oxide synthase/nitric oxide reduction, coronary artery spasm, and myocardial ischemia. Nowis et al [12] indicated that bortezomib treatment led to left ventricular contractile dysfunction, dramatic ultrastructural abnormalities of cardiomyocytes, especially within mitochondria, which was accompanied by decreased ATP synthesis and decreased cardiomyocyte contractility.

Some others believe that bortezomib treatment related cardiac toxicity is associated with its role of reduced proteasome activity. Reduced proteasome activity can increase the apoptosis of smooth muscle cells; reduce the stability of atherosclerotic plaques [13]. Carrier reported that proteasome inhibition activated the calcineurin factor of activated T cells (NFAT) signaling in cardiac myocytes and in vivo promoted maladaptive remodeling in stressed mouse hearts [8, 14]. In addition, reduction of NF-κB activity can decrease the tolerance of myocardium to hypoxia [15]. These may be due to bortezomib treatment related cardiac toxicity to born. We detected the NF-κB activity of the second patient, and analyzed that bortezomib administration restrained the P65 expression, which may increase the apoptosis of myocardial cells and decrease the tolerance of myocardium to hypoxia (**Figure 3**). Therefore, in the elderly, especially elderly patients with underlying heart disease, doctors should fully assess the cardiac function of patients before bortezomib application, including the left ventricular ejection fraction, ECG or 24 h dynamic electrocardiogram. In the bortezomib application process, doctors should closely observe the cardiac toxicity, find related symptoms, signs and reexamine related index in time. Once correlation of bortezomib determined, reduction or withdrawal of bortezomib and the corresponding treatment measures should be in time.

Bortezomib associated gastrointestinal reactions are reported frequently. Many of them are some controllable adverse reactions, such as anorexia, diarrhea, constipation etc. In early clinical trials, the bortezomib treatment related gastrointestinal adverse reaction rate was higher, main clinical symptoms include diarrhea (57%), constipation (42%), vomiting (35%), anorexia (23%) and abdominal pain (16%) [16]. These signs belong to mild and moderate adverse reactions, which are easy to control. Only 2% of the patients with gastrointestinal adverse reaction need reduction or withdrawal of Velcade [17]. However, there are also reports of bortezomib caused severe paralytic ileus and intestinal vasculitis appearing black stool or hematochezia. The first patient we reported,

presented hematemesis after received bortezomib treatment, which is considered direct intestinal side effects of velcade. At the same time, velcade administration induced her thrombocytopenia (PLT25*I0^9/L), may also cause gastrointestinal bleeding.

In conclusion, bortezomib must be classified as chemotherapy with potential direct pulmonary adverse drugs reactions (ADR), cardiac ADR and gastrointestinal ADR. Thus rigorous evaluation is needed before the initiation of this drug. Echocardiography, pulmonary CT examination etc. are recommended before, during and after bortezomib chemotherapy. In the event of these complications, active treatment is the key. Risk Minimization Action Plan (RMAP), which was collaboratively developed by the pharmaceutical industry and public health authority, seemed clinically effective minimizing the bortizomib induced severe complications in Japanese [3]. It is reported that glucocorticoids has a protective effect, therefore it is recommended that use of dexamethasone with bortezomib in MM patients, which might decrease the risk of severe complications [5]. Subcutaneous administration of bortezomib can decrease thrombocytopenia, neutropenia, anemia and peripheral neuropathy [18], so we suggest subcutaneous administration of bortezomib may be a good option for those patients with high risk factors.

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Disclosure of conflict of interest

None.

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