Abstract

Cardiac side effects due to anti-cancer drugs are various and can range from cardiac arrhythmias to severe contractile dysfunction, and potentially fatal heart failure. Anthracyclines cardio toxicity have been well reported and left ventricular ejection fraction evaluation by 2-D echocardiogram is commonly performed before their use.

Bortezomib (Velcade), a specific and reversible proteasome inhibitor, is approved for treatment of multiple myeloma (MM). The incidence of cardiac failure associated with Bortezomib therapy in clinical trials remains incidental, so cardiac evaluation is not normally requested before its use.

We report a case of acute, severe, reversible, cardiac failure during Bortezomib therapy in a 47 year old male with relapsed Multiple Myeloma without neither a previous history of cardiac disease nor risk factors. Based on literature review we hypothesize that bortezomib, through alteration of cardiomyocyte's mitochondrial energetic chain, may cause reversible cardiac failure. We recommend routinely monitoring cardiac parameters in patients undergoing this treatment.

INTRODUCTION

Bortezomib is an antitumor agent that inhibits proteasome activity. Inhibition results in the accumulation polyubiquitinated proteins and in the increase of apoptosis [1,2]. Bortezomib has demonstrated a remarkable activity in multiple myeloma (MM), systemic light chain amyloidosis, Waldenström's macroglobulinemia and non-Hodgkin lymphoma [3,4].

The most common adverse events are fatigue, gastrointestinal effects, peripheral neuropathy and thrombocytopenia.

The overall incidence of cardiac failure associated with bortezomib therapy is very low and most of the cases have been confounded by the previous use of other chemotherapeutic agents including cardiotoxic anthracyclines. In the frontline setting the incidence ranges from 0% [5] to 5% [6] and is worsened by the combination with thalidomide. Orciuolo et al. report 8/69 cases (11.6%) of cardiotoxicity ranging from heart failure to arrhythmias in previously treated elderly patients [7]. Bortezomib doesn’t induce cardiomyocyte death, but rather it causes reversible contractile dysfunction through alteration of myocardial energetic chain. No necrotic or apoptotic cells are found in histopathological heart examination and no rise in troponin I levels or increase in heart fibrosis is described [8].

CASE PRESENTATION

A man of 47 years old was diagnosed of a symptomatic multiple myeloma in November 2005 at our Department. The main symptoms at onset were anemia and diffuse lytic lesions. A high-dose therapy program was planned with pulse-VAD scheme as induction. An echocardiographic evaluation of cardiac function was performed before transplantation showing a normal ejection fraction (EF 60%) without any other cardiac abnormality. The patients underwent to autologous transplantation in May 2006 obtaining a complete response.
On March 2010, the patient relapsed and since the good response to previous therapy a second transplant was planned with a re-induction with 4 cycles of Bortezomib and Dexamethasone at the following doses: Bortezomib 1.3 mg/mq i.v. on days 1,4,8 and 11, plus Dexamethasone 20 mg i.v. on days 1-2, 4-5, 8-9, 11-12 of each 21 day cycle. Bortezomib treatment was stopped in advance after the completion of the third cycle due to emergent peripheral neuropathy. Response evaluation showed a CR. A successful second attempt of stem cell mobilization was made on October 2010 primed with G-CSF plus plerixafor. The echocardiographic evaluation made in view of high-dose therapy showed an unexpected severe cardiac failure with diffuse hypokinesis and a consequent significant reduction of the ejection fraction (EF 35%) while troponin I and BNP were normal. The patient was asymptomatic and the EKG showed no signs of cardiac ischemia. Considering the persistence of good disease control, transplantation was postponed and patient entered a follow-up phase, including cardiac evaluation made by periodic echocardiography, EKG, serum samples collection for troponin I, CKMB, B-type natriuretic peptide (BNP) plus N-terminal pro-B-type natriuretic peptide (NT-proBNP). We found a progressive spontaneous improving, reaching in may 2011 a complete recovery of the cardiac function (EF 52%).

On June 2011, myeloma progressed and third line therapy was started. Since the good response to bortezomib and the complete recovery of cardiac function, we decided to re-treat the patient with Bortezomib and Dexamethasone for three cycles and in case of response to perform a second transplant. Treatment was well tolerated and BNP, NT-proBNP and troponin I remained within normal limits. At the end of treatment, on august 2011, an echocardiography was performed and a reduction of the EF was observed (45%) with diffuse hypokinesis. The patient complained of increasing fatigue and dyspnea on exertion. The clinical examination and the cardiac enzymes were normal. For the cardiac abnormality and the poor response, therapy with Bortezomib and Dexamethasone was definitively stopped and the patient was treated with Lenalidomide and Dexamethasone. The cardiac function at the next control improved and the hypokinisis disappeared. Patient had a good response to Lenalidomide obtaining a very good partial response after three cycles so we decided to perform auto-transplant. The procedure was performed on august 2012 and was well tolerated by patients who did not show at any successive control any deterioration of cardiac function.

DISCUSSION

We attribute the significant reduction of the EF in this case to the drug therapy with bortezomib. The absence of fever, chest pain, normal EKG and cardiac enzymes, and the clinical course made the diagnosis of viral myocarditis unlikely. The lack of typical myocardial features like granular sparking infiltrates on the 2D echocardiogram excludes amyloid deposition. In conclusion, Bortezomib can cause cardiac dysfunction that in general seems to be reversible and of low clinical impact. However, since in literature are reported also more severe cases of cardiac impairment [9,10] it is advisable to closely monitor cardiac function mainly through echocardiography since the marginal role of serum parameters.

REFERENCES


Cite this article