

Case Report

Dasatinib Induced Pulmonary Arterial Hypertension and Pleural Effusion in Post allogenic Stem Cell Transplant CML Patient

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Abstract

Though Dasatinib is a second-generation tyrosine kinase inhibitor used for the first line therapy of CML, it is associated with the risk of pulmonary hypertension and pleural effusion. Pleural effusion due to Dasatinib is often reversible unlike pulmonary hypertension. Asymptomatic pleural effusion warrants only conservative management and regular follow up. For symptomatic effusions, dose reduction or dose interruption is recommended. Dasatinib induced pulmonary hypertension warrants drug discontinuation, treatment with an alternative TKI and upfront combination therapy with vasodilators if symptoms persist. We present a patient of chronic myeloid leukemia (blast crisis) post allogenic stem cell transplant in molecular response that developed bilateral pleural effusion and pulmonary hypertension following treatment with Dasatinib.

Keywords: Dasatinib; Pulmonary arterial hypertension; Pleural effusion; Tyrosine kinase inhibitor; Imatinib

Introduction

With the emergence of Tyrosine Kinase Inhibitors (TKIs), Chronic Myeloid Leukemia (CML) has become a workable disease with a remarkable improvement in the disease prognosis thereby revolutionizing its treatment. Dasatinib is a second-generation tyrosine kinase inhibitor used for the front-line therapy of CML. It provides a favorable overall survival and progression-free survival. Well! Everything comes with a price. Drugs are often associated with side effects. Dasatinib is no different from that. Adverse effects of Dasatinib include bone marrow suppression, pleural effusion, pericardial effusion, pulmonary arterial hypertension, and QT prolongation. We present a patient of chronic myeloid leukemia (blast crisis) post allogenic stem cell transplant in molecular response that developed bilateral pleural effusion and pulmonary hypertension following treatment with Dasatinib. Informed consent was obtained from the patient and attenders to share patient details and radiograph images without revealing patient identifiers.

Case Presentation

A 26-year young female presented to our department in November 2020 with complaints of exertional breathlessness and dry cough for

10 days. She was a case of chronic myeloid leukemia (myeloid blast crisis) diagnosed in 2017 for which she was given induction along with Imatinib, a first generation TKI. After achieving major molecular response patient underwent match sibling donor allogenic stem cell transplantation at our centre in 2019 and post transplantation was restarted on Imatinib. However, she was switched to Dasatinib when she lost molecular response. She had good compliance and tolerance to Dasatinib and attained major molecular response. After about two years of Dasatinib, she presented with the breathlessness and dry cough.

Her pulse rate was 90 beats per minute, 91% room air saturation, a blood pressure of 110/70 mmHg, a respiratory rate of 26/min and WHO functional class III. Physical examination showed elevated jugular vein. Chest auscultation revealed decreased vesicular breath sounds in bilateral infra-axillary and infra-scapular areas; and a loud P2. Chest radiograph showed bilateral costophrenic angle blunting (Figure 1). The pleural effusion was confirmed by ultrasonography of the thorax. It showed bilateral minimal to mild pleural effusion. In view of distended jugular veins, a transthoracic echocardiography was done to look for features of Pulmonary Hypertension (PH). The right ventricle was enlarged, with flattening of the interventricular septum. Severe tricuspid regurgitation and a right ventricular systolic pressure of 70 mmHg were noted. Left ventricular function was normal. These features suggested pulmonary hypertension. Dasatinib was withheld. A computed tomography pulmonary angiogram ruled out any underlying pulmonary thromboembolism. The main pulmonary artery measured 3.25 cm in diameter. The underlying lung parenchyma was normal (Figure 2). Laboratory specific tests for HIV, rheumatoid factor, and Anti-Nuclear Antibodies (ANA) were negative. Her spirometry was also reported normal. ESR was normal. Hence other specific diseases known to cause Pulmonary Arterial Hypertension (PAH) such as human immunodeficiency virus infection, connective tissue disorder, and obstructive airway disease were ruled out. Routine blood investigations namely the

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complete blood count, renal and liver function parameters also tested normal. Pleural fluid analysis following ultrasound guided diagnostic thoracentesis was lymphocyte rich and exudative (serum Total Protein (TP): 5.9, pleural fluid (PF) TP: 3.2 g/dL; serum LDH: 310 U/L, PF LDH: 194U/L) with low levels of ADA (10U/L), negative for gene Xpert and cytology not showing any malignant cells. Her arterial blood gas was suggestive of type 1 respiratory failure (pH-7.40, pCO₂-35 mmHg, pO₂-58 mmHg, HCO₃-22 mEq/L, anion gap-12 mEq/L, lactate-0.8 mmol/L).

Once the diagnosis of PAH was made, Right Heart Catheterization (RHC) was done. It showed markedly elevated mean pulmonary artery pressure (55 mmHg), elevated pulmonary artery diastolic pressure (35 mm Hg), pulmonary artery systolic pressure (83 mm Hg), normal pulmonary capillary wedge pressure (15 mmHg) and a pulmonary vascular resistance (12 wood units). Her 6-Minute Walk Test (6MWT) distance was 175 m.

Owing to her poor functional status following Dasatinib use due to pulmonary involvement, Dasatinib was stopped, and Nilotinib started after testing for IRMA which was negative. Though she was in functional class III, pulmonary vasodilators were not started as the cardiac index was preserved. Follow up TTE at the end of 3 months showed right ventricular systolic pressure of 50 mmHg. She has improved symptomatically and has achieved normal hemodynamic

status and a WHO functional class I. Her repeat 6MWT distance was a good 480 m.

Discussion

Pleural effusion is reported more often with Dasatinib compared to other TKIs. The 5-year analysis reports from the phase III Dasatinib versus Imatinib Study in treatment-naïve CML patients assessing the efficacy and safety outcomes of patients with CML chronic phase treated with Dasatinib 100 mg once daily or Imatinib 400 mg once daily showed that pleural effusion happened more with Dasatinib when compared to other TKIs. 28% of the patients who received Dasatinib developed drug-related effusion when compared to 1% of the patients on Imatinib [1].

Old age, history of cardiac and pulmonary abnormalities, autoimmune disease, skin rash, hypertension, hypercholesterolemia, and twice-daily Dasatinib are known predisposing factors [2,3]. The phase 3 dose optimisation studies for Dasatinib found that the occurrence of side effects was lower in the 100 mg OD arm when compared to the 70 mg BD arm. Also, the number of participants that stopped Dasatinib in the 100 mg arm was lower. Higher mean concentration when the drug is taken twice a day could have been the reason for the higher incidence of pleural effusion in the 70 mg BD arm. No cross intolerance was noted between Imatinib and Dasatinib. It was also noted that changing the dose from 70 mg BD to 100 mg OD decreases the incidence of any grade pleural effusion by more than half (16% vs.7%) [4]. Once-daily dose is sufficient to attain an appropriate cytological effect. The median time to the emergence of an effusion was 315 days for 100 mg OD, compared to 289,148 and 136 days with 50 mg BD, 140 mg OD, and 70 mg BD respectively [5].

Fluid retention due to Dasatinib occurs due to non-specific inhibition of platelet-derived growth factor receptor beta or other kinases [2,3]. Certain reports suggest that pleural effusion may be immune-related owing to the lymphocyte predominance noted [6]. Dasatinib may also impede the function of normal T cells and bind with specific regulators of the immune mechanism [7]. They usually present with complaints of shortness of breath, dry cough, and chest pain or chest tightness decreased exercise tolerance and fatigue. Detailed history taking and a thorough physical examination should be done to rule out other causes of pleural effusion. Chest radiography and ultrasonography should be done to differentiate pleural effusion from pleural thickening, to categorize the volume of pleural effusion, and to correlate with symptoms.

Management depends on the volume of the effusion and the magnitude of symptoms. In case of asymptomatic effusion, conservative management and regular follow up is recommended. The patient should be followed up every 3 months for 1 year and then every 6 months for the next one year. In case of worsening of symptoms, dose reduction is advised. Symptomatic effusions warrant dose reduction or dose interruption based on the gravity of symptoms [8].

In case of mild effusion, a dose reduction of 20% is often adequate. Chest radiograph is to be repeated after a month, then 3 and 6 months later [8]. For patients at higher risk, large or recurrent effusions, a dose reduction of 50% may be necessary. For medium to large pleural effusions, a temporary treatment interruption followed by rechallenge at lower doses and gradual increments will help maintain continuity of treatment as well as provide time for resolution of pleural effusion [9]. When rapid control of the disease is the need, Dasatinib can be

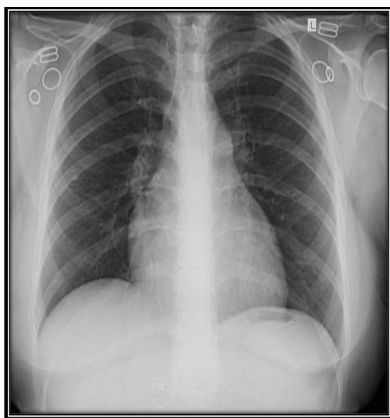


Figure 1: Posteroanterior view of chest radiograph demonstrating bilateral costophrenic angle blunting.

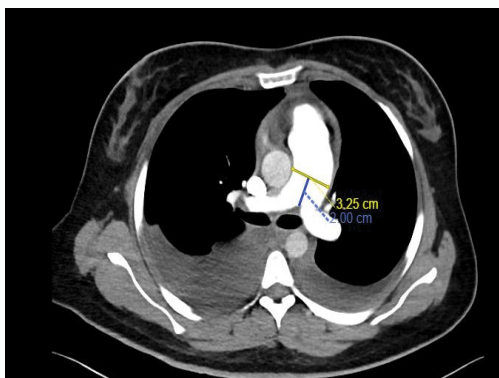


Figure 2: Computed tomography pulmonary angiogram showing an enlarged pulmonary artery measuring 3.25 cm at the level of pulmonary artery bifurcation on an axial slice vertical to its long axis. Bilateral pleural effusion is also seen.

continued at lower doses as the primary goal is to maintain clinical response wherever possible. Diagnostic aspiration of pleural effusion to rule out infection should be done when effusion persists. The effusion is usually exudative and sometimes transudative when there is an associated cardiac failure, nephrotic syndrome, or cirrhosis. It is usually lymphocyte-predominant. Hemorrhagic and chylous effusions can also occur [10]. When the aspirate is milky, pleural fluid should be investigated for triglycerides and total cholesterol.

In case of large effusions or increasing volume of effusion, consider therapeutic aspiration to relieve symptoms [9]. A repeat chest radiograph should be taken after performing thoracentesis. It is further repeated every 2 to 4 weeks until the resolution of the effusion. In case of treatment failure, persisting effusion or recurrent effusion requiring more than two therapeutic aspirations, permanent discontinuation of Dasatinib and switch to a different TKI is recommended. If Dasatinib needs to be continued whatsoever, an indwelling pleural catheter can be placed. Pleurodesis is rarely done for drug-induced pleural effusion.

When associated with congestive cardiac failure or volume overload features, diuretics can be tried. However, the use of diuretics is doubtful when the cause is inflammatory. There is no clear concordance or recommendation regarding the use of a short course of steroids. When symptoms are disproportionate compared to the extent of the effusion, an echocardiography should be performed to look for Pulmonary Hypertension (PH). Pleural effusion due to Dasatinib is often reversible, unlike pulmonary hypertension.

Pulmonary Arterial Hypertension (PAH), a subgroup of pulmonary hypertension is marked by remodeling of the pulmonary vasculature, causing an increase in the pulmonary vascular resistance and pulmonary arterial pressure. The prevalence of symptomatic PAH due to Dasatinib is reported to be low as 0.45% to 3% [11,12]. In a French group registry, symptomatic PAH was observed in 13 out of 2900 patients [13]. However a higher incidence of asymptomatic PAH was noted as 5 out of 38 patients evaluated by echocardiography showed increased RV pressure [14]. So the current ESC guidelines advocate surveillance by Transthoracic Echocardiography (TTE) every 3 months during treatment with tyrosine kinase inhibitor for early detection of PAH. A baseline TTE should be done before the commencement of Dasatinib.

Guignabert et al. [15] postulated that Src tyrosine kinase inhibition by Dasatinib to be the cause of PAH. Src tyrosine kinases occur in the vascular tissue. Its activation results in smooth muscle proliferation and vasoconstriction. Chronic Dasatinib therapy was reported to cause endothelial cell apoptosis in a dose-dependent manner and pulmonary vascular endothelial dysfunction following an increased production of reactive oxygen species. It attenuates hypoxic pulmonary vasoconstriction responses and increases the susceptibility to PAH independent of the Src family kinase-induced mechanism.

Unlike drug-induced pleural effusion, pulmonary arterial hypertension is not always reversible. In a report of 41 patients with RHC confirmed Dasatinib induced PAH, though the withdrawal of the inciting agent resulted in clinical improvement in 94% of the patients, only 58% of the patients attained a state of complete resolution [12].

No definite treatment strategy is defined so far. To start with, other causes of PH should be ruled out before attributing Dasatinib to be the causative agent. A study by Weatherald et al. [16] to look

into be the clinical outcomes of Dasatinib induced PAH conveyed that PAH persisted in one-third of the patients even after discontinuation of the drug. Based on their observations, a treatment algorithm was proposed. When PH due to Dasatinib is suspected, a TTE should be obtained. If echocardiogram shows increased tricuspid regurgitation velocity or other indirect signs of PH, RHC is done to confirm PH.

After the confirmation of Dasatinib induced PAH, the drug is discontinued. No PAH specific therapy is added in case of NYHA Functional Class (FC) I/II or NYHA FC III with preserved cardiac index ($\geq 3\text{L min}^{-1}\text{m}^2$). Follow up after 3 months is recommended. If NYHA FC I/II and mean pulmonary artery pressure $<25\text{ mmHg}$, routine surveillance using TTE every 6 to 12 months is advised [16].

In case of NYHA FC IV or NYHA FC III with cardiac index ($<3\text{L min}^{-1}\text{m}^2$), upfront combination therapy with pulmonary vasodilators is recommended [17]. On follow up after 3 months, if the functional status improves to FC I/II, vasodilators can be de-escalated if normal hemodynamic status prevails at the end of a year. If there is no improvement in functional status at the end of 3 months, continue or hike up vasodilator therapy. Optimal timing and combination of vasodilator therapy are still under debate. An alternative TKI should be started to maintain the cytological effect [18].

Conclusion

Early identification and prompt management of pleural effusion and pulmonary arterial hypertension is essential in attaining favourable clinical outcomes and safety with dasatinib. Detailed history taking for finding out the temporal association of pleural effusion or PAH with TKI, assessment of predisposing risk factors, and diagnostic aspiration of the effusion are required to confirm the diagnosis. No definite guidelines have been proposed for the diagnosis and management of pleural effusion or PAH secondary to TKIs. Treatment options include dose interruption, dose reduction, or permanent discontinuation. Drug-induced PAH warrants discontinuation of the drug, and upfront combination therapy with vasodilators if symptoms persist. Also, the assessment of response to the chosen line of action is necessary before confirming on a course of action.

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