



Bosutinib induced pleural effusions: Case report and review of tyrosine kinase inhibitors induced pulmonary toxicity



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ARTICLE INFO

Article history:

Received 17 February 2017

Received in revised form

2 May 2017

Accepted 5 May 2017

Keywords:

Bosutinib

Tyrosine kinase inhibitors

Pleural effusions

Pulmonary arterial hypertension

Interstitial lung disease

ABSTRACT

Tyrosine kinase inhibitors are known to cause pulmonary complications. We report a case of bosutinib related bilateral pleural effusions in a patient with chronic myeloid leukemia. Characteristics of the pleural fluid are presented. We also discuss other tyrosine kinase inhibitors induced pulmonary toxicities, including pulmonary hypertension and interstitial lung disease.

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1. Introduction

Tyrosine kinases play a critical role in the modulation of growth factor signaling and tumor genesis [1]. Tyrosine kinase inhibitors compete with the ATP binding site of several tyrosine kinases [2] causing effective antitumor activity.

Tyrosine kinase inhibitors (TKIs) that target the BCR-ABL1 fusion oncoprotein is the standard treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML) [3].

Reported pulmonary complications of BCR-ABL1 TKIs include pleural effusions, pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD).

Pleural effusions have been classically described for dasatinib. However, other drugs in the BCR-ABL1 TKIs group (dasatinib, imatinib, nilotinib and bosutinib) can cause pleural effusions [4]. Pleural fluid characteristics have only been described for dasatinib [5,6].

We present a case of a patient with CML treated with bosutinib who developed bilateral pleural effusions.

We review the literature of TKIs induced pulmonary toxicities.

2. Case report

A 71-year-old male with a history of CML presented for evaluation of pleural effusions as outpatient.

He had been diagnosed with CML seventeen months prior to presentation. He had been treated with imatinib and dasatinib without response. Bosutinib was then started.

Four months after starting bosutinib he developed shortness of breath with exertion and dry cough. Physical exam revealed a pulse of 62, a blood pressure of 108/62, and a respiratory rate of 18. His SaO₂ was 96% on room air. His breathing pattern was not labored. Cardiac exam was normal. His pulmonary exam was significant for dullness to percussion and reduced breath sounds in the lung bases.

Computed tomography (CT) of the chest after four months of starting bosutinib showed bilateral, non-loculated pleural effusions (Fig. 1).

Thoracentesis showed hazy pleural fluid with 1410/cumm red blood cells, 2820/cumm white blood cells, 2% polymorphs, 5% monocytes and 93% lymphocytes, lactate dehydrogenase was 131U/L, total protein was 4.1g/dl, triglycerides were 14mg/dl and albumin was 2.9g/dl. Serum lactate dehydrogenase was 212U/L and total protein was 7.4g/dl. Findings were consistent with a lymphocytic predominant exudate [7]. Cytology showed reactive mesothelial cells, macrophages and mature appearing lymphocytes. Immunohistochemistry revealed large cells positive for either Calretinin or CD68 and negative for CD34. Flow cytometry demonstrated

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Abbreviations

CML	chronic myeloid leukemia
CT	computed tomography
EGFR	epidermal growth factor receptor
ILD	interstitial lung disease
PAH	pulmonary arterial hypertension
TKIs	tyrosine kinase inhibitors

leukocytes consisting primarily of small lymphocytes with many macrophages and few mesothelial cells. It revealed no evidence of clonal B-cells, abnormal T-cells or blasts. Cultures were negative for bacteria, fungus and AFB.

Echocardiogram was normal.

Bosutinib was discontinued. Prednisone and diuretics were started. Respiratory symptoms resolved within four weeks. After three months the left pleural effusion resolved and right pleural effusion had improved (Fig. 2).

The patient had persistent positivity of BCR-ABL by PCR and subsequently underwent allogeneic hematopoietic cell transplant. The patient achieved donor engraftment and is currently in complete remission more than 6 months after transplant.

3. Discussion

BCR-ABL1 TKIs are used for the treatment of CML and they usually result in lifelong therapy. Even though they are relatively well tolerated they have significant side effect profiles, including hematologic, gastrointestinal, dermatologic, musculoskeletal,

cardiovascular, metabolic and pulmonary toxicities [8–12].

The extension of these side effects, in addition to drug interactions, inability to conceive and high economic burden has led to the investigation of the outcomes of discontinuation of TKIs after one to three years of treatment [13]. Several studies have shown that the CML treatment free-remission rate was between 41 and 67% at 12 months follow up after TKIs discontinuation [14]. Even though these are encouraging results, the current guidelines recommend continuing TKIs long term until further definitive investigation of effects of stopping TKIs are available [15,16].

Pulmonary toxicity has been classically described for dasatinib but other TKIs could cause pulmonary complications comprising pleural effusions, PAH and ILD [8].

3.1. Pleural effusions

The incidence of pleural effusions during the use of BCR-ABL1 TKIs has been reported as 29% for dasatinib and 1–10% for bosutinib [4].

Pleural effusions are classically associated with the BCR-ABL1 TKIs chemical class as they have not been described in other TKIs.

Risk factors for development of pleural effusions with the use of dasatinib consist of twice daily dosing, older age, lymphocytosis, prior cardiac history and autoimmune diseases [5]. Our case had only one of these risk factors: older age.

Pleural fluid characteristics have been described for dasatinib [5] usually as a lymphocytic predominant exudate. The similarities between dasatinib pleural fluid findings and the present case suggest that all BCR-ABL1 TKIs related pleural effusions might have the same fluid characteristics: lymphocytic predominant exudates. Transudates and chylous effusions have also been described in the literature [5].

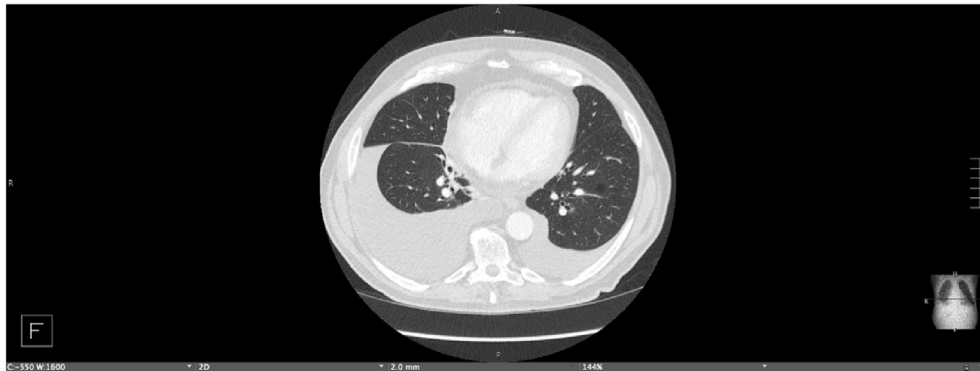


Fig. 1. Bilateral non loculated pleural effusions without parenchymal abnormalities.

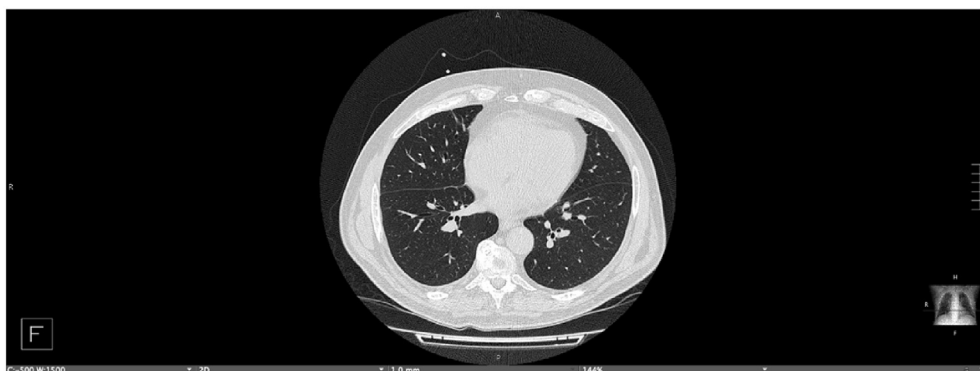


Fig. 2. Resolution of left pleural effusion with significant improvement on the right pleural effusion.

The recommended management of BCR-ABL1 TKIs associated pleural effusion depends on the radiographic findings and clinical compromise [8,17]. For asymptomatic and small effusions no treatment is necessary. For larger, symptomatic effusions diuresis and short course of steroids may be warranted in addition to discontinuation of the drug. Thoracentesis is usually indicated for exclusion of malignancy and infection.

3.2. Pulmonary hypertension

Dasatinib has been linked to cases of PAH. This adverse effect was present in 5% of patients treated with dasatinib in the DASISION study [18].

N. Shah et al. [19] examined all clinical cases of dasatinib associated PAH, from the Bristol-Myers Squibb pharmacovigilance database. No fatalities have been related to PAH. The clinical presentation was usually dyspnea. Most patients improved after discontinuation of dasatinib.

It is recommended that patients started on dasatinib should be evaluated for cardiopulmonary symptoms. Echocardiogram is a valuable screening tool to detect PAH and right heart catheterization should be used to confirm PAH. Discontinuation of the drug is the first line therapy for TKIs induced PAH [19].

3.3. ILD

Patients treated with BCR-ABL1 TKIs did not develop ILD during the pre-approval clinical trials. However, drug induced ILD case reports and case series were published in the post marketing period for imatinib, dasatinib, nilotinib and other non BCR-ABL1 TKIs [20].

TKIs induced ILD was early recognized in epidermal growth factor receptor (EGFR) TKIs such as erlotinib and gefitinib for the treatment of lung cancer. A recent meta-analysis by Takeda et al. [21] showed that the frequency of EGFR TKIs induced ILD was 2.5% in Asian and 0.9% in non-Asian patients.

Even though drug induced ILD is more frequent in EGFR TKIs, this side effect is not exclusive of this TKIs chemical class. ILD has been induced not only by EGFR and BCR-ABL1 TKIs, but also TKIs that target anaplastic lymphoma kinase, platelet-derived growth factor receptor, vascular endothelial growth factor receptor, hepatocyte growth factor receptor and fibroblast growth factor receptor among other TKIs [20].

Clinical manifestations of TKIs induced ILD include cough, dyspnea, hypoxemia and fever.

Min et al. [22] described six CT radiologic patterns of TKIs-induced ILD in patients with non-small cell lung cancer: diffuse alveolar damage, bronchiolitis obliterans, cryptogenic organizing pneumonia, hypersensitivity pneumonitis, interstitial pneumonia (non-specific interstitial pneumonia or usual interstitial pneumonia) and progressive disease of underlying ILD.

With regards to BCR-ABL1 TKIs-induced ILD, a review by M. Peerzada et al. [17] described several cases of non-specific pneumonitis, hypersensitivity pneumonitis and eosinophilic pneumonia with the use of Imatinib. Most of the patients described presented with dyspnea, cough, hypoxia and bilateral ground glass opacities.

TKIs-induced ILD is a diagnosis of exclusion. Detailed history and physical examination are necessary as well as CT chest, laboratory examination and sometimes bronchoscopic or surgical lung biopsies for accurate diagnosis.

Treatment of TKIs-induced ILD is supportive. Discontinuation of the drug is recommended. A course of steroids is usually prescribed [22].

4. Conclusions

We report a case of bosutinib associated pleural effusions consistent with lymphocytic exudate, which resolved after discontinuation of the drug. We propose that pleural effusions secondary to TKIs that target BCR-ABL may have similar pleural fluid characteristics: lymphocytic predominant exudates. TKIs induced pleural effusions have mainly been reported in BCR-ABL TKIs and not in other TKIs chemical classes.

Other TKIs pulmonary toxicities include PAH and ILD that also improve with discontinuation of the drug.

PAH has been mainly reported for BCR-ABL1 TKI dasatinib.

TKIs-induced ILD was recognized in EGFR TKIs erlotinib and gefitinib in early clinical trials. This adverse effect was then reported in other TKIs chemical classes, although not as frequently.

Conflict of interest

Natalia I. Moguillansky, MD: No conflict of interest.

Hafiz Abdul Moiz, Fakhri, MD: No conflict of interest.

John R. Wingard, MD: No conflict of interest.

Funding

None.

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