Bosutinib-Induced Interstitial Lung Disease and Pleural Effusion: A Case Report and Literature Review

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Abstract

Bosutinib is a tyrosine kinase inhibitor (TKI) approved for the management of chronic myeloid leukemia (CML). TKIs are associated with pulmonary complications but are rarely described with bosutinib. Here, we report the first description of bosutinib-induced interstitial lung disease and pleural effusion, which resolved after the discontinuation of bosutinib.

KEY CLINICAL MESSAGE

Bosutinib is a tyrosine kinase inhibitor approved for the management of chronic myeloid leukemia (CML). Interstitial lung disease and pleural effusion are pulmonary side effects of TKIs rarely associated with bosutinib treatment.

INTRODUCTION

Tyrosine kinase inhibitors targeting BCR/ABL have revolutionized the treatment of CML, changing its prognosis from an overall survival of 5 years to near normal life-expectancy. [3,6] However, TKIs are associated with potentially serious complications, such as pleural effusion, pneumonitis, and vascular and metabolic disorders.[1,2] Bosutinib is a BCR/ABL inhibitor used in frontline treatment of CML or in treatment of chronic, accelerated, or blast phase CML resistant or intolerant to prior TKIs. [3-6] The most common side effects are gastrointestinal, followed by thrombocytopenia and abnormal liver function tests.[5]However, there have been cases reporting pulmonary injury related to bosutinib. [7] Here, we discuss a case of bosutinib-induced interstitial lung disease and pleural effusion.

CASE HISTORY/EXAMINATION

A 71-year-old woman with a diagnosis of chronic phase CML since 2000 received frontline treatment with imatinib and achieved major molecular remission for 14 years. Her treatment course was interrupted for two months in 2007 by pancreatitis and for one month in 2008 after she developed nitrofurantoin-induced non-specific interstitial lung disease. Her respiratory condition almost resolved itself after discontinuing the drug and six months of prednisone treatment, which required nocturnal administration of 2L/min of oxygen through a nasal cannula. In 2014, the patient's disease progressed and was treated with dasatinib, followed by nilotinib. Both treatments were discontinued because of grade 3 gastrointestinal and dermatological side effects, respectively. In January 2015, the patient started bosutinib at a daily dose of 500 mg orally. The patient developed one-month symptoms of diarrhea, nausea, and vomiting that resolved themselves after the bosutinib dose was reduced to 400mg. She achieved complete hematological, cytogenetic remission and a major molecular response (MMR) (BCR-ABL1<0.1%) within the first year. While on MMR, she was admitted to the cancer center in August of 2019 with symptoms related to progressive dyspnea and dry cough, and her daily oxygen requirements were increased to 4L/min through a nasal cannula.

She denied any environmental or occupational exposures or other drugs except for pantoprazole for managing gastroesophageal reflux disease. The pulmonary function test at baseline revealed restrictive ventilatory defects and decreased diffusing capacity (Table 1). The echocardiogram was normal. Computed tomography (CT) of the chest showed non-specific chronic interstitial lung disease and new moderate bilateral pleural effusions with a small pericardial effusion (Figure 1). An autoimmune panel was negative. The bronchoalveolar lavage was negative for infection and with a bland count. The right diagnostic thoracentesis showed sterile exudate with 88% lymphocytes concerning drug reaction. Pleural fluid culture and cytology were negative. The bronchoscopy findings and CT scan findings raised the suspicion of bosutinib-induced interstitial lung disease and pleural effusion. The patient discontinued bosutinib in October 2019. In January of 2020, the patient noted significant improvement in her cough and dyspnea and was no longer requiring oxygen treatment. The chest CT scan in January 2020 showed almost complete resolution of pleural and pericardial effusions and decreased peribronchovascular ground-glass opacities (Figure 2). Repeat spirometry showed improved pulmonary function (Table 1) in February of 2020. The patient presented with hematological and molecular features of CML relapse, for which she initiated treatment with ponatinib. After two months of treatment, she has not reported significant side effects from the medication.

DISCUSSION

The prognosis of CML has changed from a fatal hematological malignancy to a curable disease thanks to the use of BCR-ABL TKIs. Since most patients will require treatment indefinitely, it is essential to understand the potential risks of such medications. TKI selectivity is often a critical issue as most TKIs have inhibitory actions against a wide variety of kinases. [8] Since multiple signaling pathways contribute to tumor pathogenesis, inhibiting several kinases simultaneously sometimes represents an advantage. The overall toxicity of TKIs correlates with the nonselective inhibition of several kinases.[9] Risk factors for the adverse effects include a higher dose, a longer duration of treatment, older age, and a history of cardiac disease. [10]

Among the different BCR-ABL TKIs, dasatinib is the drug most related to pulmonary toxicities. [11] Dasatinib-induced pleural effusion has an incidence of 15% to 35%. [2,12,13] Other pulmonary complications, such as pulmonary arterial hypertension (PAH) and interstitial pneumonitis, have also been reported.[2,10,12,14]

Bosutinib is uncommonly associated with pulmonary side effects. In a long-term safety study on bosutinib, the incidence of pleural effusion ranged between 4% and 8%, with a median time to onset of 33 months after initiation of treatment. [10,13–15] Moguillansky et al. reported a case of bosutinib-associated pleural effusions that resolved after discontinuation of the medication[7]. Jutant et al. reported a case of bosutinib-related pneumonitis.[12] As is in the case we are presenting, bosutinib may also be associated with interstitial lung disease and pleural effusion—the spectrum of lung complications previously described with other TKIs[16].

Although the mechanism of bosutinib-induced lung injury is unclear, it could be causing oxidative and reticular endothelium stress, similar to dasatinib[17]. Guignabert et al.'s studies showed that dasatinib mediated endothelial cell dysfunction and vascular damage in a dose-dependent manner. The risk factors for bosutinib-induced lung complications are a higher dosage, longer therapy duration, older age, and a history of cardiac disease, hypertension, or hypercholesterolemia.[2,9,10] Patients on TKIs need careful monitoring of respiratory symptoms, such as rapid weight gain, progressive dyspnea, or nonproductive cough. A physical exam result suggestive of pleural effusion includes dull percussion or focally diminished breath sounds. This requires prompt confirmation with imaging studies. Depending on the size of the effusion and the index of suspicion for possible pleural space infection, a thoracentesis confirms the diagnosis. Typically, pleural fluid in drug-induced pleural effusion is exudative with lymphocyte predominance [18], as in our patient's case. Much of the information on managing pulmonary toxicity during TKI therapy comes from case reports of events observed in dasatinib- or imatinib-treatment patients. The management of TKI-associated pleural effusion depends on the radiographic findings and clinical compromise[2]. If symptoms are minimal, no treatment is necessary. For large symptomatic pleural effusions, diuresis and a short steroid course can be used besides TKI dose reduction or discontinuation (temporarily or permanently). [2,19]

Although interstitial lung disease (ILD) was a non-reported side effect of BCR-ABL TKI during the pre-approval clinical trials, case reports in the post-marketing period suggest ILD could be a side effect of BCR-ABL TKIs. [1] Peerzada et al. showed patients with BCR-ABL TKIs-induced ILD often presented with dyspnea, cough, hypoxia, and bilateral ground-glass opacities. [20] ILD due to TKIs is a diagnosis of exclusion. A detailed history and physical examination are necessary, and CT chest and sometimes lung biopsy can guide diagnosis. The mechanism of TKIs-induced pulmonary injury seems to be dose-dependent and typically reversible with discontinuation of TKI therapy. In some cases, the addition of corticosteroids confers some clinical benefit to avoid TKI therapy cessation. [3,11]In patients who develop moderate to severe TKI-associated interstitial lung disease, re-challenging with alternative TKI therapy requires close monitoring since the risk of recurrence is high. [11.]

CONFLICT OF INTEREST

None declared

AUTHOR CONTRIBUTIONS

Q.L. completed the background research and drafted and edited the manuscript. N.A. edited the manuscript. C.A.Y. edited the manuscript and approved the final manuscript.

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