Bosutinib-induced lung injury: a report of two cases and literature review

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CASE REPORT

Abstract
The prognosis of patients with chronic myeloid leukemia (CML) has improved dramatically since the development of tyrosine kinase inhibitors (TKIs). Three second-generation TKIs, including bosutinib, are currently approved for treatment of CML, and show a faster and deeper clinical response than imatinib. Common adverse events (AEs) of bosutinib are diarrhea and hepatic toxicity; however, lung complications are rare. Here, we report two cases of bosutinib-induced severe lung injury, along with a literature review. The events of these cases occurred at early time points and severity was extremely high, requiring high-flow oxygen and steroid treatments. Compared to previously reported cases, the prevalence and severity of the damage may vary among different ethnicities. However, bosutinib-induced lung injury can cause life-threatening complications. In conclusion, patients treated with bosutinib should be monitored carefully to mitigate serious drug-induced lung injury.

Keywords Bosutinib · Chronic myeloid leukemia · Drug-induced lung injury · Steroid pulse treatment · Tyrosine kinase inhibitor

Introduction
Chronic myeloid leukemia (CML) is a hematopoietic stem cell disease characterized by a translocation between chromosomes 9 and 22, leading to the formation of the oncogenic BCR-ABL1 fusion gene. Tyrosine kinase inhibitors (TKIs) have dramatically changed the treatment of CML. However, these agents are associated with potentially serious complications, such as pleural effusion, pulmonary hypertension, and vascular occlusive events [1]. Bosutinib is a second-generation TKI with activity against BCR-ABL1 kinase. Recent studies have shown that patients with CML who received bosutinib had significantly higher rates of major molecular response (MMR) and complete cytogenetic response compared with those who received imatinib [2].

Case presentation

Patient 1
A 68-year-old woman with CML was initiated on imatinib therapy, a TKI, in 2018. The regimen was switched to bosutinib because of resistance (failure to achieve optimal response at 12 months according to the European LeukemiaNet response criteria). Two months after initiating bosutinib therapy, the patient experienced cough and dyspnea. Computed tomography (CT) of the chest revealed interstitial lung disease. Although she received moxifloxacin, her symptoms did not improve; further CT images showed lung deterioration (Fig. 1A). Thereafter, her oxygen saturation dropped to 80%, and she was admitted to our hospital. Bosutinib were discontinued based on suspected drug-induced lung injury. Lung bronchoscopy was performed, and
microscopic examination revealed edema of the bronchial mucosa. Bronchoalveolar lavage tests showed that inflammatory cells such as macrophages and lymphocytes were increased; however, there were no signs of malignancy. Microbiological examination of the collected lung fluid did not show any evidence of infection. Biomarker tests including serum β-D-glucan and cytomegalovirus antigen were negative. We searched autoantibodies to exclude the possibility of auto-immune lung injury and various autoantibody tests were negative. The serum Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) levels were elevated at 1079 U/mL (normal range < 500 U/mL) and 124 ng/mL (normal range < 110 ng/mL), respectively. The patient was initiated on high-dose (HD) steroid therapy (1000 mg methylprednisolone for 3 days), because her oxygen levels did not normalize after bosutinib cessation. She was discharged on day 34 with the prescription of 1 L/min of home oxygen therapy. Six months later, the chest CT scan showed decreased ground-glass opacities (Fig. 1B).

**Patient 2**

A 55-year-old man was diagnosed with CML in February 2021, and bosutinib treatment was initiated. Three months later, the patient experienced progressive dyspnea and sputum production. When he visited our hospital for routine examination, his oxygen saturation was at 69%. A chest CT scan showed bilateral consolidations and severe ground-glass opacities (Fig. 1C). He was admitted to the intensive care unit due to respiratory failure. Following this, nasal high-flow (NHF) treatment at 50 L/min with a fraction of inspired oxygen (FiO2) of 0.8 was started. His arterial blood gas analysis showed a PaO2 of 62.4 mmHg and a P/F ratio of 78 mmHg. Severe acute respiratory syndrome coronavirus 2 real-time polymerase chain reaction (SARS-CoV-2 RT-PCR) test was negative. Bosutinib-induced lung injury was suspected, because he did not take any other medications. He was initiated on HD-steroid therapy and levofloxacin because of deteriorated oxygenation despite bosutinib cessation. Consequently, his oxygen saturation improved, and NHF treatment was discontinued on day 11. Microbiological examination including biomarker tests did not show any evidence of infection, and all autoantibody test results were negative. Similar to case 1, the patient’s serum KL-6 and SP-D levels were extremely elevated at 2615 U/mL and 338 U/mL, respectively. Prednisolone (50 mg) was started following HD-steroid therapy and then gradually reduced to 20 mg. Chest CT images on day 21 showed decreased ground-glass opacities (Fig. 1D), and he was discharged on day 26.
Table 1  Summary of bosutinib-induced lung injury

| Author | Age/sex | Comorbidities | Smoking history | Treatment history of CML | Daily dose of bosutinib | Duration of bosutinib treatment | Bosutinib response | CT scan findings | Diagnostic method | Treatment TKI after bosutinib | Outcome |
|--------|---------|---------------|----------------|--------------------------|-------------------------|-------------------------------|------------------|----------------|----------------|--------------------------|---------|
| Jutant et al. [5] | 70/M | Hypertension | 25-pack-year | HU → IFN → imatinib → nilotinib → bosutinib | 200 mg | 2013–September 2015 | MMR | Subpleural consolidation, pleural effusion | Lung biopsy | Discontinuation of bosutinib | None | Survived |
| Liu et al. [6] | 71/F | None | NA | Imatinib → dasatinib → nilotinib → bosutinib | 400 mg | 55 months | MMR | Interstitial lung disease, pleural effusion | Bronchoscopy | Discontinuation of bosutinib, oxygen treatment | Ponatinib | Survived |
| Our case 1 | 68/F | Hypertension | None | Imatinib → bosutinib | 400 mg | 2 months | MMR | Interstitial lung disease | Bronchoscopy | Discontinuation of bosutinib, oxygen treatment, steroid pulse | Imatinib | Survived |
| Our case 2 | 55/M | None | 20 cigarettes daily for 34 years | Bosutinib | 400 mg | 3 months | CHR | Consolidation, ground-glass opacity | CT scan | Discontinuation of bosutinib, oxygen treatment, steroid pulse | None | Survived |

M male, F female, *NA* not available, *CML* chronic myeloid leukemia, *HU* hydroxycarbamide, *IFN* interferon, *MMR* major molecular response, *CHR* complete hematologic response, *CT* computed tomography, *TKI* tyrosine kinase inhibitor
report of life-threatening severe lung injury related to bosutinib therapy. Increased KL-6 levels at diagnosis have been related to poor prognosis [7] and were remarkably high in both cases reported herein.

Drug-induced lung injury can be caused by various agents. The clinical manifestations and imaging patterns vary remarkably. Although the exact frequency of drug-induced lung complications is unclear, common drugs associated with lung injury are antimicrobial agents, biological agents, cardiovascular agents, and chemotherapeutic agents [8]. Other TKI-related lung injuries have also been reported in patients treated with the epidermal growth factor receptor TKI, gefitinib. The incidence rate of gefitinib-related lung injuries is reportedly higher in patients in Japan than those in United States and Europe [9]. In addition, lung injuries related to bortezomib and leflunomide have frequently been reported in Japanese patients [10, 11]. In general, the incidence and severity of AEs during treatment with TKIs increase in a dose-dependent manner [12–14]; however, the estimated total treatment doses of bosutinib used in the currently reported cases were lower than those used in previous cases (24–36 g vs. 120–660 g, respectively). Therefore, bosutinib-induced lung injury may also be due to ethnic differences.

While further studies are warranted, our observations suggest that the incidence rate and severity of bosutinib-related lung injury requiring high-flow oxygen treatment and/or HD-steroid therapy may be higher in Asian populations. Recently, Noguchi et al. reported that interleukin-1β and high-mobility group box 1 play an important role in pathogenesis of gefitinib-induced interstitial pneumonitis [15]. Although the mechanism of bosutinib-related lung injury remains unclear, off-target effects are postulated to readily occur in these patients, and ultimately induce various reactions that cause lung injury.

We report two cases of bosutinib-induced severe lung injury, but were successfully treated with HD-steroid therapy. Therefore, patients with CML who are administered bosutinib should be considered at high risk of developing severe lung injury. Consequently, these patients need careful monitoring for respiratory symptoms, such as cough, dyspnea, and sputum.

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