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Case Report

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Clinical Spectrum of Bosutinib Related Side Effects in a Patient of CML: A Case Report and Review of Literature

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ABSTRACT

This case study outlines the complex treatment journey of a 53-year-old male diagnosed with Chronic Myeloid Leukemia (CML). Despite initial therapy with Imatinib and a subsequent switch to Dasatinib and then Bosutinib due to treatment resistance and adverse effects, the patient experienced multiple unexpected complications, including bilateral pleural effusions, pulmonary arterial hypertension, renal impairment, and neurological symptoms. Bosutinib was identified as the likely cause, leading to its discontinuation and transition to Nilotinib, which resulted in a sustained molecular response without further adverse events. Through this case report and literature review, we aim to expand the dimensions of the toxicity profile of bosutinib.

Keywords: Bosutinib; Chronic myeloid leukemia; Bosutinib toxicity; Pulmonary arterial hypertension; Pleural effusion

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the abnormal proliferation of myeloid lineage cells, including neutrophils, basophils, and eosinophils. This condition arises from a genetic abnormality known as the Philadelphia chromosome, resulting from a translocation between chromosomes 9 and 22. The fusion gene BCR-ABL1, found within the Philadelphia chromosome, encodes a hybrid tyrosine kinase that drives uncontrolled cell growth in hematopoietic stem cells. Treatment for CML primarily involves targeted therapy with tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, nilotinib, and bosutinib[1]. Bosutinib (SKI-606), a 7-alkoxy-3-quinoline carbonitrile, is notable for its dual inhibition of SRC and ABL kinases, demonstrating high antiproliferative activity[2]. However, clinicians should be mindful of the frequent and potentially serious adverse effects associated with bosutinib, including diarrhea and hepatotoxicity.

Case presentation

A 53-year-old male was diagnosed with Chronic Myeloid Leukemia (CML) in November 2019 and was initiated on Imatinib. However, the patient's BCR-ABL1/ABL1 ratio remained >10% at 6 months, prompting a switch to Dasatinib 100 mg/day after no tyrosine kinase domain (TKD) mutations were detected by Next Generation Sequencing (NGS). The patient achieved a major molecular response (BCR-ABL1/ABL1 ratio < 0.1%) on Dasatinib but developed bilateral pleural effusion after 1.5 years of therapy. Consequently, the patient was transitioned to Bosutinib 500 mg/day as of February 2022, which led

to the self-resolution of the pleural effusion within a few days, implicating Dasatinib as the likely cause.

The patient maintained a deep molecular response on Bosutinib; however, after 6 months of treatment initiation, he reported increasing dyspnea on exertion and intermittent chest discomfort. An echocardiogram revealed a dilated right atrium and right ventricle. High-resolution computed tomography (HRCT) confirmed bilateral pleural effusions with atelectatic changes in the underlying lung parenchyma and indicated pulmonary arterial hypertension, with prominence of central and peripheral pulmonary arteries, and a main pulmonary artery diameter of approximately 34 mm. Around this time, the patient experienced seizures, prompting a brain MRI, which revealed a microbleed in the right basal ganglion with ischemic foci in the cerebral white matter. Additionally, the patient complained of oliguria, exhibited visible anasarca, and had elevated blood urea nitrogen (BUN) and creatinine levels, indicating the onset of acute kidney injury.

Given the diverse presentations and extensive workup for each manifestation, all of which lacked an obvious cause, Bosutinib was considered the likely culprit and temporarily withheld. Supportive care, including supplemental oxygen therapy for symptomatic relief, was initiated. Renal parameters improved, pleural effusion resolved, and pulmonary artery pressure normalized over the subsequent days, with no further seizure episodes reported.

Conclusively, Bosutinib was deemed responsible for the unusual manifestations, prompting a transition to Nilotinib 400 mg BID after no TKD mutations were detected on NGS. The patient has since maintained a deep molecular response with Nilotinib treatment and has not exhibited any unusual side effects.

DISCUSSION

Bosutinib is an oral, dual SRC and ABL TKI that is approved for both frontline settings and as a second-line in resistant/intolerant to prior TKI therapy in Philadelphia chromosome-positive (Ph +) chronic myeloid leukemia. However, given its efficacy, it is equally important to understand the potential side effects of bosutinib for clinicians to have a thorough understanding of its toxic profile. The adverse effect profile of bosutinib is comparable to other TKIs with few exceptions like early and transient diarrhea is unique to bosutinib while there is a lack of cardiovascular and metabolic side effects seen with other TKIs[3].

Gastrointestinal Effects

Gastrointestinal (GI) side effects are the most common adverse reactions associated with Bosutinib, including nausea, vomiting, or diarrhea[4], and elevations in transaminase and lipase levels. These findings emphasize the critical need for vigilant monitoring, particularly of liver function tests, and effective management of GI side effects in patients receiving bosutinib treatment.

Pulmonary Effects

Pulmonary complications associated with TKI range from pleural effusions and interstitial lung disease (more commonly linked with imatinib) to severe pulmonary arterial hypertension (primarily associated with dasatinib, and more recently reported with ponatinib, bosutinib, and lapatinib). Although often reversible upon discontinuation, due to rare fatal cases, patients with right heart failure or persistent pulmonary arterial hypertension (PAH) after TKI cessation should receive appropriate management[5]. Early recognition and diagnosis of TKI-related pulmonary complications are crucial given their severity, potential reversibility, and impact on future treatment options for underlying chronic myelogenous leukemia. Notably, ILD has been documented in the literature where a 68-year-old female treated with high-dose steroid therapy and a 55-year-old male treated with high-dose steroid therapy and levofloxacin, both alongside Bosutinib cessation[6].

Renal Effects

Long-term treatment with bosutinib is linked to a reversible decline in renal function, comparable in frequency and characteristics to the renal decline observed with long-term imatinib therapy. Patients with risk factors for Grade ≥ 3b eGFR should be monitored closely. A significant study highlighted the importance of periodically measuring serum creatinine after bosutinib therapy to prevent

progression to severe renal dysfunction, particularly due to creatinine elevation mediated by OCT2 following bosutinib treatment[7].

Cardiac and Vascular Effects

Cardiac and vascular toxicities, fluid retention, and electrolyte abnormalities were uncommon. Additionally, serious side effects such as pneumonia and pyrexia have been reported in patients in accelerated and blastic phases[8].

Central Nervous System Effects

No prior instances of Bosutinib-linked seizures have been reported. However, a 76-year-old male developed ICA stenosis after three months of Bosutinib use, leading to treatment discontinuation and intervention for ICA stenting[9].

Other Effects

Osteonecrosis has been documented, such as in the case of a 65-year-old female with CML who underwent Bosutinib discontinuation followed by surgical removal of necrotic bone, soft tissue, and nasolabial flap reconstruction[10].

CONCLUSION

In conclusion, apart from the common side effects of Bosutinib like Gastrointestinal and liver disease, it carries the risk of rare but severe adverse effects. These include pulmonary arterial hypertension, renal impairment, and even central nervous system complications such as seizures and ischemic cerebrovascular events along with miscellaneous complications such as osteonecrosis. While these occurrences are infrequent, their potential severity underscores the importance of vigilant monitoring and prompt intervention when necessary. Clinicians should remain aware of these rare side effects to optimize patient care and outcomes in Bosutinib therapy.

Table 1: Summary of Pulmonary Arterial Hypertension and Pleural Effusion Cases Associated with Bosutinib Use in Chronic Myeloid Leukemia Patients

Age/sex	Indication	Time to onset after bosutinib use	Treatment	Reference number
Pulmonary arterial hypertension				
44/F	CML	2 months	Bosutinib discontinuation + Bosentan	11
48/F	CML	4 months	Bosutinib dose reduction + tadalafil →Bosutinib discontinuation + tadalafil + ambrisentan	
52/M	CML	10 months	Bosutinib discontinuation	12
52/M	CML	1 year	Bosutinib discontinuation + treprostinil + ambrisentan + furosemide + riociguat	13
37/F	CML	4 years	Bosutinib discontinuation + Macitentan	14
39/M	CML	3 months	Bosutinib discontinuation + ambrisentan	15
Seizures: No case reported				
Pleural effusion				
68/F	CML	6 years	Bosutinib discontinuation	16
59/M	CML	N/A	Bosutinib discontinuation + initiation of prednisolone	17
71/F	CML	4.5 years	Dose reduction to 400 mg + Bosutinib discontinuation	18
81/F	CML	1 year	Bosutinib discontinuation	11

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