



Case report

Successful treatment with nilotinib after bosutinib-induced pulmonary arterial hypertension recurrence following dasatinib in chronic myeloid leukemia in chronic phase

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ABSTRACT

A 52-year-old man was diagnosed with chronic myeloid leukemia in the chronic phase (CML-CP). He experienced bosutinib-induced pulmonary arterial hypertension (PAH) recurrence following dasatinib use. Symptoms and examination findings associated with PAH improved after bosutinib cessation. Although nilotinib was started because of the loss of response after bosutinib cessation, a deep molecular response without PAH recurrence was achieved 3 months after the initiation of nilotinib therapy. PAH recurrence after switching to bosutinib due to dasatinib-induced PAH should be closely monitored. In addition, nilotinib therapy might be an effective approach in PAH cases related to dasatinib and/or bosutinib in patients with CML-CP.

Abbreviations

CML-CP	Chronic Myeloid Leukemia in the Chronic Phase
PAH	Pulmonary Arterial Hypertension
AE	Adverse Events
BID	Twice Daily
ECG	Electrocardiography
MMR	Major Molecular Response
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide
PE	Pleural Effusion
French PH registry	French Pulmonary Hypertension registry
PDGFR	Platelet-Derived Growth Factor Receptor
PASMCs	Pulmonary Vascular Smooth Muscle Cells
QD	Once a Day
RHC	Right Heart Catheterization
TKI	Tyrosine Kinase Inhibitor
TRPG	Tricuspid Regurgitation Pressure Gradient
WHO FC	World Health Organization Functional Class
UCG	Ultrasonic Echocardiography

1. Introduction

The prognosis of chronic myeloid leukemia in the chronic phase (CML-CP) has been revolutionarily improved by the introduction of BCR-ABL 1 tyrosine kinase inhibitors (TKIs). The life expectancy after diagnosis in patients with CML-CP of all ages was almost similar to that of the general population, and survival in CML-CP is more frequently determined by non-CML-related causes than CML itself. Therefore, the management of adverse events (AEs) associated with TKIs has become more important for successful outcomes in the TKI era.

Pulmonary arterial hypertension (PAH) is reportedly one of the lethal AEs in patients with CML treated with dasatinib, and immediate switching to other TKIs is strongly recommended in clinical guidelines [1]. In such cases, bosutinib is often selected as an alternative treatment. Some recent case reports have focused on bosutinib-induced PAH following prior dasatinib treatment in patients with CML-CP [2–5]. Among these case reports, the selection of third-line TKIs for obtaining an optimal response without PAH recurrence has not been well elucidated.

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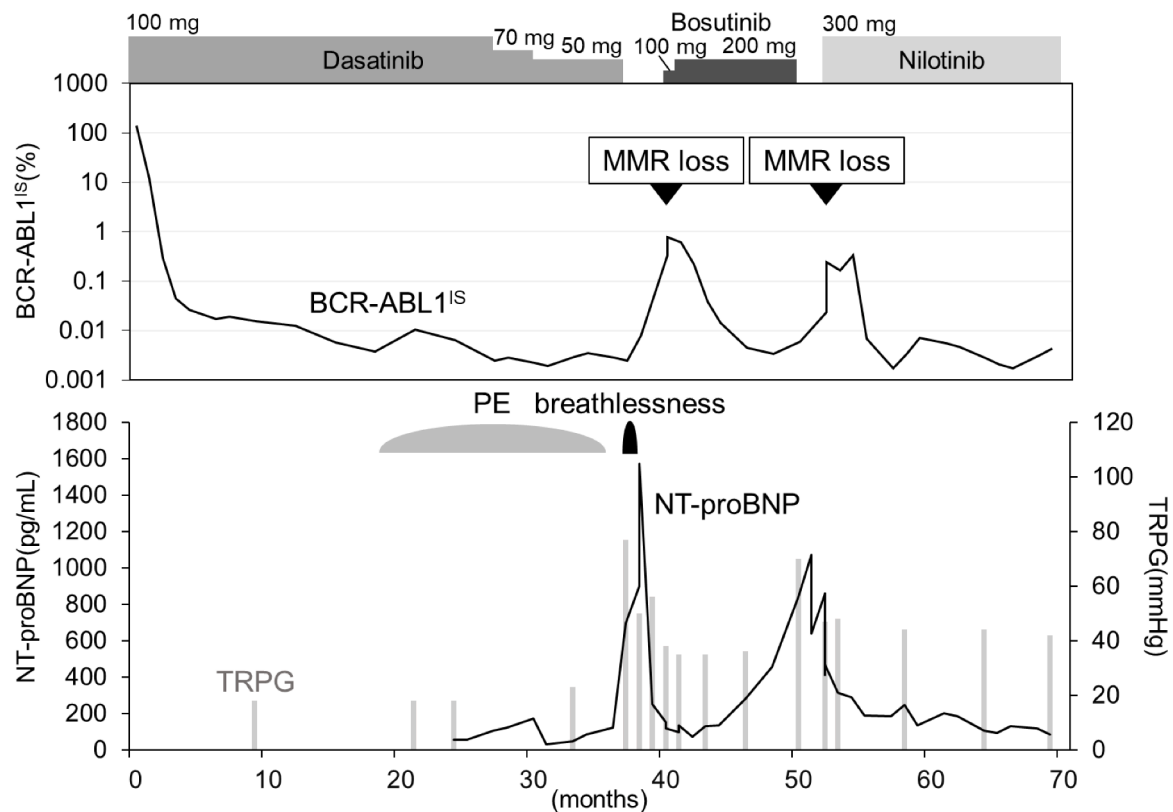


Fig. 1. Clinical course of this case. *IS* international scale, *MMR* major molecular response, *PE* pleural effusion, *TRPG* tricuspid regurgitation pressure gradient, *NT-proBNP* N-terminal pro-brain natriuretic peptide.

2. Case report

A 52-year-old man with CML-CP initiated dasatinib 100 mg once daily (QD). The patient had no medical history of cardiovascular and pulmonary diseases before treatment with TKIs, except for hypertension and diabetes mellitus well-controlled by medications. The patient had normal findings on chest radiography, 12-lead electrocardiography (ECG), and ultrasonic echocardiography (UCG) (Supplementary Figure S1A–C). A normal level of N-terminal pro-brain natriuretic peptide (NT-proBNP) before treatment was observed. The patient obtained a deep molecular response (DMR) 15 months after initiation of dasatinib treatment. After 18 months of dasatinib therapy, right-sided pleural effusion (PE) gradually increased but disappeared with a dose reduction of 50 mg QD 36 months after initiation of dasatinib. However, the patient developed dyspnea on exertion, based on the World Health Organization functional class (WHO FC) III approximately 1 month later. Chest radiography revealed right central pulmonary artery dilation without heart enlargement and PE (Figure S1D). A newly negative T wave at V1–V4 on a 12-lead ECG was observed (Figure S1E). Additionally, UCG revealed a dilated right ventricle with flattening of the interventricular septum, a small amount of pericardial effusion, and an elevated peak tricuspid regurgitation pressure gradient (TRPG; 77 mmHg) (Figure S1F). The left ventricular ejection fraction was normal (70.2%). The NT-proBNP level increased to 668 pg/mL, but no elevations of fibrin/fibrinogen degradation product α -dimer, creatine kinase, hepatic enzyme, and anti-human immunodeficiency virus antibody levels were observed. Dasatinib-induced PAH was strongly suspected based on these findings, and dasatinib was promptly discontinued. We recommended that the patient undergo right heart catheterization (RHC) for the diagnosis of PAH, but no consent was obtained.

The patient showed symptomatic improvement to WHO FC I without PAH-specific therapy following dasatinib cessation. The NT-proBNP level peaked at 1570 pg/mL and then decreased. Although the

abnormal ECG with negative T wave at V1–V4 was persistent, TRPG and NT-proBNP levels returned to normal approximately 3 months after dasatinib cessation (Figure S1G–I). The patient was started on bosutinib 100 mg QD approximately 3 months after dasatinib cessation owing to the loss of major molecular response (MMR). Nilotinib was not selected because of the coexistence of hypertension and diabetes mellitus. The dosage was increased from 100 mg QD to 200 mg QD 1 month after initiation of bosutinib, and the patient obtained a DMR after 6 months, with a normal level of TRPG on UCG. After 10 months of treatment with bosutinib, his chest X-ray imaging revealed the reappearance of dilated right central pulmonary vascularity. Moreover, the negative T wave in ECG became deeper, and UCG revealed a high TRPG of 70 mmHg with an enlarged right ventricle (Figure S2A–C). The NT-proBNP level was elevated to 845 pg/mL, without any symptoms and abnormal vital signs. Bosutinib was discontinued because of the high possibility of PAH recurrence, based on these findings. We confirmed a loss of MMR 2 months after bosutinib cessation despite the persistence of high TRPG and NT-proBNP levels (Figure S2D–F). Nilotinib was carefully administered at a reduced dose of 150 mg twice daily (BID), because the patient had hypertension and diabetes mellitus. The patient reobtained a DMR 3 months after initiation of nilotinib. After 18 months of treatment with nilotinib, TRPG and NT-proBNP levels decreased to 42 mmHg and 86 pg/mL, respectively, although a dilated right ventricle remained on UCG (Figure S2G–I). The clinical course of this case is shown in Fig. 1.

3. Discussion

PAH has been widely recognized as an uncommon but lethal adverse effect associated with dasatinib, with estimated frequency of 0.45% in the French Pulmonary Hypertension (PH) registry (13 of 2900 patients) [6]. By contrast, few cases of PAH have been reported in patients with CML-CP treated with other BCR-ABL1 TKIs, except for dasatinib in clinical trials. Cases of bosutinib-induced PAH in patients with prior

Table 1
Reports of bosutinib-induced pulmonary arterial hypertension.

	Age/ sex	Prior TKI(Duration of treatment, years)	Onset of PAH by DAS	DAS induced-PAH Treatment for PAH	PAH improvement	BOS induced-PAH Time to PAH onset	Treatment for PAH	PAH improvement	Following treatment
Riou et al.	44/F	IMA(NA),NIL(NA), DAS(3)	Yes	DAS stop	Yes	2 months	BOS stop +ERA	Yes	NA
	48/F	IMA(2),DAS(2), NIL(NA),IMA(NA)	Yes	DAS stop →+PDE- 5I	Yes	4 months	BOS reduction +PDE-5I →BOS stop +PDE- 5I+ERA	NA	NA
Hickey et al.	39/M	IMA(5.5),DAS(1), NIL(2.5)	Yes	DAS stop →+PDE- 5I →+ERA	Yes	3 months	PGI ₂ +PDE-5I →+BOS stop	Yes	PON→stop
Seegobin et al.	52/M	DAS(4)	Yes	DAS stop +ERA	Yes	1 year	BOS stop+ERA +sGC-S+PGI ₂	Yes	NA
Yo et al.	37/F	IMA(7),DAS(5)	No	NE	NE	4 years	BOS stop →+ERA	Yes	NIL
Our case	52/M	DAS(3)	Yes	DAS stop	Yes	10 months	BOS stop	Yes	NIL

NA not available, NE not evaluable, PDE5-I phosphodiesterase type 5 inhibitor, ERA endothelin receptor antagonist, PGI₂ prostaglandin 2, sGC-S soluble guanylate cyclase stimulator, PAH pulmonary arterial hypertension, TKI tyrosine kinase inhibitor, DAS dasatinib, BOS bosutinib, IMA imatinib, NIL nilotinib, PON ponatinib.

dasatinib treatment have been recently reported in clinical practice settings (Table 1).

The median time from the initiation of dasatinib to the diagnosis of PAH was 42 (8–74) months [6]. By contrast, the median duration from the onset of bosutinib-induced PAH after starting bosutinib in patients with prior dasatinib exposure was reportedly shorter at a median duration of 4 months (Table 1). In particular, bosutinib-induced PAH was most frequently observed in patients with a history of dasatinib-induced PAH within 12 months of starting bosutinib. These results in previous reports are almost the same as those in our case.

The mechanism underlying dasatinib-induced PAH has not been clearly elucidated. Several investigators have suggested possible mechanisms, including the inhibition of SRC family kinase, which activates potassium channels in pulmonary vascular smooth muscle cells (PASCs), maintains resting membrane potential, and causes depolarization of PASCs, resulting in increased pulmonary vascular resistance [7], pulmonary endothelial cell damage/dysfunction via endoplasmic reticulum stress, and mitochondrial reactive oxygen species production [8]. SRC family kinases are inhibited with similar potency by dasatinib and bosutinib, whereas platelet-derived growth factor receptor (PDGFR) is more strongly inhibited by dasatinib than by bosutinib. PDGFR promotes cellular proliferation via the upregulation of extracellular signal-regulated kinase 1/2 activation and angiogenesis. Based on these findings, the difference in the strength of inhibition against PDGFR between dasatinib and bosutinib might be one of the reasons for the discrepancy in the incidence of PAH caused by these two TKIs, both dual SRC/ABL inhibitors. In addition, all previously reported cases of bosutinib-induced PAH were treated with dasatinib for more than 1 year. Therefore, pulmonary damage associated with dasatinib may easily cause bosutinib-induced PAH.

In the Bristol-Myers Squibb pharmacovigilance database, dasatinib-induced PAH typically improved or resolved by dasatinib cessation in the majority of patients (34 of 36 patients, 94%), and no death resulted directly from dasatinib-induced PAH [9], which is a different feature observed in other types of PAH, except for TKI-induced PAH [1]. In the French PH registry, 19 of 21 patients had improved at least one WHO FC. Eleven patients received treatment with PAH-specific medication (endothelin receptor antagonist or phosphodiesterase type 5 inhibitor, $n = 9$; or calcium channel blocker, $n = 2$). However, complete improvement of RHC findings was not observed in 37% of patients, and symptoms of WHO FC II/III persisted in 43% of patients at the last evaluation in the long-term follow-up of the French PH registry data [6]. In the

previous five cases of bosutinib-induced PAH following dasatinib treatment (including four patients with episodes of prior dasatinib-induced PAH), all patients not only discontinued bosutinib but also received PAH-specific treatment [2–5]. Although the improvement of PAH in our case was observed by only bosutinib cessation, evaluation based on the severity of PAH in a larger cohort is needed to clarify the optimal treatment for PAH caused by TKIs.

The selection of imatinib with a long-term safety profile compared with second-generation TKIs may be optimal for this patient after PAH recurrence. However, we chose nilotinib, with a faster and deeper treatment response than imatinib, as the therapeutic goal of the patient was a treatment-free remission. In addition, the rate of nilotinib-induced PAH was reported to be even less than those induced by dasatinib and bosutinib, which was dose-dependent [10]. In the present case, low-dose nilotinib (150 mg BID) could contribute to the avoidance of PAH recurrence. Treatment with nilotinib, without inhibition of SRC family kinase, especially a lower dose of nilotinib for patients with TKI sensitivity, could become an optimal therapeutic approach in patients with PAH caused by both dasatinib and bosutinib.

4. Conclusion

Bosutinib-induced PAH was remarkably uncommon but could occur in patients with prior dasatinib exposure. Therefore, careful continuous monitoring by UCG and measuring NT-proBNP levels in these patients is needed. The selection of nilotinib might be an alternative treatment option for patients with PAH caused by both dasatinib and bosutinib. Among second-generation TKIs, bosutinib was more recently approved for first-line treatment in patients with CML-CP compared with dasatinib and nilotinib, and the long-term toxicities associated with bosutinib remain unclear. The present case can provide important information for optimal management of bosutinib to avoid toxicity, including PAH.

Informed consent

The informed consent was obtained from the patient for publication of this case report and accompanying images.

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Supplementary Information

Figure S1. Findings of chest radiography, 12-lead electrocardiography (ECG), and left ventricular long-axis view at the diastolic phase of ultrasonic echocardiography (UCG) during dasatinib-induced pulmonary arterial hypertension. (A–C) Normal findings of X-ray, ECG, and UCG. (D–F) Chest radiography shows enlargement of the right central pulmonary artery, the negative T wave at V1–V4 is observed on ECG, and UCG reveals a dilated right ventricle with an elevated peak tricuspid regurgitation pressure gradient (TRPG) of 77 mmHg. (G–I) Chest radiography shows almost normal findings, a negative T wave on ECG is persistent, and a dilated right ventricle on UCG is slightly residual with a normal TRPG. RV right ventricle, LV left ventricle

Figure S2. Findings of chest radiography, 12-lead electrocardiography (ECG), and left ventricular long-axis view at the diastolic phase of ultrasonic echocardiography (UCG) during bosutinib-induced pulmonary arterial hypertension. (A–C) Chest radiography shows the reappearance of the dilated right central pulmonary vascularity, the negative T wave on ECG becomes deeper, and UCG reveals a high tricuspid regurgitation pressure gradient (TRPG) of 70 mmHg with an enlarged right ventricle. (D–F) The right central pulmonary artery dilation on radiography, a negative T wave on ECG, and an enlarged right ventricle on UCG remain. (G–I) Findings of chest radiography and ECG are almost similar as those before treatment with nilotinib, and UCG reveals persistent right ventricular enlargement with a decreasing TRPG of 44 mmHg. RV right ventricle, LV left ventricle

Declarations of Competing Interest

The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.lrr.2022.100312](https://doi.org/10.1016/j.lrr.2022.100312).

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