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Tyrosine Kinase Inhibitor Induced Pulmonary Artery Hypertension: Reversible with Ponatinib?

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a disease associated with progressive and comprehensive vascular remodeling of small pulmonary arteries. The prognosis of Chronic myelogenous leukemia (CML) has been improved by tyrosine kinase inhibitors (TKIs), which inhibit BCR/ABL kinase pathway. Most of the TKIs induced PAH is limited almost exclusively to dasatinib until now. There was only one report about, PAH was caused by the novel TKI ponatinib. We present a 73 years old-female patient with chronic myeloid leukemia, who had PAH after approximately 72 months with prior exposure to dasatinib. Dasatinib was replaced by nilotinib in this patient. Nilotinib was used 11 months for CML treatment, but no recovery was seen with also this TKI. Finally, ponatinib therapy was started for CML. Signs and symptoms of PAH improved with institution of ponatinib therapy. Therefore we report that the patient with dasatinib induced PAH did not recover after institution of nilotinib as a TKI instead of dasatinib but improved with ponatinib treatment using for CML.

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Keywords: Chronic myelogenous leukemia (CML); Tyrosine kinase inhibitors (TKIs); Pulmonary arterial hypertension (PAH).

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease associated with progressive and comprehensive vascular remodeling of small pulmonary arteries. The remodeling process is the result of cellular hypertrophy, hyperplasia, apoptosis, inflammation and deposition of extracellular matrix. Vascular remodeling includes medial hypertrophy, muscularization of small arterioles, intimal thickening, and the formation of plexiform lesions [1].

Chronic myelogenous leukemia (CML) is a chronic myeloproliferative disorder characterized by a translocation between chromosome 9 and 22. This translocation pathogenically leads to a tyrosine kinase signal transduction protein, the breakpoint cluster region/Abelson (BCR/ABL). The prognosis of CML has been improved by tyrosine kinase inhibitors (TKIs), which inhibit BCR/ABL kinase pathway, such as imatinib. However up to now, 20% of imatinib treated patients with CML cannot achieve full cytogenetic response. Data suggest that, 2 new TKIs, dasatinib and nilotinib are associated with higher rates of full cytogenetic response in newly diagnosed and imatinib-resistant chronic phase CML [2,3].

The TKIs, imatinib, dasatinib, nilotinib and bosutinib are associated with significant respiratory adverse effects, including pleural and/or pericardial effusion. PAH is a rare adverse effect of TKIs. Most of the TKIs induced PAH is limited almost exclusively to dasatinib until now [4,5–7]. There was only one report of PAH caused by the novel TKI ponatinib [8].

2. CASE REPORT

We present a 73 years old-female patient with chronic myeloid leukemia, who had PAH after approximately 72 months of prior exposure to dasatinib. Dasatinib was replaced by nilotinib in this patient. Nilotinib was used for 11 months for CML treatment, but no recovery was seen with also this TKI. Finally, ponatinib therapy was started for CML. Signs and symptoms of PAH improved with institution of ponatinib therapy.

CML was diagnosed in 2009. Furthermore she had moderate systemic hypertension and atrial fibrilation. She was on long-term treatment with ramipril, hidroclorothiazid, digoksin and apixaban for these cardiac diseases. She has been treated with dasatinib (100 mg once daily in 2009-2015), then nilotinib (400 mg twice daily in August 2015-July 2016). Finally ponatinib (30 mg once daily) was started in July 2016.

In August 2015, she had dyspnea with New York Heart Association (NYHA) class III-IV. The work-up for dyspnea included transthorasic echocardiography disclosed right ventricular dilatation and systolic pulmonary artery pressure (sPAP) was estimated at 70 mmHg. The NT-proBNP was 1650 pg/ml. No thromboembolism evidence existed but dilatation of pulmonary trunk and proximal arteries was found on chest computed tomography scan. Rheumatology and chest disease consultation didn't show any other PAH causes except drug induced PAH (associated with TKIs). Dasatinib was replaced by nilotinib because of dasatinib induced PAH suspicion.

She took nilotinib between August 2015 and July 2016. The patient had dyspnea with NYHA class III-IV and NT-proBNP was 1605 pg/ml. Transthorasic echocardiography disclosed right ventricular dilatation and sPAP was estimated at 75 mmHg so no recovery was seen with nilotinib after 11 month therapy. On both treatments, the patient did not take any PAH medication.

Nilotinib was stopped and ponatinib therapy was commenced in August 2016. After 6 months-therapy with ponatinib, dyspnea improved and the patient's NYHA class became class II. The NT-proBNP was 1351 pg/mL. Echocardiogram disclosed mild right ventricular dilatation and systolic pulmonary artery pressure (sPAP) was estimated at 50 mmHg without any PAH medication. At this time, PAH therapy clinic was founded and right-sided catheterization was done. Precapillary pulmonary hypertension with a mean PAP of 33 mmHg and normal pulmonary wedge pressure of 12 mmHg was determined. PAH specific treatment was started to the patient in our cardiology clinic.

3. DISCUSSION

There are increasing number of case reports about dasatinib induced PAH in CML patients [9-12]. Quinta´s-Cardama et al. reported the first case of dasatinib associated PAH in 2007 [13]. In

2012, nine dasatinib induced PAH cases have been identified [5]. In the literature, although there were much more dasatinib induced PAH, only one case was reported with elevation of the pulmonary artery pressure attributed nilotinib [14].

PAH appears to be a late complication of dasatinib, usually occurs after 8-48 months of exposure. In the majority of cases, symptoms are improved after discontinuation of dasatinib, but some cases require PAH-specific therapy with sildenafil [9]. In present case, dasatinib induced PAH detected on 72nd month of treatment. Dasatinib was switched to nilotinib. Pulmonary artery pressure did not decrease with nilotinib therapy during 1 year nilotinib therapy period. The NT-proBNP and NYHA Class were high on both of dasatinib and nilotinib therapy periods. During nilotinib therapy we lost the patient follow up. Patient did not have any benefit or harmful effect on pulmonary artery pressure level during nilotinib therapy period. After one year using nilotinib, pulmonary artery pressure measured by echocardiography increased only 5 mmHg. But this increase can be operator variability. With these findings we cannot say nilotinib caused PAH. Because before nilotinib therapy, PAH has already occured during dasatinib therapy. During 7 years, no PAH specific therapy was given to because of lack of PAH specific department in our hospital.

We found only one PAH case with the use of ponatinib in the literature like nilotinib [8,14]. Despite the fact that, only one patient with pulmonary hypertension was reported with ponatinib therapy in the literature, we found a decrease in pulmonary hypertension findings, NTproBNP level and pulmonary artery pressure measured by echocardiography on the 6th month, after nilotinib therapy switched to ponatinib in the patient.

The previous studies showed the link between NT pro BNP levels and right ventricular function in patients with pulmonary arterial hypertension [15]. Increased plasma levels of NT-proBNP were associated with worse prognosis, while decreasing plasma level indicates successful management of pulmonary hypertension [16].

4. CONCLUSION

Our findings and pulmonary artery pressure decreasing with ponatinib therapy after dasatinib and nilotinib is very impressive in this case presentation. Therefore we report that the patient with dasatinib induced PAH did not recover after institution of nilotinib as a TKI instead of dasatinib but improved with ponatinib treatment used for CML.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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