Dasatinib-induced pulmonary arterial hypertension complicated with scleroderma: a case report

Takumi Toya*, Yuji Nagatomo, Kazuki Kagami, and Takeshi Adachi

Department of Cardiology, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan

Received 1 October 2018; accepted 20 February 2019; online publish-ahead-of-print 15 March 2019

Background

Although the BCR-ABL tyrosine kinase inhibitor dasatinib is a potent treatment for chronic myeloid leukaemia, it is associated with the risk of dasatinib-induced pulmonary arterial hypertension (DASA-PAH), for which predisposing factors have yet to be elucidated. However, animal studies have shown that dasatinib exacerbates pulmonary hypertension (PH) in rodent models of PH but not in controls, providing support for a two-hit theory of DASA-PAH pathophysiology.

Case summary

A 63-year-old man with worsening dyspnoea was diagnosed with severe DASA-PAH and concomitant scleroderma. He was successfully treated with discontinuation of dasatinib and administration of pulmonary vasodilators.

Discussion

Our case suggests that scleroderma may be a predisposing factor for the development of DASA-PAH, providing new insight into its pathophysiology.

Keywords

Case report • Dasatinib • BCR-ABL tyrosine kinase inhibitor • Pulmonary arterial hypertension • Scleroderma

Introduction

The second generation BCR-ABL tyrosine kinase inhibitor (TKI) dasatinib is a potent treatment for chronic myeloid leukaemia (CML) and Philadelphia chromosome-positive acute lymphoid leukaemia. However, growing evidence suggests that dasatinib can cause drug-induced pulmonary arterial hypertension (PAH), with more than 100 cases of dasatinib-induced PAH (DASA-PAH) having been reported.

* Corresponding author. Tel: +81 (0)4-2995-1597, Fax: +81 (0)4-2996-5200, Email: tyt0725@gmail.com

Handling Editor: Julia Grapsa

Peer-reviewers: Julia Grapsa and Hatem Soliman Aboumarie

Compliance Editor: Amir Aziz

Supplementary Material Editor: Peysh A. Patel

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Despite this, the predisposing factors for DASA-PAH remain indeterminate. Herein, we present a case of severe PAH with concomitant scleroderma that developed during dasatinib treatment. The patient was successfully managed with dasatinib withdrawal and upfront triple pulmonary vasodilator combination therapy, providing novel support for a two-hit hypothesis of DASA-PAH development.

Timeline

| Timeline | Event |
|---------|-------|
| 8 years prior to presentation | Chronic myeloid leukaemia diagnosed at clinic. Imatinib (400 mg o.d.) initiated. |
| 5 years prior to presentation | Imatinib withdrawn due to facial oedema and massive pleural effusion. Dasatinib (100 mg o.d.) initiated. |
| Initial presentation | Patient presented with a 2-year history of dyspnoea that had worsened in the previous 6 months. Pulmonary hypertension diagnosed at clinic based on electrocardiography, transthoracic echocardiography, and contrast-enhanced chest computed tomography. Dasatinib withdrawn. Tadalafil (40 mg o.d.), macitentan (10 mg o.d.), and selexipag (1.2 mg b.i.d.) initiated. |
| Day 2 | Pulmonary arterial hypertension (PAH) diagnosed on admission based on scintigraphy and right heart catheterization (RHC). |
| 1 month | Prompt improvement in PAH. |
| 4 months | Imatinib (300 mg o.d.) initiated. |
| Follow-up (1 year) | No PAH as indicated by RHC. Selexipag withdrawn. |

Case presentation

A 63-year-old man presented to our department with exertional dyspnoea. He had a 2-year history of dyspnoea that had worsened over the previous 6 months. He had also been diagnosed with CML at the age of 55, for which a first-generation TKI, imatinib (400 mg daily), was prescribed as his first-line therapy. However, since this caused facial oedema and massive pleural effusion, a second-generation TKI, dasatinib (100 mg daily), was chosen as his second-line therapy 3 years before presentation. Concomitant pleural effusion and anaemia was thought to have caused the dyspnoea 2 years prior to presentation; subsequently, an additional dose of diuretics and a reduced dose of dasatinib (50 mg daily) resulted in a transient improvement of dyspnoea following a decrease in the amount of pleural effusion and a slight increase in haemoglobin without further evaluation.

Electrocardiography (Figure 1) and transthoracic echocardiography (TTE) (Figure 2A, Table 2) on admission indicated severe right ventricular pressure overload. Physical examination showed jugular vein dilatation. His lung sounds were normal, but cardiac auscultation revealed increased intensity of the P2 sound. The liver was slightly enlarged, but splenomegaly was unclear. Laboratory data showed markedly elevated brain natriuretic peptide (442 pg/mL; normal reference value, <18.4 pg/mL), and anti-nuclear and anti-centromere antibody positivity (1280X and 166X, respectively). Contrast-enhanced chest computed tomography showed no evidence of pulmonary embolism, and perfusion-ventilation scintigraphy showed no evidence of segmental mismatch. Neither abdominal ultrasonography nor upper endoscopy showed clear evidence of portal hypertension.

Discussion

BCR-ABL TKIs such as dasatinib are potent drugs that have transformed CML from a lethal to controllable disorder, though growing evidence suggests that dasatinib induces PAH. Although the prevalence of clinically significant DASA-PAH is speculated to be as low as 0.45–3%, its occurrence requires dasatinib withdrawal, leading to an increased risk of CML recurrence as in our case. The current European Society of Cardiology guideline recommends TTE surveillance once every 3 months during dasatinib treatment. We must therefore focus on early detection of PAH to avoid interruption of CML treatment.

Despite being a BCR-ABL TKI, dasatinib is also a potent inhibitor of Src kinases, as Src kinase inhibition could be involved in DASA-PAH development. However, Guignabert et al. reported that dasatinib treatment induces pulmonary endothelial cell apoptosis in a dose-dependent manner and endothelial dysfunction via increased production of reactive oxygen species, which occur independently of Src kinases. These authors also demonstrated that dasatinib...
exacerbates PAH only in a rodent model of PAH but not in control animals, supporting a two-hit theory of the pathophysiology of DASA-PAH. We have also identified human studies that appear to support this hypothesis. In a report of 41 patients with RHC-confirmed DASA-PAH, 94% showed improvement, but only 58% achieved complete resolution. Moreover, among nine DASA-PAH patients reported in the French pulmonary hypertension registry, eight showed significant clinical, functional, and haemodynamic improvement following dasatinib withdrawal, despite only three receiving pulmonary vasodilators. However, none returned to normal haemodynamic status. Taken together, these data indicate the existence of underlying predisposing factors for DASA-PAH other than dasatinib drug toxicity, supporting the two-hit theory.

These predisposing factors, however, remain unidentified, though PAH is known to be an independent risk factor for mortality in patients with scleroderma. Despite early diagnosis and treatment using pulmonary vasodilators, the therapeutic effects of these drugs and survival rates in patients with SSc-PAH are worse than in those with idiopathic PAH. Indeed, among the REVEAL Registry cohort, 3-year survival rates were worse in newly diagnosed SSc-PAH patients than in those with other connective tissue diseases (51.2% vs. 76.4%), even though approximately one-third of patients in both groups were on multiple pulmonary vasodilators. Furthermore, a prospective cohort study of 794 scleroderma patients reported worse 2-year survival rates in patients with MPAP >45 mmHg than in those with MPAP <32 mmHg (39% vs. 78%). In our patient, whose initial MPAP was 67 mmHg, clinical symptoms and haemodynamic status promptly improved following cessation of dasatinib and the initiation of triple pulmonary vasodilator combination therapy. This indicates that the patient’s PAH was unlikely to be secondary to his scleroderma, but rather that his scleroderma might have predisposed him to developing DASA-PAH.

Figure 1  Electrocardiogram (ECG) findings at initial presentation. An electrocardiogram revealed an incomplete right bundle branch block; an R/S ratio >1 in lead V1; T wave inversion in leads II, III, aVF, and V1–V5; and an R wave in lead V1 + S wave in lead V5 amplitude sum >10.5 mm, indicating right ventricular hypertrophy.
Regarding management, a treatment strategy for DASA-PAH has not been determined, with dasatinib discontinuation only reversing pulmonary arterial pressure and PVR in some reports. Recently, Weatherald et al. reported long-term outcomes in 21 patients treated for DASA-PAH. Dasatinib was discontinued in all patients and pulmonary vasodilators were prescribed in 11; those treated with pulmonary vasodilators had worse baseline haemodynamics but could reach long-term haemodynamic outcomes similar to those in patients not treated with pulmonary vasodilators, though PAH persisted in 37% at the last follow-up (median 24 months). The authors proposed a similar treatment algorithm to ours; that is, to treat patients presenting with more severe symptoms [e.g. New York Heart Association (NYHA) functional class (FC) III or IV] and those with severe haemodynamic compromise [e.g. cardiac index (CI) <3 L/min/m²] with pulmonary vasodilators, and to consider de-escalation of pulmonary vasodilators if normal haemodynamics persists at 1 year. In our case, the patient’s initial presentation was severe (i.e. NYHA FC IV and CI 1.35 L/min/m²); therefore, 

**Table 1**  
Haemodynamic findings

|                | Initial | 1 month | 3 month | 12 month |
|----------------|---------|---------|---------|----------|
|                | Room air| Oxygen  | Room air| Oxygen   | Room air| Oxygen  |
| SPAP/DPAP (mmHg) | 94/49   | 83/42   | 57/25   | 50/22    | 41/17   | 26/12   | 24/9     |
| MPAP (mmHg)    | 67      | 58      | 35      | 33       | 27      | 18      | 16       |
| PAWP (mmHg)    | 14      | 16      | 7       | 11       | 12      | 9       | 7        |
| SAP/DAP (mmHg) | 127/95  | 117/93  | 103/72  | 96/59    | 105/61  | 129/78  | 127/72   |
| PVR (WU)       | 15      | 16      | 4       | 8        | 5       | 4       | 3        |
| CO (L/min)     | 2.25    | 2.36    | 4.88    | 5.59     | 5.92    | 6.77    | 7.12     |
| CI (L/min/m²)  | 1.35    | 1.41    | 2.92    | 3.34     | 3.54    | 3.96    | 4.17     |
| SaO₂ (%)       | 93.2    | 97.8    | 90.0    | 93.1     | 98.4    | 93.7    | 99.2     |
| SvO₂ (%)       | 45.5    | 53.6    | 68.5    | 70.5     | 77.5    | 70.8    | 78.8     |

CO, cardiac output; CI, cardiac index; DAP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; MPAP, mean pulmonary artery pressure; MRAP, mean right atrium pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SaO₂, arterial oxygen saturation; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; SvO₂, mixed venous oxygen saturation; WU, wood units.

**Table 2**  
Echocardiographic measurements

|                | Initial | 1 month | 3 month |
|----------------|---------|---------|---------|
| RVSP (mmHg)   | 86      | 55      | 28      |
| RV fractional area change (%) | 14.8 | 27.6 | 34.0 |
| LV eccentricity index | 3.3 | 1.1 | 1.0 |
| S’ wave of tricuspid annulus (cm/s) | 7.3 | 13.8 | 15.0 |
| TAPSE (cm)    | 1.3     | 2.3     | 2.5     |

LV, left ventricle; RV, right ventricle; RVSP, right ventricular systolic pressure; S’ wave, systolic wave; TAPSE, tricuspid annular plane systolic excursion.

**Figure 2** Transthoracic echocardiography. The parasternal short-axis view is shown at (A) initial presentation, (B) 1 month after dasatinib withdrawal, and (C) 3 months after dasatinib withdrawal. LVEI, left ventricle eccentricity index.
his treatment with multiple pulmonary vasodilators was justified and eventually shown to be successful.

In conclusion, we experienced a case of DASA-PAH complicated with scleroderma that provides novel support for the two-hit hypothesis of DASA-PAH pathophysiology. However, further research is necessary to identify its predisposing factors and facilitate its early detection.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

References

1. Bantscheff M, Eberhard D, Abraham Y, Bastuck S, Boesche M, Hobson S, Mathieson T, Perrin J, Rada M, Rau C, Reader V, Sweetman G, Bauer A, Bouwmeester T, Hopf C, Kruse U, Neubauer G, Ramsden N, Rick J, Kuster B, Drewes G. Quantitative chemical proteomics reveals mechanisms of action of clinical ABL kinase inhibitors. Nat Biotechnol 2007;25:1035–1044.

2. Weatherald J, Chaumais MC, Savale L, Jaı¨s X, Seferian A, Canuet M, Bouvaist H, Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bournin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubbeau P, Girerd B, Natali D, Guignabert C, Perros F, O’Callaghan DS, Jais X, Tubert-Bitter P, Zalcman G, Sitbon O, Simonneau G, Humbert M. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128–2137.

3. Galie N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Hoeper M, ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.

4. Shah NP, Wallis N, Farber HW, Mauro MJ, Wolf RA, Mattei D, Guha M, Rea D, Peacock A. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol 2015;90:1060–1064.

5. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bournin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubbeau P, Girerd B, Natali D, Guignabert C, Perros F, O’Callaghan DS, Jais X, Tubert-Bitter P, Zalcman G, Sitbon O, Simonneau G, Humbert M. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128–2137.

6. Shah NP, Rousselot P, Schiffer C, Rea D, Cortes JE, Milone J, Mohamed H, Healey D, Kantarjian H, Hochhaus A, Saglio G. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol 2016;91:869–874.

7. Uitdehaag JCM, de Roos ADM, van Doornmalen AM, Prinsen MBW, de Man J, Tanizawa Y, Kawase Y, Yoshio K, Buijsman RC, Zaman GJR. Comparison of the cancer gene targeting and biochemical selectivities of all targeted kinase inhibitors approved for clinical use. PLoS One 2014;9:e92146.

8. Guignabert C, Phan C, Seferian A, Huertas A, Tu L, Thulliet R, Sattler C, Le Hiress M, Tamura Y, Jutani EM, Chaumais MC, Bouchet S, Maniglier B, Molimard M, Rousselot P, Sitbon O, Simonneau G, Montani D, Humbert M. Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. J Clin Invest 2016;126:3207–3218.

9. Yang X, Mardeklan J, Sanders KN, Mychaskow MA, Thomas J III. Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature. Clin Rheumatol 2015;34:1519–1531.

10. Rubenfire M, Huffman MD, Krishnan S, Seibold JR, Schiopu E, Mclaughlin VV. Survival in systemic sclerosis with pulmonary arterial hypertension has not improved in the modern era. Chest 2013;144:1282–1290.

11. Chung L, Farber HW, Benza R, Miller DP, Parsons L, Hassoun PM, McGoon M, Nicollis MR, Zamanian RT. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest 2014;146:1494–1504.

12. Mukeczy D, St George D, Coleiro B, Knight C, Denton CP, Davar J, Black CM, Coghlan JG. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62:1088–1093.

13. Hong JJ, Lee SE, Choi SY, Kim SH, Jang EJ, Bang JH, Park JH, Jeon HR, Oh YJ, Yi JE, Jung HO, Youn HJ, Kim DW. Reversible pulmonary arterial hypertension associated with dasatinib for chronic myeloid leukemia. Cancer Res Treat 2014;46:337–342.