Canadian Journal of Cardiology 35 (2019) 1604.e1–1604.e3 www.onlinecjc.ca

Case Report

Dasatinib-Induced Pulmonary Arterial Hypertension

Evan Orlikow, MD,[a] Jason Weatherald, MD,[b,c] and Naushad Hirani, MD[b]

[a] Section of Respirology, Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

[b] Division of Respirology, Department of Medicine, University of Calgary, Calgary, Alberta, Canada

[c] Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada

ABSTRACT

A 73-year-old woman with chronic myeloid leukemia developed severe pulmonary arterial hypertension (PAH) and pleural effusions after treatment with dasatinib. During workup, partial anomalous pulmonary venous connection and a sinus venosus atrial septal defect were found; these anomalies may have predisposed her to developing this rare and life-threatening condition. Fortunately, her PAH was completely reversible by discontinuation of dasatinib. This case highlights dasatinib's ability to cause PAH in patients predisposed to pulmonary vascular disease.

RÉSUMÉ

Une femme de 73 ans atteinte de leucémie myéloïde chronique a manifesté une hypertension artérielle pulmonaire (HTAP) grave et des épanchements pleuraux après un traitement par le dasatinib. Au moment du bilan, une connexion veineuse pulmonaire anormale partielle et une communication interauriculaire de type *sinus venosus* ont été observées; la présence de ces anomalies pourrait avoir prédisposé la patiente à cette affection rare et mettant la vie en danger. Heureusement, l'HTAP a complètement disparu à l'arrêt du traitement par le dasatinib. Ce cas met en lumière la capacité du dasatinib de causer une HTAP chez les patients prédisposés à une maladie vasculaire pulmonaire.

Case Report

A 73-year-old woman with chronic myeloid leukemia (CML) treated with imatinib was switched to dasatinib because of side-effects including vertigo and altered taste resulting in poor oral intake. After 9 months of dasatinib treatment, she developed exertional dyspnea. A chest x-ray demonstrated small bilateral effusions. Transthoracic echocardiography demonstrated a right ventricular (RV) systolic pressure of 74 mm Hg, a mildly dilated RV with mild-to-moderately reduced systolic function. The left ventricle and valves appeared normal with an ejection fraction of >55%.

She was in New York Heart Association functional class (NYHA-FC) III. No risk factors for pulmonary vascular disease were identified apart from her myeloproliferative disease and treatment with dasatinib. Physical examination revealed a heart rate of 74 beats/min, blood pressure of 143/90 mm Hg, and oxygen saturation of 99% on room air. She was euvolemic and had bibasilar decreased breath sounds with an accentuated pulmonic component of the second heart sound (P2).

Right heart catheterization (RHC) confirmed severe precapillary pulmonary arterial hypertension (PAH) with a significant response to inhaled nitric oxide (Table 1). Unexpectedly, the oxygen saturation in the RV was significantly higher than in the upper superior vena cava (SVC), suggesting the presence of a left-to-right shunt at the atrial level. A chest computed tomographic scan was negative for thromboembolic disease but showed evidence of partial anomalous pulmonary venous connection (PAPVC). Cardiac magnetic resonance (CMR) imaging confirmed PAPVC with the right superior pulmonary vein draining into the SVC associated with a sinus venosus atrial septal defect (ASD; Fig. 1). The pulmonary to systemic blood flow ratio (Qp:Qs) was 1.6.

Because of the vasodilator response on RHC, 30 mg nifedipine daily was started. Dasatinib was discontinued, imatinib was resumed, and she improved significantly over the following 4 months. Previously encountered side-effects due to imatinib did not recur, and her CML continued to be well controlled with no evidence of imatinib resistance. Repeat RHC after 12 months demonstrated normalization of her hemodynamics (Table 1).

Discussion

Dasatinib is a second-line tyrosine kinase inhibitor (TKI) for CML that inhibits BCR-ABL and other protein kinases more potently than imatinib but also has many off-target effects that may lead to markedly different adverse effects than those associated with imatinib.[1–5] This case highlights the rare but increasingly recognized association of dasatinib with

Received for publication June 28, 2019. Accepted August 1, 2019.

Corresponding author: Dr Naushad Hirani, Peter Lougheed Center, 3500 26 Ave NE, Calgary, Alberta T1Y 6J4, Canada. Tel.: +1-403-943-4779.
E-mail: naushad.hirani@albertahealthservices.ca

See page 1604.e3 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.08.002

Table 1. Hemodynamic data

Measure	Baseline RHC		12-month RHC	
	Baseline	Post-NO	Baseline	Post-NO
RA pressure (mm Hg)	15/15 (12)	13/11 (9)	4/2 (2)	4/2 (0)
PA pressure (mm Hg)	78/33 (49)	55/33 (34)	27/8 (14)	29/6 (14)
PAWP (mm Hg)	15/16 (14)	19/15 (15)	3/4 (4)	4/5 (3)
Cardiac output (L/min)	4.57	4.50	5.34	6.11
Cardiac index (L/min/m^2)	2.87	2.83	3.34	3.82
Pulmonary vascular resistance (WU)	7.66	4.22	1.87	1.80

Mean values reported in parentheses.
NO, nitric oxide; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; RA, right atrial; RHC, right heart catheterization; WU, Wood units.

PAH.[1-3] Cases of PAH associated with bosutinib and ponatinib have been reported, but those patients had previously received dasatinib, whereas nilotinib and imatinib have not been reported to cause PAH.[1] Dasatinib-induced PAH should be managed by means of prompt discontinuation of dasatinib.[1,3] The decision to restart another TKI must be based on multidisciplinary discussion considering the patient's prognosis for CML as well as the risk of PAH recurrence when treated with alternate TKIs, such as bosutinib and ponatinib.[1]

The pathogenesis of dasatinib-induced PAH remains incompletely understood. Animal studies suggest that dasatinib may contribute to excess mitochondrial reactive oxygen species (ROS) in the pulmonary arterial endothelium, which, in combination with a "second hit," could result in endothelial cell toxicity and dysfunction.[4] The present report is the first of dasatinib-induced PAH with coexisting congenital heart disease, lending further support to the "second hit" hypothesis.[1,3,4] In our case, the "second hit" was likely left-to-right shunting from the ASD and PAPVC.

The first series of patients with dasatinib-induced PAH estimated an incidence of at least 0.45%.[2] PAH typically develops after 8 to 48 months and does not appear to be dose dependent.[1−3] A series of 21 patients with dasatinib-induced PAH found that the majority were in NYHA-FC III-IV. Despite dramatic improvement in hemodynamics after discontinuation of dasatinib, 37% of patients were left with persistent PAH.[3] In that study, the baseline median mean pulmonary arterial pressure (mPAP) was 45 mm Hg and pulmonary vascular resistance (PVR) was 6.1 Wood units.[3] During follow-up, NYHA-FC improved, median mPAP improved to 26 mm Hg, and median PVR decreased to 2.6 Wood units.[3]

As observed in our patient, dasatinib can also cause pleural effusions, which are a common complication, occurring in at least 25% of patients.[1] The effusions are typically exudative and are not thought to be related to left-sided heart failure but more likely due to increased endothelial permeability, mediated by ROS.[5]

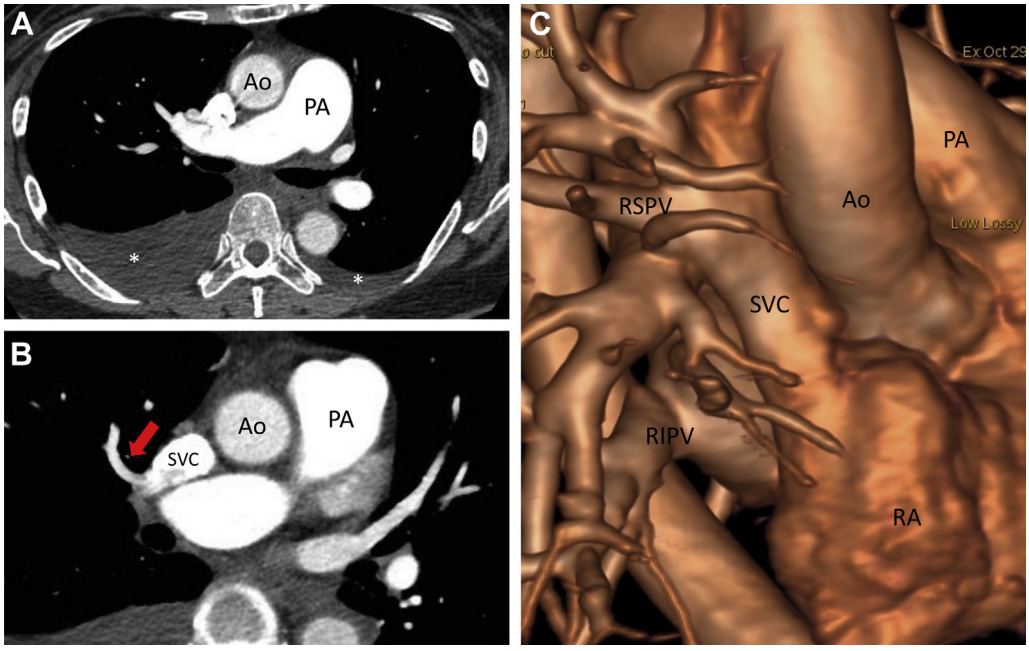

Figure 1. (**A**) Computed tomography (CT) image showing pleural effusions (**white asterisks**) and enlargement of the pulmonary artery (PA) compared with the aorta (Ao). (**B**) CT image showing anomalous connection between right superior pulmonary vein (**arrow**) and the superior vena cava (SVC). (**C**) Three-dimensional cardiac magnetic resonance reconstruction, showing the anomalous right superior pulmonary vein (RSPV) draining into the SVC. The right inferior pulmonary vein (RIPV) drains normally into the left atrium.

There are currently no known biomarkers or methods to identify patients predisposed to PAH or pleural effusions after dasatinib initiation. Baseline pretreatment chest x-ray and echocardiography could help rule out pre-existing pleural effusions, pulmonary hypertension, and intracardiac shunts.[1] Further research is needed to identify the mechanisms of TKI-induced PAH and to identify which patients are at higher risk of developing PAH before initiating therapy.

Conclusion

Our case illustrates the association of dasatinib with pleural effusions and PAH in the context of an ASD with PAPVC. These potentially serious adverse effects should be promptly recognized, because they can be completely reversible if dasatinib is discontinued.

Disclosures

E.O. has no conflicts of interest to disclose. J.W. has received grants, personal fees, and nonfinancial support from Actelion, personal fees and nonfinancial support from Bayer, personal fees from Novartis, grants from the European Respiratory Society, and grants from the Canadian Vascular Network, outside of the submitted work. N.H. has received grants and personal fees from Actelion, and grants from Bayer, Bellerophon, Northern Therapeutics, and United Therapeutics, outside of of the submitted work.

References

1. Weatherald J, Chaumais MC, Montani D. Pulmonary arterial hypertension induced by tyrosine kinase inhibitors. Curr Opin Pulm Med 2017;23:392-7.

2. Montani D, Bergot E, Gunther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128-37.

3. Weatherald J, Chaumais MC, Savale L, et al. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. Eur Respir J 2017;50:1700217.

4. Guignabert C, Phan C, Seferian A, et al. Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. J Clin Invest 2016;126:3207-18.

5. Phan C, Jutant EM, Tu L, et al. Dasatinib increases endothelial permeability leading to pleural effusion. Eur Respir J 2018;51.