Severe Recurrent Pulmonary Arterial Hypertension from Bosutinib Following Dasatinib Induced Pulmonary Toxicity

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Background

- Inhibitors of BCR-ABL Tyrosine Kinase (TKIs) revolutionized treatment of chronic myelogenous leukemia (CML), but are associated with important cardiovascular complications including hypertension, pulmonary hypertension, QTc prolongation, and vascular toxicity (peripheral arterial disease, cerebrovascular disease, and coronary artery disease).[1]

- **Dasatinib,** a 2nd generation TKI, is associated with pleural/pericardial effusions and pulmonary arterial hypertension (PAH).[2]

- **Bosutinib** is a 2nd generation TKI with low rates of cardiac and vascular adverse effects. However, recurrence of effusions with bosutunib is reported in patients after prior effusions from dasatinib.[1]

- **We present the case of a patient with history of dasatinib induced pulmonary hypertension who develops recurrent severe pulmonary hypertension on bosutinib therapy.**

Clinical Data

- **Pulmonary Function Tests normal**
- **HIV negative**
- **RF negative**
- **ANA positive 1:40**
- **Ventilation/Perfusion scan normal**

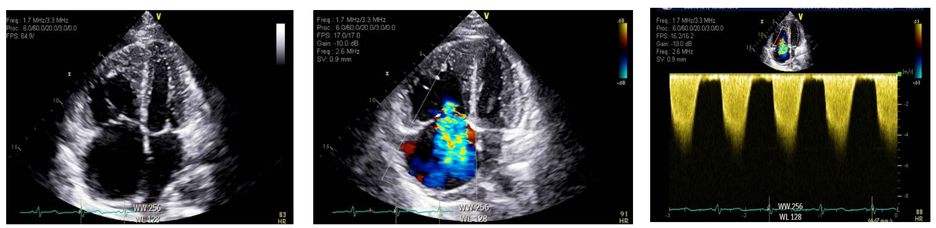
Disclosures: none

Case Presentation

A 41 year old woman with chronic phase CML on maintenance bosutinib therapy presented with progressive shortness of breath.

- Her past medical history is notable for chronic migraine headaches.
- At the time of CML diagnosis, she was treated with dasatinib 100mg daily. After 2 years of dasatinib therapy, she developed shortness of breath and was diagnosed with dasatinib induced pleural effusions, mild/moderate PAH, and moderate pericardial effusion with tamponade physiology. A right heart catheterization (RHC) showed the following: [**PA 42/20 (mean 27), PCWP 7, PVR 3.3 WU**)].
- She underwent a thoracentesis and pericardiocentesis. Dasatinib was discontinued and switched to imatinib. 6 months later, PA pressures normalized.
- Switched to bosutinib due to intolerable imatinib-related GI toxicity.

After 1.5 years of bosutinib, she developed progressive dyspnea. CT chest angiography was negative for pulmonary embolism. A TTE showed severe RV enlargement and severe pulmonary hypertension (RVSP > 70mmHg). RHC confirmed severe pre-capillary PAH (**PA 85/45, PCWP 10, PVR 16.6 WU**) unresponsive to O2 or NO.

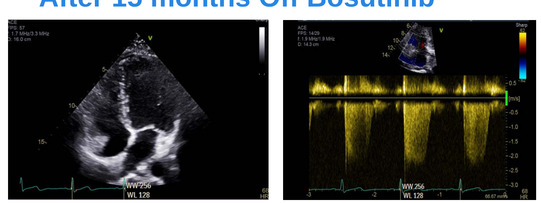


Bosutinib was discontinued, and PA pressures normalized after 6 months of treprostinil. She was switched to tadalafil and ambrisentan for an additional 6 months. A repeat RHC showed complete reversal of PAH [**PA 26/8, PCWP 5, PVR 2.36 WU].**

Nilotinib prescribed for further treatment w/ plans for close surveillance by echo

	Dasatinib	Bosutinib	Off Bosutinib
PA	42/20 (27)	85/45	26/8
PCWP	7	10	5
PVR	1.7 W	16.6 WU	2.36 WU

After 15 months Off Bosutinib



Discussion

Proposed mechanisms of dasatinib related PAH include Src kinase inhibition in the lungs and direct endothelial damage.[3] Bosutinib also inhibits Src kinase and has been associated with recurrent PAH in patients previously exposed to dasatinib.[4-7] Shared Src kinase inhibition may mediate the sequential pathogenesis of dasatinib and bosutinib induced PAH, but the role of underlying vascular substrate in predisposing to bosutinib toxicity merits further investigation

PAH should be recognized as a possible toxicity of bosutinib among patients previously treated with dasatinib, and close cardiac surveillance with echocardiography may be warranted in patients with prior history of TKI induced pulmonary or vascular toxicity.

References

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