

Control Number: 33

Abstract Category: Clinical Case Challenge in Cardio-Oncology

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

ABSTRACT BODY

Background and Purpose

Pulmonary arterial hypertension (PAH) is a well described toxicity of dasatinib, a 2nd generation BCR-ABL tyrosine kinase inhibitor (TKI) used to treat chronic myelogenous leukemia (CML). We present a case of severe PAH during treatment with bosutinib, a 3rd generation TKI.

Case Description and Outcomes

A 41 year old woman with a history of migraine and CML presented with progressive shortness of breath. She was treated previously with dasatinib for 3 years until developing pleural and pericardial effusions, as well as PAH [PA 42/20 (mean 27), PCWP 7, PVR 3.3]]. Both resolved after switching to imatinib. Imatinib was later changed to bosutinib for intolerable diarrhea. 12 months later she developed pulmonary embolism, managed with anticoagulation. After 17 months of bosutinib, she developed recurrent dyspnea and signs of right heart failure. Computed Tomography (CT) angiography and ventilation/perfusion studies were negative. Echocardiography showed pulmonary artery systolic pressure > 100mmHg and no shunt. Catheterization revealed severe pre-capillary PAH unresponsive to oxygen or nitric oxide [PA 85/45, PCWP 10, PVR 16.6]. This improved with stopping bosutinib and treatment with treprostinil, transitioned to tadalafil and ambrisentan. After 12 months, catheterization showed resolution of PAH [PA 26/8, PCWP 5, PVR 2.36]. Nilotinib was prescribed and close monitoring by echocardiogram is planned.

Discussion

TKIs dramatically improve prognosis of CML, but are associated with important vascular toxicities including hypertension, thrombosis, arterial ischemia, and PAH. Possible mechanisms include Src kinase inhibition in the lungs and direct endothelial damage. Bosutinib is used in the second line setting, often after intolerance to other TKIs. Bosutinib, also inhibits Src kinase, and is associated with recurrent PAH in patients previously exposed to dasatinib. Shared Src kinase inhibition may mediate pathogenesis of recurrent PAH, although further investigation is needed. PAH should be recognized as a possible toxicity of bosutinib among patients previously treated with dasatinib. Close cardiac surveillance with echocardiography may be warranted for patients with prior history of TKI induced pulmonary toxicity.

References

1. Damrongwatanasuk R, Fradley MG. Curr Treat Options Cardiovasc Med. 2017;19(4):24.
2. Guignabert C, et al. J Clin Invest. 2016;126(9):3207
3. Hickey PM, et al.. Eur Respir J. 2016;48(5):1514
4. Riou M, et al. Eur Respir J. 2016;48(5):1517
5. Seegobin K, et al. Pulm Circ. 2017;7(4):808.
6. Cornet L, et al. Eur Respir J. 2019;53(5):10.1183