Tyrosine Kinase Inhibitor–Induced Pulmonary Arterial Hypertension

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Université Paris–Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin Bicêtre, France The treatment of the malignant hematological diseases has been revolutionized by the use of tyrosine kinase inhibitors (TKI): for example, imatinib in patients with chronic myeloid leukemia. Dasatinib, a second-generation TKI, has been reported to induce severe pulmonary arterial hypertension (PAH). The mechanism of PAH development is presumed to be endothelial cell toxicity through the production of mitochondrial reactive oxygen species. There are other TKIs that are reported to cause PAH, such as: ponatinib, bosutinib, lapatinib, and lorlatinib. The management of PAH due to TKIs primarily involves stopping the TKI treatment, which can lead to clinical and hemodynamic normalization. A third of the patients who develop PAH can have persistent symptoms of dyspnea and right heart failure even after the interruption of the TKIs. For these patients, use of specific PAH treatment is indicated along with close follow-up. In rare cases, TKI-induced PAH can be fatal. Thus, early screening for PAH diagnosis and proper management is required.

Chronic myeloid leukemia (CML) is a myeloproliferative disease resulting from the activation of the BCR-ABL1 oncogene.¹ The incidence of CML increases with age and is estimated at 1.75 per 100,000 in the United States.² CML is characterized by the presence of the chromosomal translocation t(9;22), leading to the formation of the Philadelphia (Ph) chromosome. This mutation leads to the creation of the tyrosine kinase BCR-ABL1, which is responsible for the growth, survival, and proliferation mechanisms in CML cells.³⁻⁵ Therefore, the inhibition of the BCR-ABL1 kinase is key to disease control.⁶

Tyrosine kinase inhibitor (TKI) therapy has revolutionized the treatment of CML.⁷ Nowadays, there are 5 TKIs in use for the treatment of CML: imatinib, nilotinib, dasatinib, bosutinib, and ponatinib.⁸ The recommended first-line treatment in CML consists of imatinib or nilotinib, whereas dasatinib, bosutinib,

and ponatinib are used as second-line therapies. Imatinib was the first generation of designer therapies developed at the beginning of the 2000s to target the BCR-ABL1 tyrosine kinase and was a monumental success in the treatment of CML patients.⁹ In cases of resistance to imatinib, dasatinib was one of the first available second-line options, with good responses and reduced progression to advanced disease.¹⁰ In vitro, dasatinib has 325-fold greater activity in inhibiting wild-type ABL1 kinase than imatinib,¹¹ translating to improved long-term progression-free survival in CML.¹² Bosutinib is another TKI, used for patients who develop resistance or intolerance to other TKI treatments.¹³ Ponatinib is the only TKI active against the T315I mutation, found in 20% of resistant CML cases and which interferes with the binding of TKIs to BCR-ABL1.¹⁴ One study showed that patients with a T315I mutation had good responses to ponatinib, whereas other TKIs were not effective.¹⁵ It is also used in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)¹⁶ and resistant mutations in CML.¹⁷ Pulmonary hypertension (PH) has also been described after exposure to TKIs with other targets. Lapatinib is a TKI used in the treatment of human epidermal growth factor receptor 2-positive breast cancer.¹⁸ Lorlatinib is a new third-gen-

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eration TKI used in advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kinase (ALK) rearrangement.¹⁹

Investigating TKI toxicity is very important, as patients with CML may require lifelong treatment with a TKI and because some complications can be fatal if not diagnosed and treated expediently.¹ The most frequently described side effects of TKI therapy involve the cardiovascular, metabolic, and pulmonary systems such as QT interval prolongation, heart failure, sudden death, systemic arterial hypertension, thrombotic events, peripheral arterial occlusive disease, hepatic failure, dyslipidemia, hyperglycemia, pneumonitis, pulmonary arterial hypertension (PAH), and pleural effusions (Table 1).^{1,10} These complications can appear within the first months or even years after the treatment initiation.²⁰

Interestingly, imatinib showed encouraging results in animal studies as a treatment for PAH, having properties such as blocking platelet-derived growth factor and c-KIT signaling, which are involved in PAH pathogenesis. It was proposed that imatinib could prevent abnormal vascular proliferation and be used as PAH treatment.^{21,22} Unfortunately, the results obtained in animal models did not mirror the results obtained in a human clinical trial. Although imatinib showed clinical efficacy and met the clinical trial's primary endpoint, severe side effects of edema, anemia, and an increased risk of subdural hematoma were seen.^{23,24} As a result, imatinib was not approved by regulatory agencies and is not currently recommended as a PAH therapy.²⁵ Consequently, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PAH concluded that using TKIs as a treatment for PAH had unsatisfactory results.²⁶

TKI-INDUCED PAH: EPIDEMIOLOGY AND CLINICAL PRESENTATION

PAH diagnosis requires an invasive procedure, right heart catheterization, with confirmation of precapillary PH, defined as a mean pulmonary arterial

pressure (mPAP) ≥25 mm Hg at rest, a pulmonary arterial wedge pressure ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (WU).²³ In myeloproliferative disorders, we can observe 3 types of precapillary PH: 1) precapillary PH due to the underlying hematological disorder, which appears late in the disease course; 2) chronic thromboembolic PH; and 3) drug-induced PAH.27 TKI-induced PAH has a low incidence and appears as a late complication in TKI treatment. For dasatinib-induced PAH, an incidence of at least 0.45% has been reported, developing after a period of 8 to 48 months of administration.^{17,20} In comparison, pleural effusions are a frequent complication of dasatinib, having an incidence of 14% to 35%.²⁴ The dasatinib dosage does not seem to be correlated with the risk of developing PAH.²⁸

In 2012, Montani et al reported the first series of 9 patients with dasatinib-associated PAH from the French PH registry.²⁰ Eight of the nine patients were female, with a median age of 51 years. Eight patients required second-line therapy with dasatinib because of resistance to or intolerance of first-line imatinib. The median delay between dasatinib initiation and the PAH diagnosis was 34 months and the median dose of dasatinib used was 100 mg per day. At the time of PAH diagnosis, patients presented with progressive exertional dyspnea, and functional impairment (New York Heart Association [NYHA] functional class II in 2 patients, III in 4 patients, and IV in 3 patients). The median 6-minute walk test distance was 242 meters. The right heart catheterization showed severe precapillary PH with a median mPAP of 46 mm Hg, median cardiac output (CO) of 6 L/min, and a median PVR of 5.9 WU. Following PAH diagnosis, additional evaluation found that 6 patients had bilateral pleural effusions on computed tomography and 3 patients had mild pericardial effusions on echocardiography. While most patients had moderate or severe PAH at diagnosis, by the time of 4-month follow-up after dasatinib discontinuation, 8 patients were significantly improved. Two patients died at follow-up (1 unexplained

Table 1. Risk of PAH With TKIs

Proven	Dasatinib ^{20,29}
Possible	Bosutinib, ^{31,32} ponatinib, ³⁵ lapatinib, ³³ lorlatinib ³⁶
Unlikely	Imatinib, ^{1,20,34} nilotinib ²⁸

sudden death and 1 cardiac failure, 8 and 12 months respectively after dasatinib cessation).²⁰

In 2017, as a continuation of the previous study, the long-term follow-up of 21 cases of dasatinib-induced PAH from France were reported.²⁹ All patients were receiving dasatinib at the time of PAH diagnosis. Fifteen patients were female, and the median age was 52 years. PAH diagnosis occurred after median dasatinib treatment duration of 42 months. The median dose of dasatinib was 100 mg per day. All patients had clinical and functional impairment: 16 patients presented with NYHA functional class III/IV and the median 6-minute walking distance was 306 meters. The right heart catheterization confirmed precapillary PH in 19 patients, and combined pre- and postcapillary PH in 2 patients. Median mPAP was 45 mm Hg; cardiac index 3.3 l/min/m², and PVR was 6.1 WU. Dasatinib was discontinued in all patients; in addition, 9 patients received specific PAH treatment and 2 patients received calcium channel blockers alone. After a median follow-up of 24 months, 19 patients improved NYHA functional class, and the median 6-minute walking distance increased to 430 meters. The median mPAP decreased from 45 to 26 mm Hg, and the median PVR decreased from 6.1 to 2.6 WU.

Importantly, despite dasatinib discontinuation and frequent clinical improvement, an elevated mPAP and PVR persisted in 7 patients (37%). One patient presented hemodynamic deterioration after withdrawal of PAH-specific treatment, and 2 patients had normal hemodynamic parameters, but demonstrated exercise PH. These data suggest that dasatinib could produce irreversible pulmonary vascular dysfunction and remodeling.²⁹ No predictive factors were found to identify patients who were at higher risk of developing persistent dasatinib-induced PAH.^{20,29}

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Another report of 5 patients found almost completely reversible PAH after treatment cessation, but these patients did not achieve a full hemodynamic recovery long term. It is worth mentioning that none of the patients required specific PAH treatment.³⁰ Shah et al showed that in 58% of the 41 patients reported with dasatinib-induced PAH confirmed by right heart catheterization, dasatinib cessation was followed by total remission of PAH.¹⁰

Since 2016, cases of PAH have been reported with other TKIs: lapatinib, bosutinib, ponatinib, and lorlatinib, but the frequency of such occurrence is less defined.^{27,31-34} The first published case report of bosutinib-associated PAH was in 2016.³¹ Another paper from 2016 reported 4 cases of pulmonary vascular and pleural complications related to bosutinib. Two patients presented with bosutinib-induced PAH in the context of prior dasatinib-induced PAH, requiring bosutinib interruption and introduction of specific PAH treatment using endothelin receptor antagonist and phosphodiesterase (PDE-5) inhibitors, with a good outcome.³² The other 2 patients presented exudative lymphocytic pleural effusions with a rapid remission after bosutinib interruption. However, it could not be excluded that these cases were potentiated or facilitated by the prior exposure to dasatinib. These data suggest a common mechanism of pulmonary vascular injury between dasatinib and bosutinib.³²

A recent study reported 6 cases of lapatinib-induced PAH in patients with normal echocardiographic measurements before treatment initiation and an increase in the systolic pulmonary artery pressure (SPAP) during lapatinib. Of the 6 patients, 3 underwent a right heart catheterization, but only 1 patient ultimately had confirmed precapillary PH, which normalized after lapatinib discontinuation.³³

There also has been a case report of ponatinib-induced PAH after 6 months of therapy, in a patient with previous exposure to dasatinib. Dasatinib was withdrawn due to pleural effusions development. The echocardiography was normal at the moment of ponatinib initiation.³⁵ The first 2 cases of lorlatinib-induced PAH were reported in 2018 in patients treated for metastatic NSCLC with ALK expression. They developed severe precapillary PAH confirmed by right heart catheterization, 2 months after the treatment initiation. The lorlatinib withdrawal associated with specific PAH treatment led to rapid clinical and hemodynamic improvement.³⁶

TKI-INDUCED PAH: MANAGEMENT AND FOLLOW-UP

After PAH confirmation with right heart catheterization, TKI treatment should be immediately stopped. Patients should be referred to expert PH centers for proper diagnosis, management, and follow-up. In the case of dasatinib, reports suggest that PAH may be partially or completely reversible after the dasatinib discontinuation.^{20,30} However, animal models have shown that dasatinib may induce irreversible vascular injury and remodeling.³³

The first histopathological proof of the presence of irreversible lesions comes from a case of a 32-year-old male who had dasatinib-induced PAH after a 3-year treatment with dasatinib for CML (BCR-ABL1+). He had severe PAH, treated with dasatinib discontinuation and PAH-specific treatment (PDE-5 inhibitor, endothelin receptor antagonist, and intravenous treprostinil infusion). Even with this treatment regimen, his condition worsened necessitating lung transplantation.³¹ The analysis of the explanted lungs showed atherosclerosis and typical histological characteristics of PAH³²: major vascular wall remodeling with medial hypertrophy and concentric laminar intimal thickening, plexiform lesions, without signs of pulmonary veno-occlusive or thromboembolic disease.³¹

For patients with CML who develop TKI-induced PAH, another TKI can be used to replace the responsible drug. Currently, after dasatinib disruption, nilotinib or imatinib have been used with success, without relapse of PAH.^{20,30,35,37,38} If another TKI therapy is used, close and long-term follow-up should be undertaken in order to identify recurrent PAH at an early stage. Even after PAH remission, patients should be carefully followed with echocardiography and suspected relapses should be confirmed by right heart catheterization.

The international consensus for CML follow-up states that in cases of good response for more than 2 years, the TKI therapy can be stopped, with regular testing of RT-PCR BCR-ABL1.²⁷ Even though PAH is a rare but severe complication, there are 5 reports of TKI-induced PAH deaths.^{29,39}

THE PATHOPHYSIOLOGY OF TKI-INDUCED PAH

The number of reported cases of PAH associated with dasatinib demanded further investigation and, despite major scientific breakthroughs, the pathophysiologic mechanisms remain incompletely understood. In order to understand the pathophysiology of drug-induced PAH, studies on rats or in vitro were pursued, leading to multiple proposed hypotheses to explain the mechanism of PAH development. A central concept is that endothelial dysfunction is a key element to understanding the mechanism of drug-induced PAH and leads to vascular proliferation and migration of pulmonary vascular smooth muscle cells.⁴⁰

Dasatinib damages the pulmonary artery endothelium by producing mitochondrial reactive oxygen species as shown by Guignabert et al.³⁷ It is presumed that mitochondrial reactive oxygen species are directly toxic to endothelial cells, particularly in association with a secondary risk factor, although these second risk factors are currently uncertain (Figure 1). In fact, patients being treated with dasatinib have demonstrated elevated levels of endothelial injury markers, like ICAM-1, sVCAM-1, and sE-selectin.^{39,41,42} Secondary factors, such as hormonal or immunological factors, could increase the risk of PAH in patients on TKIs. Interestingly, while CML has a greater incidence in men,³⁸ the majority of patients with dasatinib-induced PAH are women.²⁰ The appearance of pleural effusions associated with dasatinib treatment may also be explained by the increase of the endothelium permeability, and not by left ventricular failure or



Figure 1: Potential mechanisms of dasatinib-induced endothelial dysfunction and pulmonary arterial hypertension. Reprinted with permission from Weatherald J, Chaumais MC, Montani D. Pulmonary arterial hypertension induced by tyrosine kinase inhibitors. *Curr Opin Pulm Med.* 2017;23(5):392-397. DOI: 10.1097/MCP.00000000000412.

direct cardiotoxicity.³⁷ Other hypotheses propose that the development of pleural effusion after dasatinib treatment is related to an autoimmune mechanism or by the PDGFR- β .^{20,42-44}

Dasatinib has a greater inhibitory effect on BCR-ABL1, c-KIT, and PDGF than imatinib, and it also can inhibit the Src family of kinases,^{20,41,43} leading to smooth muscle cell depolarization, vasoconstriction, and consequently, an increase in pulmonary arterial pressure.44 This fact could explain the improvement or remission of PAH after the TKI interruption; however, Guignabert et al showed that PAH development was independent of Src inhibition.³⁷ These data suggested that dasatinib alone predisposed to PAH, but probably needs a secondary pulmonary vascular insult in order to produce PAH. This idea has been supported by experimental studies in rats in which dasatinib administrated alone was not sufficient to develop PAH and required another predisposing factor.⁴¹

Regarding dasatinib-induced pleural effusions, a recent study showed that dasatinib diminishes transendothelial electrical resistance/impedance and increases permeability.⁴⁵ Using primary human pulmonary microvascular and pulmonary artery endothelial cells, it was shown that dasatinib, but not imatinib or nilotinib, provoked important endothelial leakage, associated with Src inhibition and secondary activation of ROCK signaling.45 It also induces superficial cytoskeletal reorganization and alters cell morphology, reducing stiffness of both the micro- and macrovascular cells. The clinical used dose of dasatinib of 100 mg per day produced significant loss of the continuous distribution of VE-cadherin, indicating junctional disruption at the endothelial level.45

PAH SCREENING

It is important to perform a chest x-ray and echocardiography before starting treatment with TKIs, particularly in patients that have already suffered from cardiac or pulmonary diseases.^{1,20} In patients on TKI treatment, the occurrence of symptoms such as dyspnea, fatigue, chest pain, syncope, and signs of right heart failure should prompt further evaluation, including a chest x-ray and an echocardiogram.^{26,30,46} The probability of PH is high if the peak tricuspid regurgitation velocity is >3.4 m/s or if it is between 2.9-3.4 m/s and associated with other echocardiographic findings suggestive of PH: right ventricle/left ventricle basal diameter ratio >1.0, flattening of the interventricular septum, right ventricular outflow Doppler acceleration time <105 msec, midsystolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/sec; pulmonary artery

diameter >25 mm, inferior vena cava diameter >21 mm with decreased inspiratory collapse, or right atrial area >18 cm².²⁶ If echocardiography is suspicious for PAH, right heart catheterization should be performed.^{1,20,26} Although they do not have specificity for PAH, natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-ProB-NP) should also be performed, as they can be predictive of prognosis and can be used to assess patients during follow-up.^{30,46}

CONCLUSION

Treatment with TKIs may rarely cause PAH. Dasatinib is the most common TKI associated with PAH and in most cases, PAH improves or resolves after drug discontinuation. The complex mechanism of PAH development and relapse with dasatinib and other TKI drugs is not fully understood; however, endothelial dysfunction with obliteration, proliferation, inflammation, and remodeling of small pulmonary arteries that leads to increased PVR and progressive right ventricular failure is currently the proposed mechanism. PAH induced by TKIs should be evaluated and managed in expert centers. After discontinuation of the implicated drug and switch to another TKI therapy, most patients achieve complete hemodynamic normalization. However, use of PAH-specific therapies is recommended in severe cases and in those patients who do not achieve hemodynamic resolution with discontinuation of the TKI. Patients who develop PAH during TKI therapy should have long follow-up by echocardiography and right heart catheterization, if needed. No factors have been identified to predict patients at higher risk for developing PAH with TKI use. Monitoring echocardiography should be performed, especially in older patients with prolonged TKI treatment period. The mechanism of PAH pathogenesis from TKIs is still incompletely understood and future studies will be needed in order to identify the patient profile at risk of PAH development.

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