Review Article

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Pulmonary hypertension with dasatinib and other tyrosine kinase inhibitors

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Abstract

Dasatinib and other tyrosine kinase inhibitors are commonly utilized in the management of chronic myelogenous leukemia. Pulmonary hypertension is an important adverse event associated with dasatinib. Mechanisms for pulmonary hypertension include pulmonary endothelial injury, apoptosis, and increased susceptibility to other triggers for pulmonary hypertension. The diagnosis is suspected based on symptoms, suggested by echocardiographic findings, and confirmed with right heart catheterization. Management includes discontinuation of dasatinib and initiation of pulmonary vasodilators. Persistent pulmonary hypertension is present in up to one third of patients after cessation of dasatinib. Other tyrosine kinase inhibitors, including bosutinib, lapatinib, and ponatinib have also been implicated in pulmonary hypertension in small series, although evidence for causation is less robust. A high index of suspicion, continued vigilance for pulmonary hypertension with long-term use, and early therapy are important in optimizing outcomes in this population.

Keywords

Right heart failure, pulmonary vasodilators, drug-induced pulmonary hypertension

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Introduction

Pulmonary hypertension (PH)

PH is a disease of the pulmonary vasculature, which leads to right ventricular (RV) pressure overload, hypertrophy, dilation, and ultimately right heart failure if not recognized and adequately treated.[1,2]

PH is classified into five subtypes. Group I (pulmonary arterial hypertension (PAH)) is characterized by morphological changes at the distal pulmonary arterial vasculature leading to increase in pulmonary vascular resistance. Group I includes idiopathic, heritable, drug-induced, toxin-induced PH, as well as PH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, and schistosomiasis. The majority of clinical trials of therapeutic agents in PH have studied Group I patients. Groups II–V PH is secondary to other conditions, such as left heart disease, chronic lung disease, thromboembolic disease and other pulmonary arterial obstructions, and other unclear and/or multifactorial mechanisms.

PH is usually suspected when a patient has dyspnea, exertional intolerance, signs of right heart failure, or syncope, in conjunction with an echocardiographic elevation in the RV systolic pressure and/or pulmonary artery systolic pressure over 40 mmHg. The definitive hemodynamic diagnosis of PAH is made with right heart catheterization (RHC). PAH has been defined as mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest in the absence of elevated pulmonary capillary wedge pressure ($\leq$ 15 mmHg) and pulmonary vascular resistance (PVR) $>$ 3 Woods Units (WU). The Sixth World Symposium on Pulmonary Hypertension (2018) proposed an updated hemodynamic definition of PH as mPAP $>$ 20 mmHg, with associated PVR 3 WU or greater required to diagnose precapillary PH.[3] The treatment of PH is directed toward treating the underlying etiology,

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discontinuing offending agents, and initiating pulmonary vasodilators particularly in Group I, Group IV, and in selected patients with other etiologies of PH.[1,2]

Currently commercially available pulmonary vasodilators have one of several mechanisms: phosphodiesterase inhibition, soluble guanylate cyclase stimulation, endothelin receptor antagonism, prostacyclin analogues, selective IP prostacyclin-receptor antagonism. Despite the rapid development of many drugs to treat PAH, patients are still diagnosed late, remain untreated, or inadequately treated. Survival has improved with modern combination therapies, and three-year survival is now in the 70% range, making it imperative to maintain a high index of suspicion and awareness of different agents associated with PH, since early diagnosis, withdrawal of the offending agent, and early treatment may help prevent irreversible RV failure and prolong survival.[4,5]

Dasatinib

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) used for treatment of newly diagnosed adults with Philadelphia chromosome positive (ph+) chronic myelogenous leukemia (CML) in chronic phase; or ph+ chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib and Ph+ acute lymphoblastic leukemia with resistance or intolerance to prior therapy. It was approved in the United States in November 2007 for treatment of chronic phase CML. Data suggest that dasatinib is associated with higher rate of cytogenic remission in imatinib-resistant patients and in chronic phase CML.[6] In addition, dasatinib is currently being tested in other malignancies including melanoma, breast, lung, ovarian, and head and neck cancer.[7] However, reports of PH in patients receiving dasatinib led to the 2015 European Society of Cardiology guidelines reporting a likely association of PH with dasatinib, defined as "a single-centre case – control study or multiple case series demonstrate an association or if clinical and haemodynamic recovery occurs after stopping exposure."[1] Based on accumulated evidence so far, the Sixth World Symposium on Pulmonary Hypertension (2018) has now classified the association of dasatinib with PH as definite.[3]

Epidemiology

The first major population-based incidence was reported from the French PH registry. Among 2900 patients receiving dasatinib between 2006 and 2010, nine patients developed PH in the registry, and four additional cases of dasatinib-associated PH were reported to French regulatory agencies; therefore, the lowest estimate of PH in dasatinib-associated patients was 0.45%.[6] In an updated report from the Bristol-Myers-Squibb (BMS) pharmacovigilance database of patients who received dasatinib between June 2006 and October 2013, 41 patients had PAH diagnosed by RHC. It was estimated that approximately 75,000 people had been prescribed dasatinib during that time period.[8] In a pooled population of 2712 patients treated with dasatinib in 11 clinical trials, six (0.2%) were found to have PH.[8] A phase 3 study of 670 patients on dasatinib followed for seven years, reported incidence of any PH as diagnosed by invasive and noninvasive tests at 2.4% (16 patients). Only one case of PAH confirmed by RHC was reported, suggesting that not all patients suspected of having PH were being assessed with a RHC to document PAH.[9] A study of 212 patients at 17 Australian institutions reported a 5% incidence of PH as measured by echocardiogram.[10] A phase II trial of 113 children with CML treated with dasatinib and followed for a median of 48.4 months found no cases of PH.[11]

The true incidence and prevalence of PAH in association with dasatinib has been challenging to estimate because (1) many of the studies in the published literature are case reports or series that do not report the total number of patients receiving dasatinib at those institutions during that time period; (2) large-scale formal echocardiographic screening studies for asymptomatic PH have not been performed; (3) suspected cases have not uniformly been confirmed with catheterization; and (4) symptoms of PH may overlap with other, more common, complications of dasatinib, such as pleural effusions. Despite these limitations, based on available estimates, PH appears to be an important complication of dasatinib.

Pathogenesis

Dasatinib, imatinib, nilotinib, bosutinib, lapatinib, and ponatinib are commonly used TKIs. Different drugs have different potencies and effects on breakpoint cluster region-Abelson leukemia (BCR-ABL). These drugs target not only BCR-ABL but several other molecules including c-ABL, c-KIT, platelet-derived growth factor receptor, and SRC-tyrosine kinase. It is thought to be the varying specificities of the different drugs for these additional targets that are responsible for the differential association of PH with some TKIs, in particular dasatinib. Proteomic analysis of imatinib, nilotinib, and dasatinib revealed that dasatinib bound over 30 tyrosine and serine/threonine kinases, substantially more than imatinib and nilotinib. Furthermore, there were important differences in the interaction profiles of the three drugs.[12] SRC kinases are important in vascular regulation, including vasodilation and vascular proliferation,[6,13,14] and SRC inhibition has been postulated to lead to pulmonary vascular dysregulation and PH in association with dasatinib.[15] However, recent data suggest that at least some pathways of PH associated with dasatinib may be independent of SRC inhibition.[16] It is also important to note, however, that most patients diagnosed with PH on dasatinib had received other chemotherapeutic agents, which along with the underlying myeloproliferative disease, could lead to some confounding of dasatinib effects.

An important study by Guignabert and colleagues highlights several pathophysiologic findings. In rats,

pretreatment by dasatinib by itself did not lead to PH, but led to an exaggerated response to monocrotaline and chronic hypoxia. Dasatinib increased markers of endothelial dysfunction including soluble ICAM-1, soluble VCAM-1, and soluble E selectin; attenuated hypoxic vasoconstriction; and induced pathways implicated in endoplasmic reticulum stress in rats. In cultured human pulmonary endothelial cells, dasatinib induced apoptosis in a dose-dependent manner, and the mechanism was likely related to mitochondrial reactive oxygen species and independent of its action on Src family kinases. Finally, humans treated with CML treated with dasatinib had higher levels of sICAM-1, sVCAM-1, and sE-selectin compared to those treated with imatinib suggesting endothelial toxicity. The authors conclude that dasatinib causes endothelial toxicity, and while it may not necessarily cause PH by itself, increases susceptibility to PH in conjunction with other factors.[16]

A study on a rat model found that dasatinib increased pulmonary arterial pressure, and that the Rho-kinase inhibitor Y27632 partially reversed the changes in vitro and ex vivo, and co-administration of Y27632 blunted the increased pulmonary response to dasatinib, suggesting potential targets for intervention.[17]

A recent study utilizing the World Health Organization pharmacovigilance database evaluated 28 protein kinase inhibitors and found that dasatinib, bosutinib, ponatinib, ruxolitinib, and nilotinib displayed pharmacovigilance signals for association with PAH. When these pharmacological signals were correlated with the affinity for different targets of interest, the signals were associated with four nonreceptor protein kinases belonging to Src protein kinase pathway (c-Src, c-Yes, Lck, Lyn) as well as TEC. Furthermore, the dasatinib affinity profile for protein kinases implicated in PAH was unique.[18]

Early reports suggested that dasatinib-related PAH may be reversible upon discontinuation of dasatinib. However, more recent data suggest that PAH may persist in over one third of patients despite dasatinib discontinuation.[19] Daccord and colleagues reported on pathologic findings on explanted lungs of a patient with CML who developed PAH on dasatinib, which worsened on nilotinib despite vasodilator therapy and required lung transplantation. They observed typical lesions of chronic PAH, including medial hypertrophy, concentric laminar intimal thickening, and plexiform lesions.[20] These findings of chronic and potentially nonreversible findings support the recommendation of close long-term follow-up for persistent/worsening clinical disease.

Clinical manifestations

Common symptoms of PH are shortness of breath and exertional intolerance. Patients with dasatinib commonly (up to 35%) develop pleural effusions, which is not related to PH, but clinical symptoms of pleural effusion such as dyspnea overlap with those of PH.[6,21] However, findings of peripheral edema, jugular venous distension, congestive hepatopathy, RV heave, or enlargement should raise suspicion for PH rather than effusion alone. Pleural effusions and PH may occur individually, concurrently, or sequentially. Most patients who have pleural effusion do not have PH. However, a high index of suspicion for PH should be maintained, particularly in patients who do not improve with drug dose reduction or thoracentesis.[22,23] Most reported cases of PH presented with shortness of breath, exertional intolerance/fatigue, and fluid retention.

The timing of development of PAH after initiation of dasatinib is not predictable. Shah and colleagues reviewed 41 cases of RHC-confirmed PAH in dasatinib treated patients from the BMS pharmacovigilance database. Patients presented with PAH at a median duration of 31.5 months after dasatinib initiation, with a wide range from 1 week to 75 months.[8] In a French PH registry, the median time between initiation of dasatinib and diagnosis of PAH was 42 months.[19] Therefore, a high index of suspicion should be maintained while patients are receiving dasatinib regardless of how long they have been on it.

Evaluation

In the context of appropriate symptoms, an echocardiogram is the initial screening test. Elevated pulmonary pressure is usually detected using tricuspid regurgitation velocity by Doppler. Ancillary findings of RV hypertrophy or enlargement, right atrial enlargement, RV dysfunction, and septal deviation to the left provide supporting evidence of PH. A patient with completely normal echocardiogram is unlikely to have severe PH. However, it is important to emphasize that patients with severe PH and failed right ventricle may not be able to generate a high pulmonary artery pressure, so management decisions should not be made solely using estimated PA pressures by echocardiogram. In patients with clinical and echocardiographic suspicion of PH, a RHC is mandatory to evaluate pulmonary artery pressures, left sided filling pressures, and RV function, and serves as a baseline to assess response to discontinuation of dasatinib or addition of pulmonary vasodilators. Other variables with known prognostic value in PH, such as 6 minute walk test, brain natriuretic peptide (BNP), and World Health Organization functional class, can also be measured.

Once PAH is diagnosed, potential causative or risk factors other than dasatinib should be also excluded. These include autoimmune diseases, pulmonary thromboembolism, parenchymal lung disease, other drugs or toxins associated with PAH, sleep apnea, liver disease, and the underlying myeloproliferative disease itself.[1]

In asymptomatic patients, data are insufficient to recommend routine periodic screening echocardiograms to detect occult PH.

Management

Once a diagnosis of dasatinib-induced PAH is made, dasatinib should be permanently discontinued, as per guidelines

from the Food and Drug Administration and the manufacturer.[24,25] This is imperative, since the majority of published studies have reported that the PAH may be at least partially reversible after discontinuation of drug. Dose reduction alone is inadequate, since PAH may not improve, and in fact may progress despite dasatinib dose reduction.[22,26] Furthermore, patients may not respond to pulmonary vasodilators if dasatinib is continued.[27] Finally, if pulmonary pressures normalize after dasatinib discontinuation, patients should not be rechallenged with dasatinib.

The question of whether dasatinib discontinuation alone is sufficient or when specific pulmonary vasodilators are necessary has not been conclusively answered. In the initial report of nine cases from the French PH registry, two patients were treated with endothelin receptor antagonists, one with calcium channel blocker, and six were not treated with any pulmonary vasodilator. Among these patients, eight showed significant hemodynamic and clinical improvements after dasatinib discontinuation, but none showed complete normalization, and two died during follow-up (one from sepsis and one after a long-distance plane flight).[6] In an updated analysis of 21 patients with RHC-confirmed PAH from the French PH registry, all patients had dasatinib discontinued, and 11 had PAH medications prescribed. Mean PA pressure decreased from 45 to 26 mmHg on follow-up. However, at four months, seven patients had persistent PAH by RHC. Of these seven, four normalized their PVR on long-term follow-up.[19] In the BMS pharmacovigilance report, follow-up data were available for 36 patients, of whom 21 had complete resolution of PAH and 15 had partial resolution.[8] Details of pulmonary vasodilator use were not reported. In a retrospective analysis of 138 patients on dasatinib, 48 had pleural effusions, of which 18 had echocardiograms with elevated pulmonary pressure. Discontinuation of dasatinib led to normalization of PA pressure in 10 patients.[21] Although initially thought to be a largely reversible process, recent pathophysiologic evidence and follow-up studies suggest persistence in a substantial minority of cases, and it would seem reasonable to initiate pulmonary vasodilators concurrent with dasatinib cessation, particularly in symptomatic patients or those with severe PAH and/or RV failure. If pulmonary pressure and RV function subsequently normalizes, decisions regarding discontinuation of pulmonary vasodilators should be made in a center with experience treating PH under close monitoring. Successful weaning of vasodilators after normalization of PA pressures has been reported.[15,28] Some investigators have developed treatment algorithms to decide on vasodilator use, but note lack of strong evidence, and there are no formal society guidelines at this time.[19]

Based on currently available data, no recommendations can be made regarding choice of specific pulmonary vasodilator. The majority of cases that noted the specific vasodilator utilized sildenafil, a few used bosentan, and one reported calcium channel blocker use. The role of the newer pulmonary vasodilators or initial combined vasodilator therapy has not been clearly defined. Vasodilator adjustment according to existing standard PH guidelines is most likely the best approach.

It is also important to ensure that the underlying myeloproliferative disorder is treated, since myeloproliferative disease itself can lead to PH. Imatinib remains the first line treatment for CML. In patients whose resistance or intolerance to imatinib was the reason for institution of dasatinib, nilotinib has been commonly used and generally well tolerated.[15,23,29,30] Nilotinib has a similar safety profile to imatinib, likely related to more limited molecular targets compared to dasatinib[12] (see ''PH and other TKIs'' section).

Prognosis

The relatively higher resolution rate with discontinuation suggests a better prognosis than comparable incident idiopathic PAH. Among the 41 cases with dasatinib-related PAH in the BMS pharmacovigilance registry which included the nine patients initially reported in the French registry, there were three deaths: one due to progression of AML, one due to candidemia sepsis with concomitant residual PAH and CHF (where the RV dysfunction could have contributed to the poor prognosis), and one after a long-distance flight. The first reported death directly attributable to PAH was a 36-year-old woman who presented with severe dyspnea 34 months after dasatinib initiation and was diagnosed with PAH by RHC. She deteriorated on sildenafil and catecholamines, and had a cardiac arrest four days after presentation.[31] Despite the low reported mortality rate, it is not known in the general population how many patients on dasatinib experienced sudden death from RV failure or arrhythmias without PAH ever having been diagnosed. Therefore, vigilance to potential early signs and symptoms of PH, and prompt discontinuation of dasatinib before the PAH is advanced is necessary.

PH and other TKIs

TKIs, primarily imatinib, have been extensively evaluated in PH. In vitro studies implicated platelet-derived growth factors in the pathophysiology of PH.[32,33] Imatinib, a BCR-ABL inhibitor, also inhibited PDGF-R. In animal models, imatinib reversed PH caused by monocrotaline or chronic hypoxia.[34] This led to several small human studies, and ultimately the Imatinib in PAH, a Randomized Efficacy Study trial in which patients with PH who were symptomatic on two or more vasodilators were randomized to imatinib versus placebo. Imatinib led to an increase in six minute walk distance by 32 m, a decrease in PVR of 379 d.s.cm^{-5}, and increased cardiac output by 0.88 l/min. However, time to clinical worsening was no different between the groups, and there was a high rate of adverse events, including subdural hematomas, in the imatinib group. Therefore, while pathophysiologic improvements

were seen, the authors note that the drug can have pleiotropic effects with deleterious consequences.[35]

In contrast to the potentially salutary effects of imatinib, several TKIs other than dasatinib have been implicated in PH, although the numbers are small and the associations sometimes confounded. In a single-center study of 27 patients treated with lapatinib, six were found to have pulmonary artery hypertension, defined as PASP >50 mmHg by echocardiogram. Three had confirmatory RHC, and all three normalized their PA pressures after lapatinib discontinuation.[36] Other case reports have described patients who initially had dasatinib-induced PAH with initial improvement after dasatinib discontinuation who again had clinical worsening and severe PAH by RHC after they were switched to bosutinib.[37,38] Quilot and colleagues report a patient who had previously been on dasatinib with normal echocardiogram, who subsequently developed severe PAH after being transitioned to ponatinib. Ponatinib was stopped and she was initiated on sildenafil and ambrisentan with clinical improvement. RHC 10 months after discontinuation showed mild PH (mPAP 30 mmHg).[39] A 72-year-old man with hypertension and evidence of mild left ventricular dilation and diastolic dysfunction had worsening dyspnea and elevated BNP levels after nilotinib initiation, in conjunction with elevated PA pressure by echo. Symptoms improved after diuresis and nilotinib discontinuation. No RHC was performed.[40] A trial evaluating nilotinib as a therapy for PH was terminated early because of high incidence of adverse events.[41] Another patient with dasatinib-related severe PAH had clinical improvement with sildenafil, although post-sildenafil RHC was not reported. He had clinical worsening after nilotinib was initiated, with severe PAH on repeat RHC. He was stabilized clinically with ambrisentan and tadalafil. Because of loss of CML response, he was switched from nilotinib to bosutinib with severe deterioration requiring parenteral prostaglandin therapy, which improved after bosutinib discontinuation. He subsequently was started on ponatinib and again had clinical worsening.[42] This challenging case illustrates the difficulty in attributing PAH to a particular agent given the complex clinical course.

A comparative analysis of 105 patients with CML treated with dasatinib, nilotinib, or imatinib evaluated PA pressures by echocardiogram and a peak tricuspid regurgitation velocity gradient of 31 mmHg or higher was considered "possible PH." With this measure, 2.7% of patients on imatinib, 10% on nilotinib, and 13.2% on dasatinib met criteria for PH.[43] Given the liberal diagnostic criteria and lack of RHC confirmation, this criterion may significantly overestimate the incidence of PH, but underscores the fact that early subclinical PH may be more prevalent than previously appreciated.

Conclusions

In general, PH is a treatable but not curable disease, and frequently progresses despite medical therapy. Even with the many currently available drugs, morbidity and mortality remain high. The high rate of reversibility of dasatinib-induced PAH in contrast to many other causes of PAH is intriguing. The mechanisms behind the reversibility or lack of reversibility of dasatinib-induced PAH are not clear. However, further study of these pathways may provide important information into the pathophysiology of PAH in other populations, and potentially new targets to combat this serious condition.

Authors' contribution

AE-D: inception, planning, literature review, draft manuscript, revision. DA: planning, manuscript writing, revision, supervision.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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