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REVIEW ARTICLE

A narrative review on adverse effects of dasatinib with a focus on pharmacotherapy of dasatinib-induced pulmonary toxicities

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Abstract

Chronic myeloid leukemia (CML), a myeloproliferative disorder caused by the over activity of BCR-ABL1 (breakpoint cluster region-Abelson), has been successfully treated by Tyrosine kinase inhibitors (TKIs). While imatinib is known as the first-line treatment of CML, in some cases other TKIs including dasatinib, nilotinib, bosutinib, and ponatinib may be preferred. Dasatinib, a second-generation TKI, inhibits multiple family kinases including BCR-ABL, SRC family kinases, receptor kinases, and TEC family kinases. It is effective against most imatinib-resistant cases except *T315I* mutation. Despite the superiority of dasatinib in its hematologic and cytogenetic responses in CML compared to imatinib, its potentially harmful pulmonary complications including pleural effusion (PE) and pulmonary arterial hypertension (PAH) may limit its use. Appropriate management of these serious adverse reactions is critical in both improving the quality of life and the outcome of the patient. In this narrative review, we will scrutinize the pulmonary complications of dasatinib and focus on the management of these toxicities.

Key Words Dasatinib, Pleural effusion, Pulmonary arterial hypertension, Chronic myeloid leukemia, Pharmacotherapy

INTRODUCTION

An overview to CML

Chronic myeloid leukemia (CML) is a myeloproliferative disorder associated with Philadelphia chromosome t (9;22)(q34;q11) and/or the *BCR-ABL1* (breakpoint cluster Region-Abelson) fusion gene. Cytogenetic abnormality results in the expression of *BCR-ABL1* protein with a constitutive tyrosine kinase (TK) activity. The incidence of CML is one to two cases per 100,000 adults [1, 2].

BCR-ABL1 promotes cell proliferation by downstream pathways like *MYC, STAT, RAS, RAF* and *JUN* kinases [2]. Although it can occur at any age, the median age of patients is 67 years [3].

The disease is defined as 3 phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP). Uncontrolled chronic phase will lead to accelerated and blast phases of CML within 3 to 5 years [3]. The diagnosis of CML is based on the detection of the Philadelphia chromosome, the *BCR-ABL1* fusion gene or the *BCR-ABL1* fusion mRNA by conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis or reverse transcriptase polymerase chain reaction (RT-PCR) on peripheral blood or bone marrow samples [4]. About 50% of patients are asymptomatic at the time of diagnosis and others have non-specific symptoms such as left upper quadrant pain, fullness, fatigue, malaise and night sweats. Bleeding is likely to occur when significant thrombocytopenia is present [2, 5].

Evolution of treatment of CML

Previously, recombinant interferon-alfa, low dose of cytarabine and allogeneic hematopoietic cell transplantation (HCT) were used as standard of care for CML [6]. HCT may be associated with a definite cure but complications and related mortality limits the utility [2]. Over the past 2 decades, patients with *Ph+/BCR-ABL1* CML have been successfully treated by tyrosine kinase inhibitors (TKIs). TKIs have been effectively used against neoplasms associated with inappropriate activation of different tyrosine kinases and were associated with a better complete cytogenetic response (CCyR) compared to other treatments. In newly diagnosed CML cases who receive TKIs as standard treatment, the 5-year survival rates increased from 40–50% to 90% so that

the lifespan of CML patients is nearly the same as general population [7, 8].

Different TKIs in CML

Imatinib, nilotinib, dasatinib, bosutinib, and ponatinib are TKIs approved by the US Food and Drug Administration (FDA) for treatment of patients with CML. These agents are different in efficacy and toxicity. Selection of a TKI depends on particular clinical feature and toxicity profile of each agent and also patient's age, underlying diseases, and the goal of treatment [4, 9]. Imatinib 400 mg daily is the gold standard for treatment of CML. In patients who did not achieve clinical response or those did not tolerate treatment, higher doses (600 or 800 mg daily) is not recommended due to more adverse effects without improvement of clinical outcomes. Some second generation TKIs including nilotinib (300 mg twice daily) and dasatinib (100 mg once daily) may be used as the first line treatment [10, 11]. Efficace *et al.* [12] reported a better quality of life of chronic phase CML patients who were treated with dasatinib at the first line compared to imatinib. Bosutinib, another second generation TKI is approved for CML cases that are intolerant or resistant to prior first line therapies. Recent evidences from BFORE trial showed better clinical responses for bosutinib 400 mg once daily in comparison with imatinib 400 mg in newly diagnosed *Ph+/BCR-ABL1* CML [13]. Ponatinib is the only TKI that was approved for CML patients with *T315I* mutation. It is also used as a second line treatment for cases who were resistant to imatinib, or experienced treatment failure/intolerance to other TKIs such as dasatinib, nilotinib or other second line agents [4].

TKIs-induced pulmonary toxicities

The incidence of pulmonary toxicities of TKIs is less than 1% [14]. The most reported toxicities were pulmonary artery hypertension (PAH), pleural effusion (PE), interstitial lung disease (ILD), pulmonary edema, chylothorax, cough, pneumonitis, bronchospasm and upper respiratory tract infection [15-21]. Most of these adverse reactions need discontinuing treatment and initiating a medical intervention [22]. Although PAH was not reported by using imatinib or nilotinib and rarely reported with lapatinib, ponatinib, and bosutinib, it is a known complication of dasatinib [23-27]. PE mostly occurres following treatment with dasatinib and bosutinib which could alter the patient's compliance to the therapy. TKIs associated ILD is less likely to happen in which different histological markings lead to various clinical presentations [28]. In the following sections, we will focus on dasatinib-induced PE and PAH as two major pulmonary toxicities and their management will be discussed.

METHODS

We searched scientific databases for indexed studies on PubMed and Google-scholar based on the terms: "dasatinib", "chronic myeloid leukemia", "tyrosine kinase inhibitors", "pulmonary arterial hypertension", "pleural effusion", and "pulmonary toxicity". The Boolean operators (AND/OR) were also used to combine search terms. All case reports, case series, clinical trials, and relevant review articles were selected without limitation of the year of publication. Studies in languages other than English and those with only abstracts available were excluded.

DASATINIB

Efficacy in CML

Dasatinib, an oral potent second generation TKI, was approved in 2010 by FDA for management of newly diagnosed CML patients who are in chronic phase (100 mg once daily), and any phases of disease that is resistant or intolerant to previous treatment (70 mg twice daily) [29]. It is also used with 70 mg twice daily regimen in *Ph+* acute lymphoblastic leukemia (ALL) [30-32]. Dasatinib inhibits *BCR-ABL*, *SRC* (v-src sarcoma viral oncogene homolog) family kinases (including *SRC, LCK ,LYN, FYN, YES, HCK, FGR, BLK, YRK*), receptor kinases (*c-KIT, PDGFRβ, DDR 1* and *2*, *c-FMS, ephrin* receptors), and *TEC* family kinases (*TEC* and *BTK*) [20, 30]. Dasatinib with its thiazole-carboxamide structure binds to the both active and inactive conformations of *BCR-ABL1* while imatinib only inhibits inactive form [33]. It was efficacious on 18 out of 19 imatinib-resistant *BCR-ABL* mutations with the exception of *T315I* mutation [33, 34]. Results obtained from numerous prior studies demonstrated that dasatinib is superior to imatinib in terms of clinical outcomes including hematologic and cytogenetic responses with more potent activity against *BCR-ABL1* (325 to 350 folds) [29, 31]. Various investigations have shown clinical efficacy of dasatinib over imatinib in both resistant and intolerant patients and also in newly diagnosed CML cases [29]. DASISION study was performed on treatment-naïve chronic phase CML patients to compare imatinib and dasatinib at the dose of 400 and 100 mg once daily, respectively. Analysis of long term results showed that dasatinib was associated with a faster and profound molecular response (MR), major molecular response and CCyR. Progression-free survival (PFS) and overall survival (OS) were high in both groups however patients in dasatinib group achieved an earlier response with a fewer CML-related death [35]. Another trial evaluated efficacy of different doses of dasatinib in imatinib-resistant or intolerant patients. The results showed that 100 mg daily dosing was associated with a better tolerability. A faster treatment response and also improvement in long term clinical benefits was reported with dasatinib [8].

Dasatinib adverse effects

Despite a dramatic improvement of survival of CML patients following approval of TKIs, various early and late adverse effects including gastrointestinal, cardiovascular, endocrine, hematologic and pulmonary toxicities were reported [36-39]. Gastrointestinal adverse effects include nausea and

vomiting, diarrhea, abdominal pain, hemorrhagic colonic ulcers, acute hepatitis, anorexia, dyspepsia, and gastrointestinal bleeding as a result of platelet dysfunction. The mucosal inflammation including mucositis/stomatitis, constipation, acute pancreatitis, abdominal distension and colitis were seen in less than 10% of the cases. Endocrine disorders were gynecomastia, irregular menses, hypoglycemia, hyperglycemia and increased triglyceride and cholesterol levels [30, 32, 38, 40-42]. The most common cardiovascular effects were fluid retention, pericardial effusion, and to a lesser extent, cardiac dysfunction including cardiomegaly, angina, congestive heart failure and cardiac dysrhythmia including tachycardia and QTc prolongation [43-46]. Anemia, thrombocytopenia and neutropenia were reported with dasatinib which are most observed in Ph+ ALL patients and advanced phase CML patients compared to chronic phase. Thrombocytopenia is more clinically substantial and may result in central nervous system hemorrhage and gastrointestinal bleeding so that it is recommended to administrate dasatinib with caution in those receiving anticoagulation or antiplatelet agents [38, 46].

Dasatinib-induced pleural effusion: Pleural Effusion (PE) is a lymphocyte-predominant exudate, which has been observed with all *BCR-ABL1* TKIs, but dasatinib has the most frequency (up to 35%) [14, 16, 47]. According to the Quintás-Cardama *et al.* [47] about 50% of dasatinib-induced PE cases were in accelerated phase of leukemia. Autoimmune inhibition of the PDGFR β which causes fluid retention has been suggested as involved mechanism of dasatinib-induced PE [48]. The occurrence of PE is one important cause of treatment withdrawal [49, 50]. The phase 3 of final DASISION trial has shown that the incidence of PE following use of TKIs were more common with dasatinib (28%) versus imatinib (0.8%) [35]. More dasatinib-induced PE occurred at the 5 years study results (29%) compared to the first year (10%). Most PE cases were in grade 1 (asymptomatic) or 2 (symptomatic; intervention such as diuretics or ≤2 therapeutic thoracenteses indicated) [51]. The incidence of PE was not associated with a negative effect on achieving clinical CCyR [35, 52]. Predisposing factors for PE were twice-daily dasatinib regimen, the initial daily dose of dasatinib (140 mg vs. 100 mg), other pulmonary diseases, the age of patient (60% in patients age ≥65 yr vs. 25% in patients younger than 65 yr), skin rash, hypercholesterolemia, as well as presence of hypertension, and a history of cardiac or autoimmune diseases. Based on the higher incidence of PE with twice-daily dosing of dasatinib, once-daily dosing regimen is now recommended for treatment of CML and ALL [16]. Univariate analysis of association between disease phase and development of PE revealed that treatment with dasatinib in accelerated phase and blast crisis is a risk factor for developing PE and patients whom treated particularly with higher doses of dasatinib should be accurately monitored for PE sign and symptoms [47]. Several studies reported that hypertension is a major comorbidity in patients with PE [35, 47, 49, 53, 54]. The animal model of dasatinib-induced PE indicated that in a dose-dependent manner, dasatinib could lead to altered pulmonary endothelial permeability which was reversible by decreasing dose or holding treatment and switching into other TKI. It was proposed that changes in intercellular junctions along with production of stress fibers in cytoplasm and reactive oxygen species (ROS) involve in the development of dasatinib-induced PE [54, 55].

Dasatinib-induced chylothorax is a rare pulmonary adverse effect that is a subgroup of PE and defined as triglycerides and cholesterol concentrations of pleural fluid more than 110 mg dL^{-1} (1.24 mmol L^{-1}) and less than 200 mg dL^{-1} (5.18 mmol L^{-1}), respectively [56]. Chylothorax results from obstruction or disruption of thoracic duct which leads to leakage of chyle into pleural space [19]. Despite aforementioned explanations, the exact molecular mechanism of PE and chylothorax has not been elucidated and needs further investigation [54, 57].

Dasatinib-induced pulmonary arterial hypertension: Pulmonary Arterial Hypertension (PAH) is one of the most severe pulmonary toxicities of TKIs and was mostly reported with dasatinib [14, 58]. PAH is a rare complication (0.45%) which is defined as increased mean pulmonary arterial pressure (mPAP) >25 mmHg at rest or >30 mmHg by exercising in the absence of elevated pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR) >3 woods units that leads to right ventricular and progressively left ventricular failure [59]. In the presence of dyspnea, atypical chest pain, fatigue or unexplained syncope, Chest X-Ray (CXR) or trans-thoracic echocardiography (TTE) should be used and if PAH was proposed, right heart catheterization (RHC) should be performed to confirm the diagnosis [22]. On the basis of RHC results, PAH is determined as elevated right ventricular systolic pressure (RVSP) and/or pulmonary arterial systolic pressure above 40 mmHg. In addition, Toya *et al.* [60] conducted a study on 60 dasatinib treated cases and investigated whether which of the following items is more reliable for early predicting PAH: 1) recent electrocardiographic changes indicating right ventricular pressure overload; 2) estimated systolic pulmonary arterial pressure >40 mmHg measured by Doppler echocardiography; 3) computed tomography (CT)-measured pulmonary artery to aorta diameter (PaD/AoD) ratio >1; and 4) mean pulmonary arterial pressure >25 mmHg and pulmonary artery wedge pressure <15 mmHg measured by right heart catheterization. Although an increase in PaD/AoD ratio measured by CT imaging occurred in all cases, it was found that a significantly higher PaD/AoD ratio (>1) at baseline was seen in those developed PAH and it could be used as an early predictor of dasatinib-induced PAH. PAH happens on prolonged treatment with dasatinib (19–52 mo), confirming the chronicity nature of the involved pathological mechanism. Dasatinib-induced PAH predominantly occurs in women and is often concomitant with previous or present PE [15]. PAH in a CML patient may be drug-induced (group 1) or related to CML pathophysiology [15, 61-63]. It has been demonstrated that treatment with dasatinib causes a dose-dependent increase in production of mitochondrial ROS; resulting to endothelial apoptosis, pulmonary endothelial dysfunction and

pulmonary hypertension. Another proposed mechanism is related to SRC family kinases and platelet-derived growth factor (PDGF) pathway [54, 62, 64]. SRC family kinases have a role in smooth muscle cells reproduction and also reducing pulmonary artery tone while their inhibition result in apoptosis and raised vascular resistance. Some recent studies indicated that pathways other than SRC may also play a role in endothelial dysfunction, which leads to dasatinib-induced PAH. Animal studies showed that the levels of soluble ICAM-1, soluble VCAM-1, and soluble E-selectin, markers of endothelial dysfunction, rises with dasatinib leading to less hypoxic vasoconstriction and subsequently impaired endoplasmic reticulum function [65]. There is no specific biomarker for PAH, but brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have been used in clinical practice to evaluate the patient's condition before and after the treatment [66-68]. Evaluation of the 6 minute walk distance (6-MWD) and world health organization (WHO) functional class is also useful in predicting prognosis of PAH treatment [59]. In a descriptive study of PAH cases in the French pulmonary hypertension registry from November 2006 to September 30, 2010, nine patients of dasatinib-induced PAH were reported. None of them had a chronic respiratory disease, family history of PAH or history of medications with the risk of PAH. Discontinuation of dasatinib led to improvement in clinical status of all patients except 3 who required further pharmacotherapy [15]. Although PAH is clinically reversible, the hemodynamic of patients may not completely improve after discontinuation of therapy [64].

MANAGEMENT

Since the widespread use of TKIs has made a tremendous change in the treatment of CML, the complications associated with these medications need to be identified and managed appropriately.

Pleural effusion

As noted above, treatment of CML with dasatinib was associated with a high prevalence and recurrence rate of PE. In a multivariate analysis, the most significant risk factor for incidence of PE was the patient's age [69]. Dasatinib-induced PE has a clinically ameliorative nature in most cases. Dose interruption, dose reduction and drug therapy have been suggested for PE management [50, 54]. Based on radiographic features, patients with class 1 PE do not need any intervention. In patients who are categorized in class 2 or more and are asymptomatic, treatment should be interrupted and diuretics may be started in the presence of fluid retention. Therapy of CML should be resumed after resolution of effusion. Dose should be reduced in the case of further episodes. In symptomatic patients with PE≥class 2 or asymptomatic patients with PE≥class 3, dasatinib should be discontinued and corticosteroids (prednisone 40 mg daily for

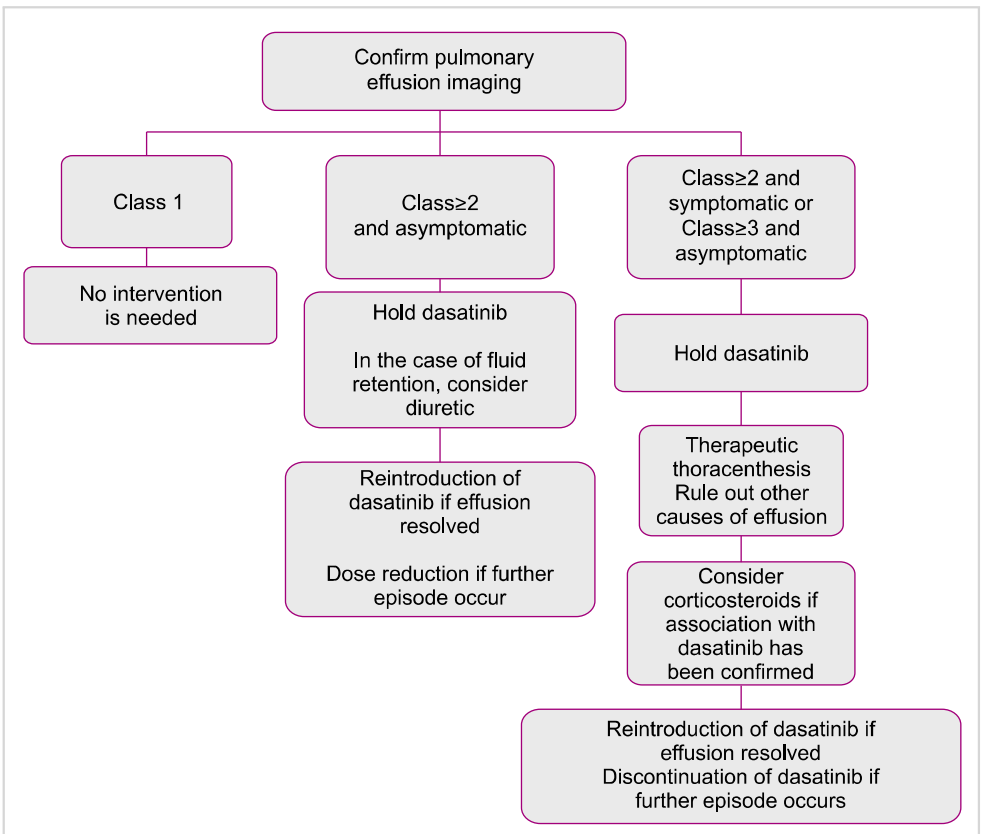

Fig. 1. Management of dasatinib-induced pleural effusion.

four days) should be initiated. Therapeutic thoracentesis should also be performed and the pleural fluid should be investigated to rule out other effusion causes. Dasatinib could be reintroduced in the case of effusion resolution. In symptomatic patients with PE≥class 2 or asymptomatic patients with PE≥class 3, dasatinib should be discontinued with recurrent PE [16].

Another approach for treatment is based on a different classification of PE severity. Cortes *et al.* [55] defined PE as following: "Small effusion" (volume of effusion <500 mL with a blunting view of costophrenic angle), "medium effusion" (with opacity above costophrenic angle) and "large effusion" (effusions more than 30 to 50% of hemithorax). Small effusion can be either symptomatic or asymptomatic. In patients with small asymptomatic PE, follow up of symptoms should be performed periodically with CXR monitoring every 3 months in the first year followed by every 6 months in the second year. For symptomatic patients, CXR should be repeated more frequently. Reducing the dose may be considered according to the level of therapeutic response in the chronic phase. In symptomatic PE, management includes dose reduction according to clinical response accompanied with a CXR after one month. If the size of PE was stable, the CXR monitoring should be repeated as mentioned above. In the case of persistent or worsening symptoms, its management is similar to medium/large effusion as will be noted. Medium/large effusions can be a result of worsening small symptomatic PE or diagnosed at presentation. For the first episode, treatment should be interrupted immediately until the effusion disappears and re-administered with lower dose based on the response of patient in the chronic phase. Prompt therapeutic thoracentesis is necessary for the first diagnosed medium/large PE followed by CXR every 2 to 4 weeks to evaluate volume of effusion. If more than 2 thoracenteses are needed, discontinuing of treatment is recommended. If the size of effusion did not change after thoracentesis, dose interruption and treatment with a lower dose of TKI based on response in the chronic phase is recommended (Fig. 1) [55].

Based on radical scavenging property, N-acetylcysteine (NAC) was effective in preventing increased pulmonary endothelial permeability which is one of the underlying causes of PE [54].

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a life threatening complication of long-term therapy with dasatinib, especially in the presence of PE. PAH may lead to right ventricular failure if left untreated [70, 71]. Reports represent low mortality rate due to dasatinib-induced PAH. Early diagnosis of PAH and cessation treatment with dasatinib are strongly recommended [59]. Discontinuation of dasatinib leads to notable symptomatic improvement, however this may not be associated with a complete hemodynamic recovery [64, 72]. Phosphodiesterase type-5 inhibitors, prostacyclin derivatives, and endothelin receptor antagonists (ERAs) are FDA approved pharmacological classes used for treatment of PAH. Riociguat, an oral soluble guanylate cyclase stim-

Table 1. FDA approved pharmacological classes for treatment of PAH.

Class	Drug	Rout of administration	Dose
Prostacyclin derivatives	Epoprostenol	IV	Initial dose of 2 ng $kg^{-1}min^{-1}$ Iv infusion, titrated by 1–2 ng $kg^{-1}min^{-1}$q 15 min if tolerated
	Iloprost	Inhaled	2.5 μg inhaled, if tolerated then 5 μg, 6–9 times a day PRN; Maintenance: 2.5–5 μg $dose^{-1}$ (max: 45 μg daily)
	Treprostinil	PO	PO: 0.125 mg TID or 0.25 mg BID, titrated by 0.125 mg TID every 3–4 days
		Continuous IV or SC infusion	IV or SC infusion: 1.25 ng $kg^{-1}min^{-1}$ titrated by no more than 1.25 ng $kg^{-1}min^{-1}$per wk based on clinical response; after 4 wk, titrated by no more than 2.5 ng $kg^{-1}min^{-1}$ per wk based on clinical response
Endothelin receptor antagonists	Bosentan	Oral	125 mg twice daily
	Ambrisentan	Oral	5 or 10 mg once daily
	Macitentan	Oral	10 mg once daily
Phosphodiesterase type-5 inhibitors	Sildenafil	Oral IV Injection	20 mg TID
	Tadalafil	Oral	40 mg once daily
Soluble cGMP stimulators	Riociguat	Oral	0.5–1.0 mg TID (titrated by 0.5 mg every 2 wk as tolerated to maximum dose 2.5 mg)
Prostacyclin receptor agonists	Selexipag	Oral	200 mg twice daily, titrated as tolerated to maximum dose of 16,000 mg twice daily

Abbreviations: cGMP, Cyclic guanosine monophosphate; FDA, Food and Drug Administration; h, hour; IV, Intravenous; PAH, pulmonary arterial hypertension; SC, subcutaneous.

ulator, is also another choice for management of PAH. A prostacyclin receptor agonist, selexipag has been approved by the FDA for PAH in 2015 [73]. Different FDA approved pharmacologic drugs, routes of administration and doses have been presented in Table 1. Several reports have been published according to the management of dasatinib-induced PAH. Clinical characteristics of patients, the intervention and outcome of therapy have been presented in Table 2.

Phosphodiesterase-5 inhibitors: Phosphodiesterase-5 (PDE-5) is the dominant isotype of PDE in the pulmonary vascular smooth cell muscles which is upregulated in PAH. It metabolizes cyclic guanosine monophosphate; hence PDE-5 inhibitors could induce nitric oxide-mediated vasodilation and possibly have some anti-proliferative effects [74, 75]. Sildenafil, tadalafil, and vardenafil have been studied in PAH and only sildenafil and tadalafil which are different in chemical structure have been approved by FDA for treatment of PAH [76, 77]. Due to the longer half-life of tadalafil (17.5 hr) as compared to that of sildenafil (~4 hr), it is prescribed once daily whereas the other is taken 3 times per day [78]. They are similar in adverse effects profile and both tadalafil and sildenafil were associated with beneficial effects in exercise tolerability, hemodynamic parameters and clinical status of dasatinib-induced PAH [79].

WHO functional class, 6-MWD, mPAP, and clinical worsening were assessed in 278 PAH patients who received either placebo or sildenafil (20 mg, 40 mg, or 80 mg) orally 3 times daily for 12 weeks. A notable improvement in all mentioned values was achieved after all doses. Since complete inhibition of PDE-5 at the dose of 20 mg 3 times was achieved, dose escalation to get much more response is not reasonable [75]. The efficacy of sildenafil in dasatinib-induced PAH has been evaluated in numerous case reports [80-84]. Groeneveldt and coworkers reported a case with mPAP of 55 mmHg and NYHA functional class 4 who had no improvement in NYHA functional class after being treated with sildenafil. Actually, dasatinib was not discontinued in spite of emphasis on stopping treatment immediately after the appearance of PAH [59, 85]. Sildenafil was also evaluated in combination with bosentan (20 mg TDS and 62.5 mg BD, respectively) in a patient with mPAP of 37 mmHg, WHO functional class 2 and BNP 685 pg mL^{-1}. All variables improved after 6 months of treatment [86]. In another case, right ventricle systolic pressure (RVSP) was reduced from 71 mmHg to 55 mmHg after treatment with 25 mg once daily sildenafil. Re-challenging of dasatinib after reduction of RVSP was associated with a faster incidence of PAH appearance [61].

In a large trial, tadalafil, another PDE-5 inhibitor, was investigated in doses of 2.5 mg, 10 mg, 20 mg and 40 mg once daily for management of PAH in 405 patients. Borg dyspnea score (BDS), 6-MWD, clinical worsening, health-related quality of life and WHO functional class were assessed. Only the 40 mg/day dose showed statistically significant improvement in all of measurements except WHO functional class and BDS [87]. Until today there is no study to evaluate tadalafil monotherapy in dasatinib-induced PAH, as it was used in combination with other drugs. An abstract published in January 2020 in European Heart Journal Cardiovascular Imaging showed that combination of tadalafil and ambrisentan is effective in improvement of systolic PAP and secondary myocardium changes caused by dasatinib [88]. Two other different dosage regimens of tadalafil and ambrisentan combination were used: "tadalafil (40 mg daily)+ambrisentan (10 mg daily)" and "tadalafil (20 mg daily)+ambrisentan (5 mg daily)". Both revealed improvement in pulmonary symptoms, mPAP, 6-MWD, BNP level and WHO functional class [62, 64].

Endothelin receptor-1 antagonists (ERAs): Bosentan, ambrisentan and macitentan are ERAs approved by FDA for management of PAH. Bosentan, the oldest member of ERAs is a non-selective competitive antagonist of endothelin receptor-1 (ET-1) that irreversibly blocks both ET-1A and ET-1B [89, 90]. The efficacy of bosentan in PAH was evaluated in BREATHE-1 study. Patients were treated with 62.5 mg BD bosentan for 4 weeks and then randomly assigned to receive 125 mg or 250 mg twice daily for a minimum of additional 12 weeks. Amelioration of exercise capacity as primary outcome of the trial was seen in both bosentan-treated groups ($P<0.001$). Changes in the BDS, WHO functional class, and the time to clinical worsening were considered as secondary endpoints. Reduction in BDS was greater in patients received 250 mg twice daily in comparison with 125 mg twice daily. In total, WHO functional class decreased 42% in patients received bosentan versus 30% in patients received placebo. Time to clinical worsening was longer in patients in bosentan group compared to patients in placebo group after 16 weeks. Hepatic dysfunction occurred in a dose dependent manner and was more frequent with 250 mg BD dosing. Surprisingly, the changes in mPAP were not clinically significant notwithstanding in study group received high dose of bosentan (250 mg BD) (88±13 mmHg at baseline versus 85±11 mmHg at the end of trial) [91]. Reversible elevation in aminotransferases, anemia, headache and edema were the complications associated with bosentan [92, 93]. The only published paper about dasatinib-induced PAH treated with bosentan was a patient with acute lymphoblastic leukemia (ALL). Titration of bosentan to a dose of 125 mg twice daily led to significant decrease in systolic pulmonary artery pressure (SPAP) and pro-BNP level. NYHA functional class and also 6-MWD significantly improved during the intervention [94].

Among above mentioned three agents, ambrisentan is a selective blocker of ET-1A which is responsible for smooth muscle cells vasoconstriction. The incidence of liver impairment and drug interactions of ambrisentan was lower but it was associated with a more frequency of peripheral edema [95-97]. Data demonstrated that selectivity on ETR blockage was not an important factor in choosing an agent for PAH management. The role of ambrisentan in combination with tadalafil in dasatinib-induced PAH was evaluated just in case reports as mentioned previously [98]. Along with discontinuation of dasatinib, ambrisentan in combination with sildenafil and treprostinil was associated with improvement

Table 2. Cases of dasatinib-induced PAH and their pharmacotherapy.

Study	N of participants/ diagnosis	Age, yr/ gender, M or F	Time from dasatinib initiation to PAH diagnosis (mo)	DASA dose, mg/day	Treatment line of DASA	Concomitant PE	Intervention	Improved items
Jose *et al.* (2017) [64]	1, CML	61, M	26	140	Second	Yes	DASA D/C Tad 20 mg QD and Amb 5 mg daily. The Tad was up-titrated over a period of 4 wk to 40 mg QD, followed by an up titration of Amb to 10 mg QD over the following 4 wk	After 4 mo, mPAP PCWP PVR 6-MWD WHO FC
Ibrahim *et al.* (2019) [62]	1, CML	46, F	120	70	Second	Yes	DASA D/C Amb 5 mg daily+ Tad 20 mg QD	After 1 wk, PAP
Orlandi *et al.* (2012) [80]	1, CML	53, F	31	100	Second	No	DASA D/C Sil 20 mg TID	After 2 mo, WHO FC PAP 6-MWD
Sano *et al.* (2012) [81]	1, CML	61, F	27	140	Second	Yes	DASA D/C Sil 60 mg QD	After 1 mo, WHO FC RVSP NT-pro BNP PAP
Wang *et al.* (2015) [82]	1, CML	33, M	63	100	Second	No	DASA D/C Sil	After 3 mo, PASP
Taçoy *et al.* (2015) [94]	1, ALL	50, M	24	140	Second	Yes	DASA D/C Bos 62.5 mg BID and in 2 wk increased to 125 mg BID	After 1 mo, NYHA FC After 9 mo, Pro BNP 6-MWD
Groeneveldt *et al.* (2013) [85]	1, CML	57, M	37	70	Second	No	Sil DASA D/C	The patient did not improve in NYHA FC class by sildenafil and diuretics. 3 mo after substitution DASA with NIL, NYHA FC after start NIL
Nishimori *et al.* (2018) [86]	1, CML	24, M	48	100	Second	Yes	DASA D/C Sil 20 mg TID+Bos 62.5 mg BID	After 1 mo, WHO FC PAP BNP
Helgeson *et al.* (2016) [115]	1, CML	30, F	36	NR	Second	Yes	DASA D/C EPO 20 ng kg^{-1} min^{-1} for 5 mo, then EPO 4 ng kg^{-1} min^{-1} for 5 mo and discontinuation with mild rebound of MPAP, therefore, Sil was initiated	After 1 wk EPO, Dyspnea
Toya *et al.* (2019) [104]	1, CML and scleroderma	63, M	36	100	Second	Yes	DASA D/C Tad 40 mg QD+Mac 10 mg QD+Sel 1.2 mg BID	After 1 mo, mPAP PVR 6-MWD
Buchelli *et al.* (2014) [71]	1, CML	50, M	48	100	Second	Yes	DASA D/C Sil 20 mg TID	After 21 mo, WHO FC RVSP NT-pro BNP mPAP PVR 6-MWD CO CI

Table 2. Continued.

Study	N of participants/ diagnosis	Age, yr/ gender, M or F	Time from dasatinib initiation to PAH diagnosis (mo)	DASA dose, mg/day	Treatment line of DASA	Concomitant PE	Intervention	Improved items
Seegobin *et al.* (2017) [98]	1, CML	52, M	48	NR	Second	Yes	DASA D/C Amb	NR, Symptoms as well as effusions improved
Daccord *et al.* (2018) [99]	1, CML	32, M	36	NR	Third	Yes	DASA D/C PDE-5 inhibitor+ERA	NR, NYHA FC mPAP 6-MWD PVR CI
Dumitrescu *et al.* (2011) [83]	1, CML	47, M	72	100	Second	Yes	DASA D/C Sil	After 2 mo, WHO FC PAP CO
Skride *et al.* (2017) [70]	1, CML	67, M	42	100	Second	Yes	DASA D/C Sil 20 mg TID	NR, mPAP 6-MWD PVR CO
Orlikow *et al.* (2019) [147]	1, CML	73, F	9	NR	Second	Yes	DASA D/C Nif 30 mg QD	After 12 mo, CO CI PVR
Hennigs *et al.* (2011) [84]	1, CML	70, M	32	140	Second	Yes	DASA D/C Sil 20 mg TID	After 10 mo, CO RVSP NT-proBNP 6-MWD Mpap WHO FC PVR
Hong *et al.* (2015) [61]	2, CML	43, M	69	140	Second	Yes	DASAD/C Sil+CCB+Diuretics	NR, NYHA FC PAP RVSP
		52, M	38	140	Second	Yes	DASA D/C Sil 25 mg QD	NR, RVSP BNP 6-MWD
Montani *et al.* (2012) [15]	3, CML	74, F	33	100	Second	Yes	DASA D/C CCB for 6 mo, then stopped	After 3 mo, NYHA FC, mPAP 6-MWT PVR BNP
		29, F	36	100	Second	Yes	DASA D/C Bos	After 2 mo, NYHA FC After 6 mo, mPAP 6-MWT PVR
		39, F	34	100	Second	Yes	DASA D/C Bos	After 1 mo, NYHA FC

Abbreviations: 6-MWD, 6-minute walk distance; ALL, acute lymphoblastic leukemia; Amb, ambrisentan; BID, two times a day; BNP, b-type natriuretic peptide; Bos, bosentan; CCB, calcium channel blocker; CI, cardiac index; CML, chronic myeloid leukemia; CO, cardiac output; DASA, dasatinib; D/C, discontinuation; EPO, epoprostenol; ERA, endothelin receptor-1 antagonist; F, female; FC, functional classification; M, male; Mac, macitentan; mPAP, mean pulmonary artery pressure; Nif, nifedipine; NIL, nilotinib; NT-pro BNP, N-terminal pro b-type natriuretic peptide; NYHA, New York heart association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PDE-5, phosphodiesterase-5; PE, pulmonary embolism; Pro BNP, pro hormone b-type natriuretic peptide; PVR, pulmonary vascular resistance; QD, once a day; RVSP, right ventricular systolic pressure; Sel, selexipag; Sil, sildenafil; Tad, tadalafil; TID, three times a day; WHO, world health organization; WU, wood unit.

in mPAP, 6-MWD and NYHA functional class. However, an unexpected progression of PAH occurred after 3 years which was not controlled by intensive anti PAH therapy and resulted in need for lung transplantation. It is notable that the CML therapy may be resumed with nilotinib in patients with PAH following dasatinib use [99].

Macitentan is a novel non-selective ET-1 antagonist with an active metabolite with a longer half-life compared to the parent drug. Macitentan and its active metabolite have a higher tendency to tissue and bind more potently to ET receptors compared to the other ET-1As [100]. It has a good safety profile with well-tolerated adverse events include nausea, vomiting and headache and less liver toxicity compared to bosentan and ambrisentan [101]. This highly potent ERAs was studied in SERAPHIN trial with the dosage regimens of 3 mg and 10 mg once daily versus placebo in 742 PAH cases (not dasatinib-induced PAH). Both 3 mg (P=0.01) and 10 mg ($P<0.0001$) once daily dosing reduced the risk of morbidity/mortality by 30% and 45%, respectively. NYHA functional class and 6-MWD changes from baseline were the secondary endpoints of study. Overall, macitentan was well tolerated and adverse effects including nasopharyngitis, headache and anemia were similar in all groups [102]. It also reduced PAH-related hospitalization and chronic thromboembolic pulmonary hypertension [103]. In a case of Dasatinib-induced PAH with concurrent scleroderma, macitentan was used along with tadalafil and selexipag. Rapid improvement of mPAP, 6-MWD and NYHA functional class were reported [104].

Sitaxentan, a selective ERA, was eliminated from the market because of its lethal liver toxicity [105-107].

Epoprostenol and prostaglandin I2 (PGI2) derivatives: Epoprostenol as a synthetic derivative of PGI2 received FDA approval in 1995. PGI2 acts as a direct vasodilator and also a cytoprotective agent which inhibits platelet aggregation [108-110]. Epoprostenol has beneficial effects on PAH symptoms, disease progression, 6-MWD and survival [111-115]. A case of dasatinib-induced PAH was treated successfully with epoprostenol along with discontinuation of dasatinib [116]. According to epoprostenol instability in plasma, continuous intravenous infusion (IV) is the preferred route of administration, though it is linked to catheter-related thrombosis and infection [114, 117, 118]. Other adverse effects were ascites, thrombocytopenia, flushing, headache, nausea, loose stool, jaw discomfort and musculoskeletal pain [110, 119].

Treprostinil is another prostanoid with longer half-life used in treatment of PAH. It was associated with improvement in quality of life, exercise capacity, functional class, pulmonary hemodynamics, and survival of patients [120-123]. Treprostinil can be used in oral, inhaled, subcutaneous or IV routes which the 2 latter are assumed bioequivalent at steady state in the dose of 10 ng $kg^{-1}min^{-1}$. It is also used as SC infusion. Local pain following infusion may occur and could be decreased by titrating of dose during 6 months [124, 125]. Transition from IV epoprostenol to IV or SC treprostinil is rational when patient is intolerant to epoprostenol or in the case of worsening of clinical status [126-128]. Inhaled treprostinil in patients with severe pulmonary hypertension revealed a significant sustained impact on pulmonary vascular resistance compared to the same doses of inhaled iloprost with a better tolerability profile [129]. According to a double-blind, randomized, placebo-controlled trial, continuous SC infusion of treprostinil enhances exercise capacity regardless of the PAH etiology. Considering this dose-related effect, treprostinil could be an appropriate agent for management of dasatinib-induced PAH [130].

Iloprost, an analog of PGI2 has a short half-life of 20–25 minutes and was used as inhalation or IV forms with frequent doses (e.g., 6–9 times daily) [131]. It can improve 6-MWD, Mahler dyspnea index, quality of life and NYHA functional class in PAH by inhaled formulation [132]. Despite its inhalation form, IV iloprost did not receive FDA approval for PAH. Both iloprost and treprostinil inhalation formulations lead to cough [133].

Beraprost is an oral rapid onset analog of PGI2 that improves 6-MWD, disease progression and WHO functional class. Considering WHO functional class, the beneficial effects is limited to 6 months [134]. Beraprost and Iloprost have not yet studied for management of dasatinib-induced PAH, but they could be acceptable drugs since both have proven efficacy in ameliorating the PAH with other etiologies.

Selexipag is another oral prostacyclin IP2-receptor (IP2r) agonist with a non-prostanoid structure. It has a vasodilator effect on large and small pulmonary arterial branches [135-137]. Selexipag has the highest affinity for IP2r with similar side effect profile of other IP2r agonists. Headache is the most common adverse effect along with jaw pain, nausea and diarrhea which are often observed with rapid dose-titration and are reduced over time [138]. Selexipag showed a significant improvement in the primary composite endpoint of death, complications related to PAH, pulmonary vascular resistance and 6-MWD in GRIPHON trial [136]. As mentioned previously, selexipag has been studied in dasatinib-induced PAH in combination with macitentan and tadalafil resulted in rapid improvement of mPAP, 6-MWD and NYHA functional class [104].

Calcium channel blockers (CCBs): CCBs reduces the influx of calcium in smooth muscle cells leading to systemic peripheral arterial dilation. Therapeutic effects of CCBs will be obtained when used at high doses for a long time [139-143]. Among long acting nifedipine, diltiazem and amlodipine, diltiazem is preferred when the heart rate is above 80 beats min^{-1} [144, 145]. Verapamil is not recommended due to its notable negative inotropic effect [146]. Although CCBs have been noted nearly in all PAH treatment guidelines, in fact a very few numbers of patients with PAH including idiopathic-PAH patients, genetically associated PAH, or anorexigen-induced PAH will benefit from using high doses and long term CCB therapy [147]. It doesn't seem that CCBs are effective in dasatinib-induced PAH [148].

CONCLUSION

Pulmonary complications of TKIs need to be diagnosed and managed promptly. Dasatinib was associated with a higher prevalence and recurrence rate of PE and PAH among TKIs. In symptomatic patients with mild PE, dasatinib should be interrupted and in the case of fluid retention, diuretics should be initiated. Therapy of CML should be resumed after resolution of effusion. In symptomatic patients with PE ≥class 2 or asymptomatic patients with PE ≥class 3, dasatinib should be discontinued and corticosteroids (prednisone 40 mg daily for four days) should be initiated along with therapeutic thoracentesis. PAH is a life threatening complication of long-term therapy with dasatinib. Phosphodiesterase type-5 inhibitors (e.g., sildenafil and tadalafil) alone or in combination with endothelin receptor-1 antagonists (e.g., bosentan and macitentan) and also synthetic derivatives of PGI2 or non-prostanoid prostacyclin-receptor agonist (e.g., selexipag) were successfully used in the management of dasatinib-induced PAH. Current recommendations regarding the management of pulmonary toxicities of TKIs including dasatinib are based on published case reports and evaluating the safety and efficacy of different available pharmacotherapies require conducting multi-center randomized controlled trials.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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