# Pulmonary complications of Bcr-Abl tyrosine kinase inhibitors

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**Bcr-Abl tyrosine kinase inhibitors have been associated with certain pulmonary complications, including exudative pleural effusions, chylothorax, interstitial lung disease and pulmonary arterial hypertension** https://bit.ly/3cG6QnG

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ABSTRACT Tyrosine kinase inhibitors (TKIs) targeting the Bcr-Abl oncoprotein revolutionised the treatment of chronic myelogenous leukaemia. Following the success of imatinib, second- and third-generation molecules were developed. Different profiles of kinase inhibition and off-target effects vary between TKIs, which leads to a broad spectrum of potential toxicities.

Pulmonary complications are most frequently observed with dasatinib but all other Bcr-Abl TKIs have been implicated. Pleural effusions are the most frequent pulmonary complication of TKIs, usually associated with dasatinib and bosutinib. Pulmonary arterial hypertension is an uncommon but serious complication of dasatinib, which is often reversible upon discontinuation. Bosutinib and ponatinib have also been associated with pulmonary arterial hypertension, while imatinib has not. Rarely, interstitial lung disease has been associated with TKIs, predominantly with imatinib.

Mechanistically, dasatinib affects maintenance of normal pulmonary endothelial integrity by generating mitochondrial oxidative stress, inducing endothelial apoptosis and impairing vascular permeability in a dose-dependent manner. The mechanisms underlying other TKI-related complications are largely unknown. Awareness and early diagnosis of the pulmonary complications of Bcr-Abl TKIs is essential given their seriousness, potential reversibility, and impact on future treatment options for the underlying chronic myelogenous leukaemia.

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BOX 1 Key messages

1. Bcr-Abl tyrosine kinase inhibitors have been associated with certain pulmonary complications, including exudative pleural effusions, chylothorax, interstitial lung disease and pulmonary arterial hypertension. Due to its broader range of off-target protein kinase inhibition and its effects on endothelial cell function, dasatinib is the tyrosine kinase inhibitor most frequently associated with pleural effusion and pulmonary arterial hypertension.
2. Clinicians and patients should be aware of the potential adverse pulmonary effects of tyrosine kinase inhibitors prior to initiation. Unexplained respiratory symptoms require further evaluation including chest x-ray and/or computed tomography of the chest, transthoracic echocardiography, pulmonary function tests and cardiac biomarkers such as NT-proBNP.
3. Many pulmonary complications are reversible upon discontinuation of the offending medication and usually do not recur if another tyrosine kinase inhibitor is introduced. However, multidisciplinary management and close clinical follow-up is necessary to ensure resolution and detect early recurrences.

## Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder characterised by a cytogenetic hallmark in the Philadelphia chromosome and its associated t(9;22)(q34;q11.2) translocation. This translocation results in a *BCR–ABL1* fusion gene which codes for a Bcr-Abl1 oncoprotein with constitutively active tyrosine kinase activity [1]. The ability of Bcr-Abl to induce a similar disease in mice confirmed its pathogenic role and led to the development of tyrosine kinase inhibitors (TKIs), a new class of anticancer agents. The discovery and clinical use of TKIs, led by imatinib and subsequently enriched with second-generation (dasatinib, nilotinib and bosutinib) and third-generation (ponatinib) TKIs, has revolutionised the treatment of chronic CML [2]. In the TKI era, a patient diagnosed with CML in the chronic phase may anticipate a normal life expectancy [3]. Thus, the prevalence of CML is increasing in western countries. Most patients will experience a long-enduring treatment with an "optimal" or an intermediate "warning" response as defined by European LeukemiaNet criteria [4]. In this situation, no difference in survival can be demonstrated between imatinib and second-generation TKIs used as first line [5, 6]. In patients who achieve a sustained deep-molecular response, defined by a Bcr-Abl1$^{IS}$ quantification less than 0.01% for at least 1 year after a treatment duration of at least 3 years, more than half can successfully stop their TKI to enter a treatment-free remission period [7]. Second-generation TKIs may achieve faster and deeper molecular response than imatinib and are increasingly proposed as first-line options for patients, despite the recognised higher risk of adverse events, including notable pulmonary complications. The objectives of this narrative review are to summarise current knowledge on the epidemiology, clinical features, pathophysiology and management of pulmonary complications of Bcr-Abl TKIs.

## Search strategy

References included this narrative review were identified by searching PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) for articles published up to June 1, 2019 and an updated search was done on April 21, 2020, using the terms "pulmonary hypertension", "pleural effusion", "pneumonitis" OR "interstitial lung disease" AND "kinase inhibitor", "bcr-abl", "imatinib", "dasatinib", "nilotinib", "bosutinib" or "ponatinib", which resulted in 2190 articles. Articles resulting from these searches and relevant references cited in those articles were screened. Articles in English or French were reviewed in full. Articles in other languages with abstracts in English were reviewed if sufficient detail was present in the abstract. Articles relating to non-Bcr-Abl protein kinase inhibitors were not evaluated.

## Bcr-Abl TKIs

Imatinib was the first Bcr-Abl protein TKI developed for CML. Imatinib is a competitive inhibitor of adenosine triphosphate (ATP) targeting the inactive form of Bcr-Abl. When bound in the catalytic site in place of ATP, imatinib maintains Bcr-Abl in its inactive form inhibiting both proliferation and promoting apoptosis of Bcr-Abl cells [8]. However, mutations in the *Abl* gene leading to imatinib inefficacy or resistance have been observed. These mutations involve modifications on the catalytic site and decrease imatinib binding. More than 80 specific types of substitutions have been reported; of which, the T315I mutation is the most resistant. Therefore, a second generation of Bcr-Abl TKIs (dasatinib, nilotinib, and bosutinib) was developed, followed by a third generation with ponatinib. Nilotinib and ponatinib have the same mechanism of action as imatinib in blocking the inactive form of Bcr-Abl (type II inhibitor), whereas dasatinib and bosutinib block the active form (type I inhibitors) [9]. Dasatinib, nilotinib and bosutinib have a higher potency than imatinib and could be active on the majority of imatinib of Bcr-Abl-resistant cells [10]. However, only ponatinib is capable in the case of a T315I mutation [11].

Imatinib, nilotinib, bosutinib and dasatinib are indicated in the first-line treatment of CML in the chronic phase [12]. Regarding benefit, there is no significant survival difference reported between these three TKIs. However, in France for example, due to an insufficient clinical benefit judged by authorities, dasatinib is not reimbursed as a first-line treatment for CML. In addition to the issue of reimbursement, choice of TKI should be based on a patient's characteristics (age, comorbidities, associated medications, *etc*.) and the risk of adverse events for each TKI. Bcr-Abl TKIs have many potential adverse effects. Some of them are common, such as skin and subcutaneous tissue reactions or hepato-biliary disorders. However, certain TKIs have a predilection for causing specific complications. For example, dasatinib can promote the development of pleural effusions, pulmonary arterial hypertension (PAH) and haemorrhagic complications; nilotinib may induce metabolism and nutrition disorders and vascular events, and ponatinib is associated with venous and arterial thrombosis. The characteristics of the Bcr-Abl TKIs are detailed in table 1.

Despite their monikers as Bcr-Abl-targeted therapies, imatinib, nilotinib, dasatinib, bosutinib and ponatinib are actually multi-kinase inhibitors, with off-target effects depending on the particular drug and dosage. The spectrum of off-target inhibition, in addition to Bcr-Abl, ranges from six (nilotinib) to 28 (dasatinib) other protein targets (table 2). For example, imatinib also blocks the platelet derived growth factor (PDGF) receptors and the mast/stem cell growth factor receptor Kit; dasatinib inhibits the proto-oncogene tyrosine-protein kinase Src, and ponatinib inhibits the vascular endothelial growth factor receptor 2 and fibroblast growth factor receptors 1 to 4 [13]. The other targets for each Bcr-Abl TKI are depicted in table 2. Modulation of these targets may have a clinical impact in terms of tolerance of each

TABLE 1 Main characteristics of Bcr-Abl TKI

| | 1st generation | 2nd generation | | | 3rd generation |
|---|---|---|---|---|---|
| | **Imatinib** | **dasatinib** | **nilotinib** | **bosutinib** | **ponatinib** |
| **Year of EMA** | 2001 | 2006 | 2007 | 2013 | 2013 |
| **Type of Bcr-Abl inhibition** | II | I | II | I | II |
| **Potency compared with imatinib** | _ | 300× | 30× | 45× | 500× |
| **Indications in CML treatment (chronic phase)** | | | | | |
| **1st line therapy** | yes | yes* | yes | no | no |
| **2nd line therapy** | | | | | |
| Intolerance to 1st line TKI | yes | yes | yes | yes | no |
| Failure of 1st line imatinib | - | yes | yes | yes | yes |
| Failure of 1st line nilotinib or dasatinib | no | yes | yes | yes | yes |
| **3rd line therapy** | | | | | |
| Failure and/or intolerance to 2nd line TKI | any of the remaining tyrosine kinase inhibitors | | | | |
| **Any line, T315I mutation** | No | no | no | no | yes |
| **Dose** | 400–800 mg·day$^{-1}$ | 100 mg·day$^{-1}$ | 300 mg–400 mg twice a day (without food) | 500 mg·day$^{-1}$ (with food) | 45 mg·day$^{-1}$ |
| **Main adverse events** | Hepatobiliary disorders, Diarrhoea, skin disorders, pleural effusion | Pleural effusion, PAH, Haemorrhage, Hepatobiliary disorders, | skin disorders, hypertension, ischaemic heart disease, ischaemic cerebrovascular events, Hepatobiliary disorders, metabolism and nutrition disorders | skin disorders, diarrhoea, Hepatobiliary disorders, pleural effusion | Hypertension, ischaemic heart disease, ischaemic cerebrovascular events, venous thrombosis, skin disorders, diarrhoea, Hepatobiliary disorders |

CML: chronic myeloid leukaemia; EMA: European marketing authorisation; PAH: pulmonary arterial hypertension; TKI: tyrosine kinase inhibitor.

TABLE 2 Targets of imatinib, dasatinib, nilotinib, bosutinib and ponatinib

| Number of common targets | Target | Imatinib | Dasatinib | Nilotinib | Bosutinib | Ponatinib |
|---|---|---|---|---|---|---|
| **All** | | | | | | |
| | ABL | ✓ | ✓ | ✓ | ✓ | ✓ |
| **4** | | | | | | |
| | Kit | ✓ | ✓ | ✓ | | ✓ |
| | PDGFRA | ✓ | ✓ | ✓ | | ✓ |
| | PDGFRB | ✓ | ✓ | ✓ | | ✓ |
| | DDR1 | ✓ | ✓ | ✓ | | ✓ |
| | CSF1R | ✓ | ✓ | ✓ | | ✓ |
| | LCK | ✓ | ✓ | | ✓ | ✓ |
| | EGFR | ✓ | ✓ | | ✓ | ✓ |
| **3** | | | | | | |
| | RET | ✓ | ✓ | | | ✓ |
| | FYN | ✓ | ✓ | | ✓ | |
| | SRC | | ✓ | | ✓ | ✓ |
| | YES1 | | ✓ | | ✓ | ✓ |
| | LYN | | ✓ | | ✓ | ✓ |
| | HCK | | ✓ | | ✓ | ✓ |
| | NTRK1 | ✓ | | | ✓ | ✓ |
| **2** | | | | | | |
| | CA1,2,9,12 | ✓ | | ✓ | | |
| | AKT1 | ✓ | | | | ✓ |
| | CSK | | ✓ | | ✓ | |
| | TNK2 | | ✓ | | ✓ | |
| | BTK | | ✓ | | ✓ | |
| | SYK | | ✓ | | ✓ | |
| | FLT3 | | ✓ | | | ✓ |
| | EPHA2 | | ✓ | | | ✓ |
| | EPHA5 | | ✓ | | | ✓ |
| | EPHB1 | | ✓ | | | ✓ |
| | FGFR1,2 | | ✓ | | | ✓ |
| | EPHB4 | | ✓ | | | ✓ |
| | PTK2B | | | | ✓ | ✓ |
| **None** | | | | | | |
| | ACVR1B | | ✓ | | | |
| | ACVRL1 | | ✓ | | | |
| | ACVR1 | | ✓ | | | |
| | TUBA1A | | ✓ | | | |
| | MAPK14 | | ✓ | | | |
| | FGFR3,4 | | | | | ✓ |
| | VEGFR1,2,3 | | | | | ✓ |

Number of targets ranges from seven (nilotinib) to 29 (dasatinib). 28 targets are common to at least two TKIs. Among those, tyrosine-protein kinase ABL is systematically reported explaining their benefit in CML. Targets were extracted from Supertarget Database (http://insilico.charite.de/supertarget/index.php) and article by Greuber *et al.* [13]. Each tick signifies inhibition by the TKI in the corresponding column. ABL: abelson murine leukaemia viral oncogene; PDGFRA: platelet-derived growth factor receptor A; PFGFRB: platelet-derived growth factor receptor B; DDR1: discoidin domain receptor 1; CSF1R: colony stimulating factor 1 receptor; LCK: lymphocyte cell-specific kinase; EGFR: epidermal growth factor receptor; HCK: haemopoeitic cell kinase; NTRK1: neurotrophic tyrosine receptor kinase 1; CSK: C-terminal src kinase; TNK2: tyrosine kinases non-receptor 2; BTK: Bruton's tyrosine kinase; SYK: spleen tyrosine kinase; FLT3: fms-like tyrosine kinase 3; EPHA2: ephrin type A receptor 2; EPHA5: ephrin type A receptor 5; EPHB1: ephrin type B receptor 1; FGFR: fibroblast growth factor receptor; EPHB 4: ephrin type B receptor 4; PTK2B: protein tyrosine kinase 2 beta; ACVR1B: activin receptor type-1B; ACVRL1: activin receptor like type 1; ACVR1: activin receptor type 1; TUBA1A: tubulin alpha-1A; MAPK14: mitogen-activated protein kinase 14; FGFR: fibroblast growth factor receptor; VEGFR: vascular endothelial growth factor receptor.

drug and need to be known by prescribing clinicians. It is important to emphasise that, since TKIs are multi-kinase inhibitors, off-target inhibition of Bcr-Abl TKIs overlaps with those of TKIs used for other indications. For example, the Bcr-Abl TKIs used to treat CML share several off-target kinase inhibitory with epidermal growth factor receptor (EGFR) inhibitors used to treat non-small cell lung cancer (*e.g.* erlotinib, gefitinib) [14]. Examination of overlapping inhibition profiles could potentially shed some light

on the underlying mechanisms of toxicities common to both groups of Bcr-Abl and non-Bcr-Abl TKIs, such as interstitial lung disease (ILD) or pneumonitis [15, 16].

## Pathophysiology of Bcr-Abl TKI toxicities

In terms of pathophysiology of pulmonary toxicity, most of the available data involve dasatinib. Dasatinib is a highly effective multi-kinase inhibitor approved for first-line treatment of Philadelphia-positive CML and for all phases of Philadelphia-positive CML with resistance or intolerance to prior therapy, including imatinib. However, pleural effusions and PAH are two undesirable pulmonary effects observed with dasatinib use [17–22]. Although many of the exact cellular events and specific signalling pathways are incompletely understood, these side effects are often partially or completely reversible after drug withdrawal. As a result, we lack effective marker-based screening strategies and mechanism-based treatment options for PAH occurring in dasatinib-treated patients. In addition, a better understanding of mechanisms involved in dasatinib-induced PAH would not only help to ameliorate the management of dasatinib-treated patients, but also would improve our knowledge about the pathophysiological mechanisms underlying the development of PAH. An understanding the mechanisms of cardiopulmonary toxicities is also critical for developing future evidence-based preventive strategies [23, 24]. Similarly, mechanisms underlying TKI-related ILD remain unclear. Drug hypersensitivity reactions or a pharmacological effect of tyrosine kinase inhibition are possibilities but there are no mechanistic data available.

### *Endothelial cell injury and dysfunction*

The maintenance of the integrity of the endothelial lining is essential for a myriad of biological molecules and functions under its control [25], and some *in vivo* and *in vitro* evidence indicates that certain TKIs might contribute to the weakening of some specific endothelial functions. For example, rats treated with high doses of dasatinib exhibit increases in Evans blue dye extravasation into the lung parenchyma, supporting that dasatinib can alter endothelial integrity in rat lungs [22]. Consistent with these *in vivo* observations, it has been demonstrated that dasatinib leads to a rapid and reversible increase in paracellular permeability in monolayers of human pulmonary endothelial cells or umbilical vein endothelial cells (HUVECs) [22, 26]. Indeed, when confluent endothelial monolayers are exposed to increasing doses of dasatinib, there is an increase in the passage of macromolecules, loss of vascular endothelial cadherin and *zonula occludens* (ZO)-1 from cell-cell junctions, and development of actin stress fibres [22]. These phenomena are not found with imatinib [22]. Remarkably, this increase in endothelial permeability was dependent on reactive oxygen species (ROS) production induced by dasatinib. Indeed, co-treatment with the antioxidant agent *N*-acetyl-L-cysteine (NAC) was found to protect pulmonary endothelial cells against this loss of integrity both *in vivo* and *in vitro* [22]. Using immunofluorescence and confocal microscopy analyses, these authors also noted dilation of the lymphatic vessels in rat lungs treated with high doses of dasatinib compared with vehicle or high-dose imatinib-treated rats [22].

It is an open question whether these specific effects of dasatinib on pulmonary vessels are related to vascular cell sensitivity to oxidative stress or to their specific expression/activity of certain protein kinases. Nevertheless, it has been demonstrated that chronic dasatinib therapy causes pulmonary endothelial damage in humans and rodents [21]. Indeed, at a high dose, dasatinib treatment attenuated hypoxic pulmonary vasoconstriction responses and increased susceptibility to experimental pulmonary hypertension (PH) in rats [21]. It has been shown that pretreatment of rats with high doses of dasatinib, but not imatinib, increases their response to known inducers of PH, which closely mimics the findings observed in humans [21]. It has been shown that dasatinib induces pulmonary endothelial cell apoptosis in a dose-dependent manner, while imatinib does not. Among the processes of endothelial damage, induction of endoplasmic reticulum stress, and mitochondrial ROS production were shown to be play a central role (figure 1), a phenomenon that was demonstrated to be independent of Src family kinases [21]. High levels of ROS cause damage to proteins, nucleic acids, lipids and membranes, but also cause DNA damage. When repair of DNA damage is sufficient, this can result in altered transcription of specific vital genes, followed by cellular dysfunction and, ultimately, apoptosis [27]. Consistent with these findings, elevations in markers of endothelial dysfunction and vascular damage are more abundant in the serum of CML patients who were treated with dasatinib, compared with CML patients treated with imatinib [21]. Furthermore, these data are consistent with a report from Daccord *et al.* [28] which described the presence of irreversible pulmonary vascular lesions in explanted lungs of a case of severe dasatinib-induced PAH.

### *Smooth muscle ion channels and regulation of vascular tone*

Other mechanisms for the pulmonary complications of TKIs have been proposed such as inhibition of different potassium ion ($K^+$) channels [29], activation of the Rho kinase pathway [22, 26] or alterations of smooth muscle contractions and dysfunction [29–33]. However, further studies are required to elucidate the underlying mechanisms of pulmonary vascular dysfunction, as several TKIs such as imatinib [31, 33, 34],

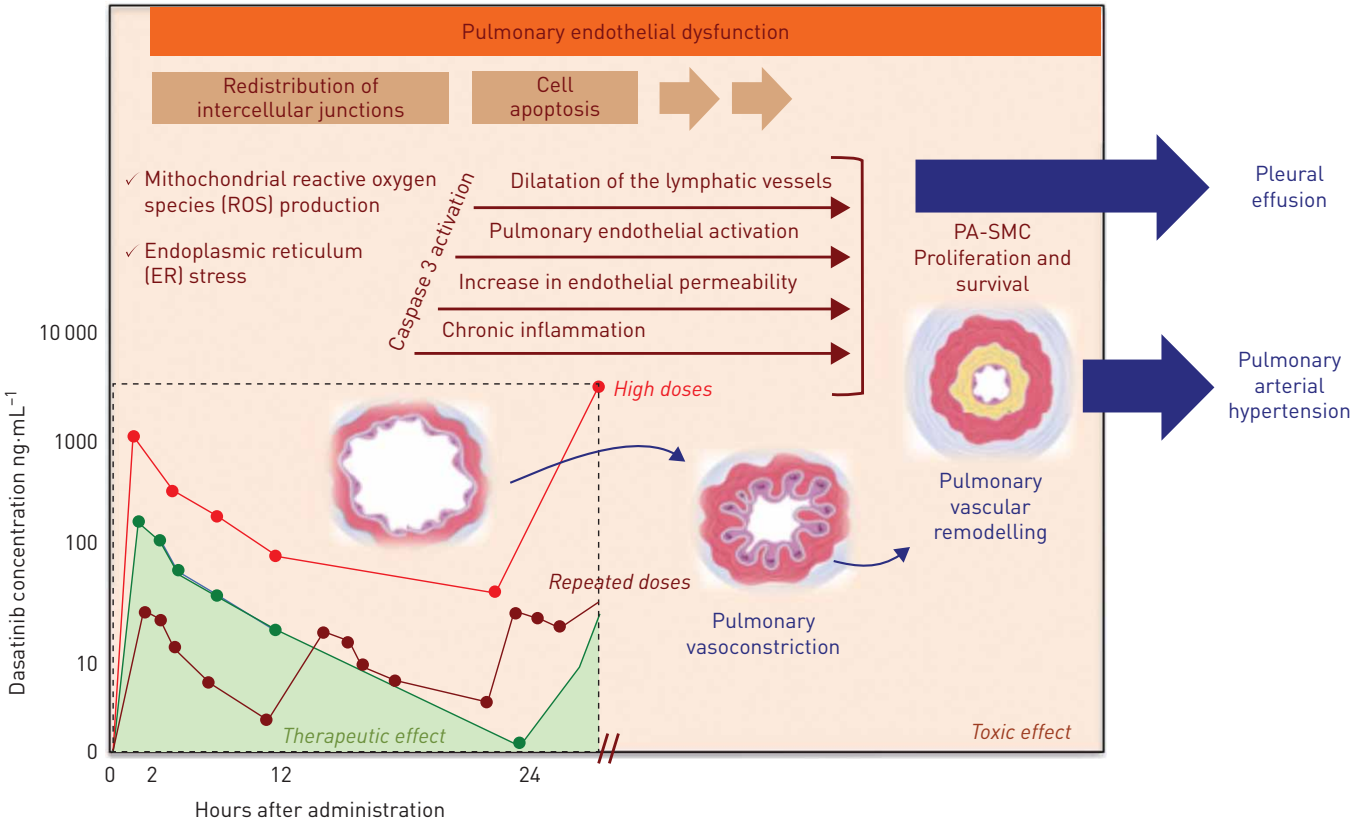


FIGURE 1 Mechanisms of dasatinib-induced pleural effusion and pulmonary arterial hypertension. PA-SMC: pulmonary artery smooth muscle cell.

nilotinib [31, 33] and sorafenib [33] have been shown to have potent vasorelaxant effects. In a recent study, Rieg *et al.* [31] reported that the vasorelaxation mechanisms of imatinib and nilotinib in precision-cut lung slices (PCLS) are linked to the generation of cAMP and mainly dependent on activations of $K_{ATP}$, $BK_{Ca^{2+}}$ and $K_v$ channels. Nagaraj *et al.* [29] reported that TWIK-related acid-sensitive potassium channel 1 (TASK-1, encoded by KCNK3) and Src co-localise in the plasma membrane of human pulmonary artery smooth muscle cells (PA-SMCs) and that Src is required for the functioning of TASK-1 channels. In isolated perfused and ventilated rat lungs, Fazakas *et al.* [26] also found that 100 nM of dasatinib increased pulmonary pressure, a phenomenon totally abolished by the Rho-kinase inhibitor Y27632 (10 µM); however, co-administration of Y27632 with 100 nM of dasatinib did not have a positive effect on pulmonary oedema in this *ex vivo* model. These observations are consistent with the results of Phan *et al.* [22] which demonstrated that this endothelial cell permeability is not sufficiently explained by ROCK activation or Lyn inhibition.

### *Other proposed mechanisms for TKI toxicities*

The signalling mechanisms underpinning TKI toxicities are complex, and may include alterations in the bone morphogenic protein [35], nuclear factor-κB [36, 37], and Akt/mTOR [38, 39] signalling pathways. However, it has also been shown that the dose, dosing regimen and interpatient variability in drug exposure play a role in the occurrence of some of these undesirable effects of TKIs [40–44], strongly supporting the concept that a pharmacokinetic-guided dose individualisation strategy may help to improve their safety profile. In a phase III dose finding trial, Shah *et al.* [45] have indeed shown that the incidence of pleural effusions was lower in patients receiving a dose of 100 mg once daily than in those given a 70 mg twice-daily dosing regimen. Consistent with these observations, it has been reported that rats treated with high dose of dasatinib (10 $mg \cdot kg^{-1} \cdot day^{-1}$, which is the equivalent to 10× the clinically relevant dose) developed pleural effusion over the period of 8 weeks, starting from week 5 [21]. Remarkably, this phenomenon was not observed in rats treated with dasatinib at the clinically relevant dose (1×) or in rats treated with a high dose of imatinib [22]. This dose–response relationship observed in humans and rats strongly suggests that these adverse events are likely to due to the loss/inhibition of some of the low-affinity target kinases of dasatinib, either alone or in combination with inhibition of Src or other Src family kinases such as Lyn, Yes, and Fyn [35, 46, 47].

In summary, it is likely that several overlapping mechanisms contribute to TKI toxicities; however, direct cell toxicity, endothelial dysfunction, excess cellular levels of ROS or indirect inflammatory-mediated events are strongly suspected to play a role.

## Pleural effusions and interstitial lung diseases

### *Epidemiology and clinical features*

Pleural effusions are the most common respiratory complications that may complicate the administration of TKIs. Their incidence varies according to the TKI, with pleural effusions being most frequently associated with dasatinib. Due to the more recent approval of both bosutinib and ponatinib, less data exist regarding their long-term toxicity profiles, including respiratory complications. A better knowledge of the incidence, the risk factors and the clinical characteristics of TKI-induced pleural effusions allowed the optimisation of their management over time. Although rarer, interstitial lung diseases have also been associated with TKI, with more or less acute clinical presentation and corresponding to various histological patterns. Both effusions and interstitial diseases should be suspected with the onset of nonspecific respiratory symptoms such as dyspnoea, cough or chest pain, or they may be diagnosed fortuitously on follow-up chest imaging.

#### *Dasatinib*

The occurrence of pleural effusions complicating the administration of dasatinib has been described in the earliest studies evaluating the efficacy of dasatinib in CML [48]. Further studies confirmed that up to 28% of patients treated with dasatinib for CML for a 5-year period and 33% for a 7-year period developed pleural effusions [5, 20] with an incidence of new cases that was similar each year [5, 49]. Dasatinib regimen, including both dosage and the number of doses per day, was quickly noted to be associated with the occurrence of pleural effusions [50], leading to a modification of drug administration to 100 mg once daily. A recent study further found a 6% incidence of pleural effusion in newly diagnosed chronic-phase CML treated with dasatinib 50 mg·day [51]. Other risk factors were identified for TKI-induced pleural effusions, such as CML phase (with an increase in patients with advanced phases) [52], presence of a cardiac history, hypertension, hypercholesterolaemia and a history of autoimmune disease [53–55]. The plurality of risk factors found probably accounts for different aetiologies of effusions in addition to dasatinib-induced, such as cardiac dysfunction, infectious or malignant causes, including related to the underlying haematological disease. However, in clinical studies, the most significant risk factor for developing pleural effusions is age, which was associated with dasatinib exposure (*i.e.* high minimum concentration value, $C_{min}$) [5, 43, 49]. Of note, pleural effusion-associated with dasatinib was not found to be associated with fluid retention [53]. Pleural effusions can be unilateral or bilateral and can be of variable size ranging from minimal to large volume. Analysis of pleural fluid mostly demonstrated exudates with a predominance of lymphocytes; however, some transudates have also been reported [54, 56]. Chylothorax has also been reported [54, 56–59]. The incidence of chylothorax has probably been overlooked because pleural fluid has not always been macroscopically chylous and the diagnosis of chylothorax requires systematic pleural fluid triglyceride quantification. A case of fibrothorax, characterised by a diffusely thick firm fibrous pleura on pleurectomy, has been reported in association with dasatinib following a history of recurrent chylothoraces [60]. In some cases, pleural effusion was reported to be associated with other side effects, such as pericardial effusion, interstitial pneumonia or pulmonary hypertension [5, 19, 54, 56]. Overall response to dasatinib, progression-free survival and overall survival were similar between patients who developed pleural effusion and those who did not [49].

More rarely, dasatinib has been associated with parenchymal lung abnormalities either alone or associated with pleural effusion (figure 2) [54, 61–64]. In a retrospective study, Bergeron *et al*. [54] identified that nine (22.5%) out of 40 patients with chronic-phase CML who received dasatinib developed lung abnormalities. Among them, seven patients had parenchymal abnormalities such as ground glass opacities, consolidations and/or septal thickening associated with pleural effusions for four of these patients. Respiratory symptoms included dyspnoea, cough and chest pain with a median time between dasatinib treatment initiation and respiratory symptoms of 229 days (range 20–510 days). Two patients presented with fever and myalgia. Bronchoalveolar lavage shows lymphocytic alveolitis in most cases [54, 64]. After dasatinib interruption, lung parenchymal manifestations usually resolve without treatment but corticosteroids have been instituted in some cases [54, 62–64]. Pneumonitis relapsed in only one of the patients for whom dasatinib was reintroduced at a lower dose [54].

#### *Imatinib*

Although peripheral and periorbital oedema are the most frequent imatinib-associated adverse events, occurring in 60% of the patients, pleural effusions were reported in only 0–0.8% of patients treated with imatinib for 5 years [5, 65]. Few cases of pleural effusion, mostly in associated with pericardial effusion, have been reported, often in a context of peripheral fluid retention [66, 67]. Several cases of imatinib-associated

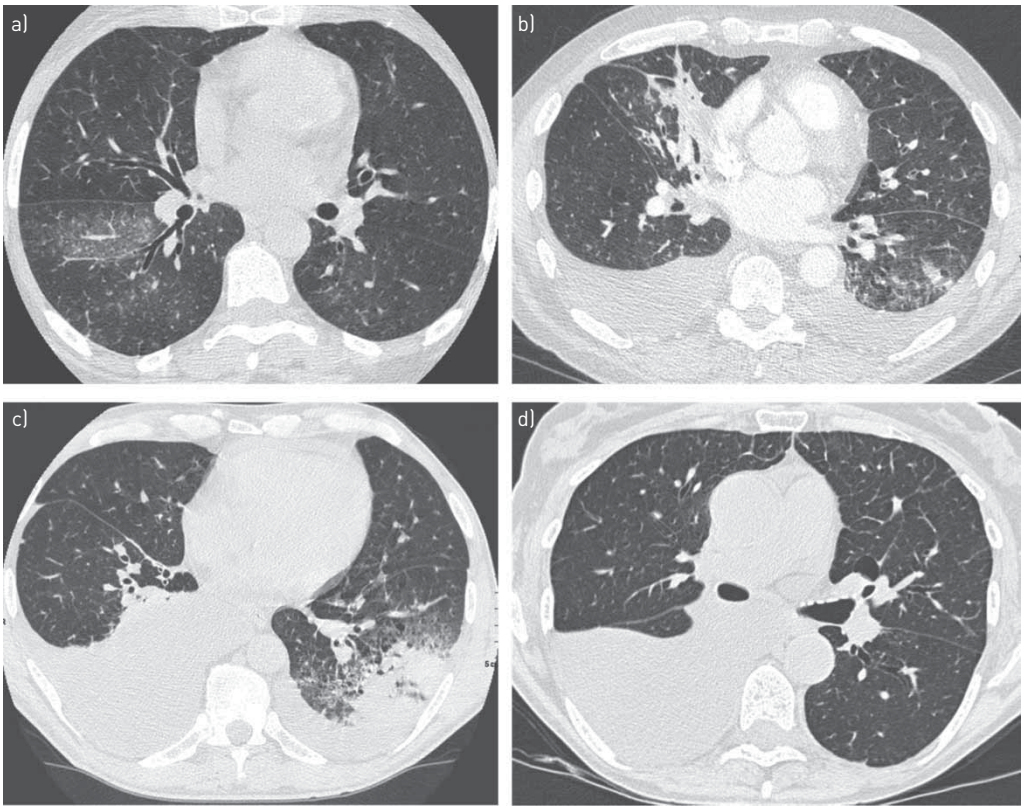


FIGURE 2 Various chest computed tomography scan patterns of dasatinib-related pleuro-parenchymal complications. (a) ground-glass opacities in the lower right lobe; (b) alveolar consolidation in the middle lobe associated with bilateral pleural effusion; (c) alveolar consolidation in the lower left lobe associated with bilateral pleural effusion; (d) right-sided pleural effusion.

interstitial lung diseases have been reported [68–72]. Ohnishi *et al.* [72] reported 27 cases of drug-induced interstitial disease (ILD) associated with imatinib. All patients presented with dyspnoea and 16 had hypoxaemia with a median time from imatinib initiation of 49 days (range 10–282 days). The median daily dose of imatinib was 400 mg (range 200–600 mg). The authors found no clear correlation between the development of imatinib-related pneumonitis and either the dose or duration of imatinib therapy. Computed tomography (CT) scan patterns included diffuse ground glass opacities, nodules consolidative patterns consistent with organising pneumonia, with or without signs of pulmonary fibrosis. Transbronchial biopsies found nonspecific histological patterns including inflammation and fibrosis. Imatinib was discontinued in all patients and 24 patients were treated with corticosteroids. After treatment, ILD either resolved completely (26%), improved (59%) or did not improve (15%), while one patient suffered from pulmonary fibrosis. After the ILD improved, imatinib was reintroduced at a lower dose (range 100–400 mg·day$^{-1}$) in 11 patients leading to recurrence in four patients. Another case, in which imatinib was reintroduced, developed irreversible pulmonary fibrosis [71]. A case of pulmonary alveolar proteinosis, characterised by accumulation of alveolar proteinaceous material and a "crazy paving" pattern on chest CT, has been reported in association with imatinib, which was exacerbated when switching to dasatinib [73].

### *Nilotinib*

Nilotinib-associated pulmonary side effects have rarely been reported [74]. Only scattered case reports of pleural effusion and pneumonitis have been published [74–76]. In a retrospective study in 120 patients receiving nilotinib as second-line therapy, pleural effusion was reported in 2% of patients [74]. A case of biopsy-proven organising pneumonia was described 3 years after nilotinib initiation [75]. The patient presented with cough for 4 weeks, without other respiratory symptoms, and alveolar consolidation in both lower lobes on CT scanning. After improvement following corticosteroid administration, nilotinib was reintroduced at a lower dose with no pneumonitis recurrence.

### *Bosutinib*

The incidence of bosutinib associated pleural effusions was less than 5% of the patients treated up to 5 years with bosutinib [77, 78]. Pleural effusions were more frequently reported in older patients [78, 79].

One case of bosutinib-related pneumonitis associated with pleural effusion has also been reported [80]. In this case, the CT pattern suggested organising pneumonia and the lung histology confirmed organising pneumonia with fibrinous exudate, interstitial eosinophilic infiltrate and small pulmonary arteries abnormalities [80].

#### *Ponatinib*

No cases of pleural effusions or interstitial pneumonitis have been specifically associated with ponatinib to date, with the exception of one case of interstitial lung disease reported in the phase 1 study evaluating the effect of ponatinib in refractory CML [11]. Since ponatinib and bosutinib are newer and less widely used, the actual risks of pulmonary complications are likely not yet known.

#### *Management of TKI-associated pleural effusion and interstitial lung disease*

The treatment of TKI-associated pulmonary side effects should take into account the severity of the respiratory involvement but also the control and prognosis of the underlying CML, including the available therapeutic alternatives. This management plan must involve a close collaboration with haematologists and should be discussed on a case-by-case basis.

As different causes of pleural effusions have been identified, detailed investigations are required. If the effusion has a sufficient volume, a diagnostic thoracentesis should be performed to differentiate exudate from transudate, to culture and exclude pleural infection, and to analyse the cellularity differential to narrow the differential diagnosis. The administration of empiric diuretics and/or corticosteroids has been reported [81]; however, this strategy has never been evaluated in an interventional study. It is likely that the efficacy of any treatment will depend on the underlying cause of the pleural effusion. Specific management will be different depending on the size and consequences of the pleural effusion. In cases with minimal fluid, continuation of the TKI with close clinical and radiological monitoring may be considered, whereas in cases of moderate or large pleural effusions, dose reduction, withdrawal or change of TKI should be considered according to alternative CML treatment options. However, in a recent study, dasatinib dose reduction after a first episode of pleural effusion did not prevent recurrence of this adverse event [81]. In the 5-year analysis from a phase III dasatinib *versus* imatinib study in CML (DASISION) trial, 22% of the patients who developed pleural effusion required drug interruption [5]. Therapeutic thoracentesis may rarely be necessary [5]. In an uncontrolled case series of six patients with refractory dasatinib-induced pleural effusions and severe dyspnoea, Aoyama *et al.* [82] reported that tolvaptan, a vasopressin V2-antagonist, in addition to diuretics improved symptoms and pleural effusions in five out of six patients, such that dasatinib could be continued or reintroduced in these patients. Therapeutic drug monitoring of TKI may be helpful to minimise the incidence of pleural effusions but is not widely used in practice [83].

Of note, patients who developed dasatinib-associated pleural effusion and subsequently received bosutinib may develop the same side effect with bosutinib [77, 84]. In a retrospective study, including 20 CML patients developing pleural effusion during dasatinib and who subsequently received bosutinib, only 30% had recurrence of pleural effusion [85].

The occurrence of pulmonary parenchymal opacities in a patient treated with TKIs must also lead to detailed assessment. Since ILD appears to be a rare complication of TKIs, other causes such as atypical infections, concomitant medications, exposures, and other unrelated medical conditions should be considered. The evolution of TKI related pneumonitis appears to be favourable with spontaneous resolution with TKI withdrawal [68, 80] or after corticosteroids [54, 70, 71, 75]. Any re-challenge with the suspected offending TKI should be considered according to the perceived risk–benefit balance for the individual patient. Based on limited data, imatinib-associated interstitial lung disease may not recur when switched to nilotinib [86, 87].

## Pulmonary arterial hypertension

### *Epidemiology*

PAH is characterised by elevated mean pulmonary arterial pressure (mPAP) (>20 mmHg) and pulmonary vascular resistance (PVR) (3 Wood units) with normal left heart filling pressures (pulmonary artery wedge pressure (PAWP) $\leqslant$15 mmHg) [88]. The first case reports of reversible PAH with dasatinib were published in 2009 [89, 90]. Then, in 2012, Montani *et al.* [17] described a series of nine patients with severe PAH (mPAP ranged from 30–59 mmHg) in patients treated with dasatinib, which was reversible in some cases following dasatinib discontinuation. From the Montani *et al.* [17] study, the estimated minimum annual incidence of PAH in dasatinib-treated patients in France was 0.45%. However, a recent multi-centre study of 212 dasatinib-treated patients from Australia found a much higher estimated prevalence of pulmonary hypertension on echocardiogram at 5%, although none of them had confirmation with right heart

catheterisation [91]. There were over 440 cases of PAH associated with protein kinase inhibitors reported to the World Health Organization's pharmacovigilance database (Vigibase) as of December 31, 2017 [35]. Dasatinib is, by far, the most frequently implicated Bcr-Abr TKI associated with PAH and is now considered a "definite" cause of drug-induced PAH in the recent 6th World Symposium on Pulmonary Hypertension [88]. New-onset PAH and/or PAH worsening has been reported with other Bcr-Abl TKIs such as bosutinib [18, 92, 93], ponatinib [94], nilotinib [95]. However, the association between these molecules and PAH is less established than for dasatinib, as many patients in these reports were incompletely characterised with right heart catheterisation or had been previously treated with dasatinib. In the Vigibase study by Cornet *et al.* [35], the reporting odds ratio (ROR: the proportion of PAH cases associated with a TKI compared with the proportion of PAH cases associated with all other drugs) was highest for dasatinib (28.6), followed by bosutinib (13.4) and ponatinib (3.88). Imatinib, the first most frequently used TKI for CML, has not been associated with the development of PAH. In fact, preclinical data and a phase II study suggested that imatinib may be an effective treatment for PAH [96]. However, despite improvements in exercise capacity and haemodynamics in the phase III randomised, placebo-controlled trial, the safety profile of imatinib was unacceptable with high rates of discontinuation and unexpected adverse events compared to placebo, including subdural haematoma [97].

### *Clinical features and outcomes*

In a long-term follow-up study of 21 patients from the French Pulmonary Hypertension Registry with right heart catheterisation-confirmed dasatinib-induced PAH, 71% of patients were female and the median age was 52 years old [19]. The median exposure to dasatinib before PAH diagnosis was 42 (8–74) months. There were concurrent pleural effusions in 62% and a pericardial effusion was present in six patients (29%). All patients had dasatinib discontinued, and 11 out of 21 patients received PAH-targeted therapies, such as sildenafil, bosentan or calcium channel blockers, with significant improvements in clinical and haemodynamic parameters at the time of a follow-up right heart catheterisation (figure 3). Interestingly, although the median mPAP decreased from 45 to 26 mmHg and PVR decreased from a median of 6.1 to 2.6 Wood units, there was persistent PAH in 37% of cases [19]. Furthermore, two patients had abnormally haemodynamic exercise responses consistent with exercise pulmonary hypertension, likely indicating some residual pulmonary vascular disease. Up to 68% of PAH patients have concurrent pleural effusions, which is much higher than the 25% rate in dasatinib clinical trials in CML [98].

While reversible cases could be caused by intense pulmonary arterial vasoconstriction, the frequent persistence of PAH suggests increased susceptibility to the development of irreversible pulmonary arterial remodelling in some dasatinib-treated patients. This was subsequently demonstrated in a histological analysis of explanted lungs from a patient with severe, progressive dasatinib-induced PAH who required lung transplantation [28]. Typical PAH histopathological features of severe arteriopathy, such as arteriolar obliteration, plexiform lesions, medial hypertrophy and intimal thickening were found in this patient. Two recent case reports lend further credence to a "second-hit" hypothesis of dasatinib-induced PAH in susceptible humans. The first case described dasatinib-induced PAH in a patient with systemic sclerosis [99], a disease in which patients are predisposed to PAH, with up to a 24% lifetime risk [100]. Another reported reversible PAH during dasatinib treatment for CML in the context of an occult anomalous pulmonary venous connection and sinus venosus atrial septal defect, a lesion associated with pulmonary vascular disease but which more likely contributed to dasatinib-induced PAH in light of the complete reversibility in this case [101]. Of the 62 right heart catheterisation-confirmed cases from the two largest studies of dasatinib-induced PAH, no deaths directly attributable to PAH were reported [19, 102]. Survival at 1, 3 and 5-years in the French registry study were 90.5%, 90.5% and 85.7%, respectively, which is very similar to long-term survival in randomised trials of dasatinib for CML [5, 19, 20]. However, one case of fatal dasatinib-induced PAH in a 36-year old woman has been reported [103].

### *Diagnosis and management of TKI-associated PAH*

Given the relatively low incidence of symptomatic PAH in TKI-treated patients, systematic screening in asymptomatic patients is not practical and is not recommended. When possible and feasible, a baseline echocardiogram may be performed prior to initiating dasatinib as a reference, in order to document the presence or absence of pre-existing pulmonary hypertension. In patients who have unexplained dyspnoea and/or symptoms of right heart dysfunction in the context of TKI treatment, the first step is to assess the likelihood of pulmonary hypertension by echocardiogram and to perform chest radiography, pulmonary function tests, and cardiac biomarkers (such as troponin or *N*-terminal pro-brain natriuretic peptide (NT-pro-BNP)) to evaluate other potential explanations such as pleural effusions, interstitial or obstructive lung diseases, pneumonia, ischaemic heart disease or left-sided heart failure (figure 4). According to current PAH guidelines, if an echocardiogram demonstrates an elevated tricuspid regurgitation velocity (TRV) >3.4 $m \cdot s^{-1}$, or if the TRV is <3.4 $m \cdot s^{-1}$ with secondary signs of pulmonary hypertension (such as

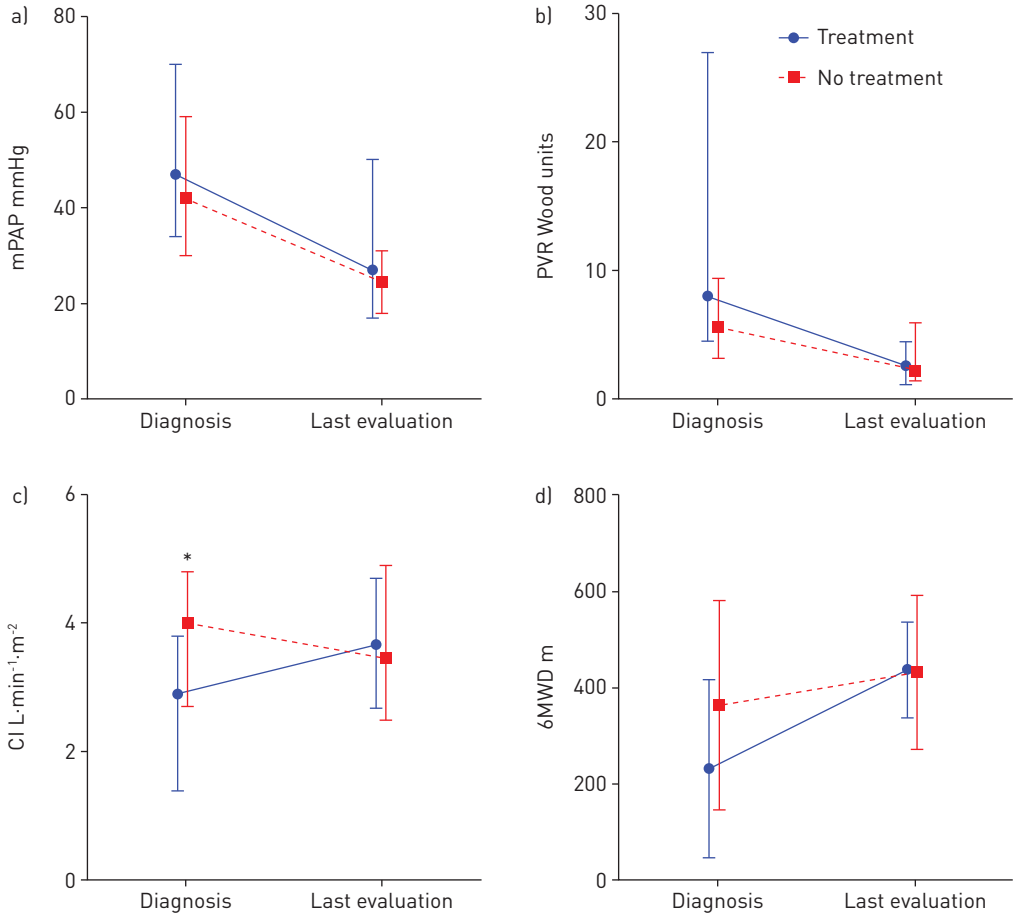


FIGURE 3 Changes in haemodynamic variables and 6-min walk distance (6 MWD) by treatment strategy. Changes in haemodynamics (n=19) from baseline to last evaluation according to initial treatment strategy after the discontinuation of dasatinib: no treatment (n=8), treatment group that received pulmonary arterial hypertension (PAH)-specific treatment (n=9) and calcium channel blocker therapy (n=2). Median (range) values for (a) mean pulmonary artery pressure (mPAP) and (b) pulmonary vascular resistance (PVR) were not significantly different between treatment groups at baseline or last evaluation, although baseline PVR was higher in the group who received PAH-specific treatment compared with those who received no treatment (8 *versus* 5.8 Wood units (WU); p=0.14). (c) Baseline median cardiac index was significantly lower in the treatment group.*p<0.01. (d) Baseline median 6 MWD was nonsignificantly lower in the treatment group (p=0.15). Reproduced from [19].

flattening of the interventricular septum or right heart chamber dilation), then a right heart catheterisation is recommended. Other causes of pulmonary hypertension, such as parenchymal lung disease or chronic thromboembolism, should be excluded with a high-resolution CT scan and ventilation–perfusion scan, respectively [104]. Although a 6% risk of venous thromboembolic disease has been associated with ponatinib [105], no cases of chronic thromboembolic pulmonary hypertension have been reported in association with TKIs. It must be emphasised that right heart catheterisation is crucial for proper diagnosis and to delineate the haemodynamic profile, since patients with TKI-induced PAH may have concurrent bilateral pleural effusions that would otherwise and erroneously suggest post-capillary pulmonary hypertension due to left heart disease. Patients receiving TKIs may also have post-capillary pulmonary hypertension due to elevated left heart pressure (mPAP >20 mmHg and PAWP >15 mmHg) or they may have elevated pulmonary artery pressure due to a hyperdynamic circulation from anaemia or infection, which is characterised by high cardiac output and normal PVR.

In such cases where right heart catheterisation confirms post-capillary pulmonary hypertension or hyperdynamic state, it is not necessary to stop the TKI. However, if PAH is confirmed, the offending TKI should be discontinued immediately.

For patients with intermediate or high-risk features such as severe symptoms (New York Heart Association (NYHA) functional class III–IV), severe haemodynamic derangement (cardiac index <2.5 $L \cdot min^{-1} \cdot m^{-2}$), or clinical signs of right heart failure, PAH therapies should be instituted in

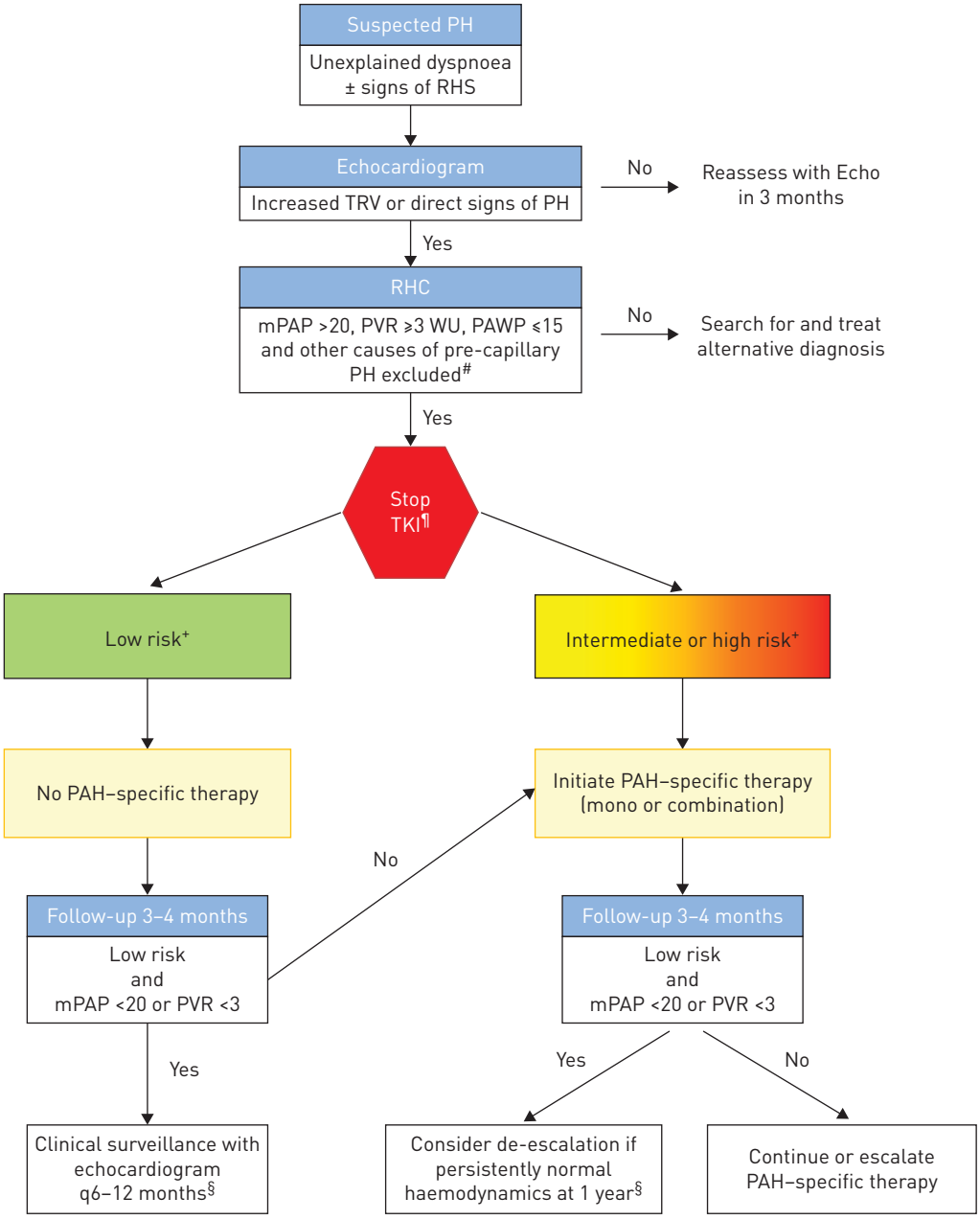


FIGURE 4 Diagnosis and management of suspected PAH related to tyrosine kinase inhibitor therapy. PH: pulmonary hypertension; TRV: tricuspid regurgitation velocity; RHC: right heart catheterisation; PAH: pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; TKI – tyrosine kinase inhibitor. #: other causes of pre-capillary PH include obstructive lung diseases, restrictive lung diseases, chronic hypoxemia, and acute or chronic thromboembolic disease. ¶: A multidisciplinary discussion is recommended to decide which Bcr-Abl tyrosine kinase inhibitor should replace the suspected causative drug. +: Risk assessment should be performed using a multidimensional tool such as the REVEAL score or the ESC/ERS 2015 Guidelines Risk assessment tool (table 13 in reference [103]). §More frequent follow-up evaluations or continuation of PAH specific treatment may be warranted if bosutinib or ponatinib are initiated due to the potential risk of recurrent/worsening PAH with these tyrosine kinase inhibitors.

concordance with PAH treatment guidelines [19, 104, 106]. The currently available treatment options for PAH include phosphodiesterase type-5 inhibitors (*e.g.* sildenafil, tadalafil), soluble guanylate cyclase stimulators (*e.g.* riociguat), endothelin receptor antagonists (*e.g.* bosentan, macitentan), prostacyclin analogues (*e.g.* epoprostenol, treprostinil) and oral prostacyclin receptor agonists (*e.g.* selexipag). There have been several reports of successful treatment of TKI-induced PAH with initial combination therapy of an endothelin receptor antagonists and a phosphodiesterase type-5 inhibitor [19, 107, 108]. For low-risk

patients with mild symptoms (NYHA I–II), no right heart failure and low risk haemodynamics (right atrial pressure <8 mmHg and cardiac index >2.5–3 $L \cdot min^{-1} \cdot m^{-2}$), expectant management without PAH therapies and discontinuation of the TKI can be considered [18]. However, short-term re-evaluation in 3–4 months should be performed in all patients regardless of whether PAH therapies are started, and should include invasive haemodynamic reassessment wherever possible, given the high rate of persistent PAH [109]. A multidisciplinary approach is necessary to determine which alternative TKI is appropriate and when it should commence, depending on severity of PAH and status of the underlying CML. Dasatinib should not be re-introduced and patients who are switched to bosutinib or ponatinib should be closely monitored given the possibility of worsening or recurrent PAH in this setting [18, 93, 94].

## Conclusions

The design and clinical development of Bcr-Abl tyrosine kinase inhibitors have revolutionised the treatment and prognosis of patients with chronic myelogenous leukaemia. Nevertheless, these molecules are not specific for Bcr-Abl and have effects on numerous other protein kinases and non-protein kinases. Serious and potentially fatal pulmonary complications can occur from Bcr-Abl TKI therapies, including pleural effusions, ILD and PAH, which requires a comprehensive evaluation and usually requires discontinuation of the TKI. Unexplained respiratory symptoms in a patient receiving a TKI should prompt further investigations including chest radiograph, pulmonary function testing, natriuretic peptides such as NT-proBNP, transthoracic echocardiography and CT of the chest. Knowledge of the adverse effect profiles of each Bcr-Abl TKI can be helpful for clinicians since, for example, PAH is most frequently associated with dasatinib but has not been associated with imatinib. Thus, the finding of pulmonary hypertension in a patient taking imatinib should prompt an exhaustive search for other causes. A deeper understanding of the mechanisms underlying these complications may help practitioners anticipate the potential risks of new TKIs under development and may guide monitoring and surveillance strategies in the future.

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