Multi tyrosine kinase inhibitor dasatinib as novel cause of pulmonary artery hypertension?

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Abstract.

Background:
Pulmonary arterial hypertension (PAH) is a life-threatening disease with poor prognosis. Encouraging efforts have been made to target the main vasoproliferative aspects of the disease. Promising therapeutics emerging are tyrosine kinase inhibitors such as imatinib.

Case presentation:
Here, we discuss the relevance of previously published cases and add another well-characterised patient who developed PAH under long-term therapy with the multi-tyrosine kinase inhibitor dasatinib approved for therapy of chronic myeloic leukemia (CML) and Philadelphia chromosome positive acute lymphocytic leukaemia (mean time of all patients on dasatinib: 26 months). Hence, we discuss the possibility of dasatinib itself causing PAH after long-term therapy and turn specialist’s attention to this possible severe side effect.

At present, the true incidence of dasatinib-associated PAH remains illusive and systematic data regarding haemodynamics are missing.

Conclusion:
We therefore recommend the systematic screening and subsequent collection of haemodynamic data of dasatinib-treated patients.

Keywords.
Pulmonary hypertension, drug induced, antiproliferative therapy, leukaemia, side effects
**Background.**

Pulmonary artery hypertension (PAH) is a severe and progressive, mainly vasoproliferative disease characterised by increased pulmonary artery pressure and vascular resistance eventually leading to right heart failure and death [1]. Different drugs have been identified to be causative of PAH such as anorectic drugs which gained notoriety in the 1970s [2]. Dasatinib is a multi tyrosine kinase inhibitor approved for therapy of chronic myeloic leukemia (CML) and Philadelphia chromosome positive acute lymphocytic leukemia, resistant or intolerant to treatment with another tyrosine kinase inhibitor imatinib [3].

During the last months there have been two reports connecting dasatinib with the development of PAH [4, 5]. Alarmingly, another patient was referred to our centre presenting with severe PAH under dasatinib therapy.

Here, we report on this case and would like to turn attention to this possible severe side effect of dasatinib.

**Case presentation.**

A 70-year old male with chronic phase CML diagnosed in 1996 was changed to dasatinib therapy due to subsequent haematological progress under hydroxyurea combined with interferon alpha (1996-2002) and imatinib (2002-2004: 400 mg/day, 2004-2005: 800 mg/d). Dasatinib treatment with a dose of 70 mg bid was applied for 32 months. Side effects during this period were minor as the medication was generally tolerated well. However, suddenly the patient developed tachy-dyspnea (25/min), transudative, non-malignant pleural effusions and fatigue increasing within a few weeks.

Echocardiography showed highly increased right ventricular systolic pressure (RVSP) of 73 mm Hg. Invasive haemodynamic evaluation confirmed severe PAH with consecutive right heart failure (details on prognostic factors and haemodynamics listed in Table 1). Clinically, the patient was assigned to WHO/NYHA functional class IV.

As other underlying pathophysiological reasons were ruled out by serological tests, chest CT, scintigraphy of the lung and abdominal ultrasound, dasatinib was consequently discontinued. Normal wedge pressures at right heart catheterisation also excluded tyrosine kinase inhibitor-induced cardiomyopathy or other left heart diseases as possible underlying pathologies. Dasatinib medication was discontinued and low-dose PAH-specific therapy with vasodilative phosphodiesterase-V inhibitor sildenafil (3x20 mg) was initiated. Acute symptoms relieved within days.
During the following 10 months prognostic parameters such as the N-terminal fragment of pro brain-natriuretic peptide (NT-proBNP), 6-minute walking distance (6MWD), RVSP, pulmonary artery mean pressure (PAP\textsubscript{mean}) and pulmonary vascular resistance (PVR) improved significantly (see Table 1). Additionally, the patient’s subjective well-being decisively advanced which was also reflected by functional class improvement to NYHA II (Figure 1).

**Discussion.**

*Does dasatinib itself trigger PAH?*

Pulmonary complications of dasatinib therapy have been reported ranging from pleural effusions to lung parenchymal affections [6]. In particular, pleural effusions caused by dasatinib are well recognised and have been documented in various studies [3, 6, 7]. In addition to the EMEA data set [3], in a retrospective analysis of 138 patients receiving dasatinib in once or twice daily treatment schedules, pleural effusions of any grade were detected in 35% of the complete study population comprising chronic phase, accelerated phase and blast crisis [7].

Statistically significant, dose-dependent increase in RVSP was reported in a subgroup of 18 patients and dasatinib cessation led to normalisation of RVSP in 10 patients [7]. Pleural effusion, dyspnoea, nausea, fatigue and oedema - unspecific yet classical symptoms found in PAH – are among the most frequently observed unwanted dasatinib effects. Up to now, the extent of dasatinib-associated PAH in contribution to these symptoms remains illusive since data regarding haemodynamics are lacking. However, all three detailed cases with dasatinib-related PAH developed disease after a 2 years of treatment (Figure 1C).

In our patient, connection of PAH with the patient’s myeloproliferative disease is possible in general but unlikely in this very case since (1) the CML was stable under dasatinib therapy for almost three years and no acceleration was detected until the end of dasatinib therapy and (2) a recent report shows a preferential connection of myeloproliferative disease-associated pulmonary hypertension with chronic thrombembolism [8], which was ruled out.

Most interestingly, although dasatinib also inhibits the platelet-derived growth factor receptor (PDGFR) pathway there may be a contrary effect on proliferative aspects of PAH compared to imatinib which has been shown to be an effective treatment improving PAH and animal survival as well as reversing pulmonary remodelling in rodent model systems and a series of case reports [9-13]. Hence, safety and efficacy trials are currently on the way (IMPRES, *ClinicalTrials.gov*: NCT00902174).
As key mechanisms, imatinib reversed overexpression and increased phosphorylation of PDGFRβ in pulmonary arteries from rat models of pulmonary hypertension, inhibited PDGFR-related ERK1/2 activation in lungs of these animals thereby suppressing rat pulmonary artery smooth muscle cell (PA-SMC) proliferation and inducing PA-SMC apoptosis [9].

While dasatinib inhibits Bcr-Abl at significantly lower inhibitory concentration (IC$_{50}$) as compared to Imatinib, its effect on c-kit and the platelet-derived growth factor receptor (PDGFR) are rather similar. In addition, however, and different from imatinib, dasatinib also inhibits the SRC family of kinases [14]. Whether this aspect of the compound is causally related to PAH development remains unclear.

**Conclusion.**

There are emerging data, that dasatinib could trigger drug-associated PAH. We therefore recommend the systematic screening and collection of haemodynamic data of dasatinib-treated patients.

**Competing interests.**

CB and THB have received travel grants, presentation fees and research grants form Bristol Myers Squibb. All other authors state no competing interests.

**Consent.**

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Authors’ contributions.**

FH, HJB, HK, THB and CB were involved in diagnostics and treatment of the patient. JKH, GK, HJB, SK and HK drafted the manuscript. All authors contributed to writing and editing the manuscript for important intellectual content.
**FIGURE LEGEND**

**Figure 1: Haemodynamics and prognosis factors of dasatinib-associated PAH**

Time courses of haemodynamics (Right ventricular systolic pressure, RVSP and mean pulmonary artery pressure, PAPmean, A) as well as exercise capacity (6MWT), WHO functional class and concentration of NT-proBNP (B) of the Hamburg patient are shown. Dashed horizontal line in (B) represents upper normal limit of NT-proBNP concentration (<197 ng/l). RVSP time courses of all three dasatinib-associated PAH cases characterised so far are shown in (C). Vertical dashed line represent time of discontinuation of dasatinib treatment.

<table>
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<th>TABLE 1: Haemodynamic and prognostic data</th>
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<td><strong>Time of presentation</strong></td>
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<tr>
<td>(w/o dasatinib)</td>
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<tr>
<td>Month:</td>
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<tr>
<td>RVSP [mm Hg]</td>
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<td>PAPmean [mm Hg]</td>
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<td>PVR [dyn*s/cm⁻⁵]</td>
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<td>HR [/min]</td>
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<td>proBNP [ng/l]</td>
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<td>6MWD [m]</td>
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<td>WHO/NYHA FC</td>
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**References.**


