Vascular Medicine

Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

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Background—The French pulmonary hypertension (PH) registry allows the survey of epidemiological trends. Isolated cases of precapillary PH have been reported in patients who have chronic myelogenous leukemia treated with the tyrosine kinase inhibitor dasatinib.

Methods and Results—This study was designed to describe incident cases of dasatinib-associated PH reported in the French PH registry. From the approval of dasatinib (November 2006) to September 30, 2010, 9 incident cases treated by dasatinib at the time of PH diagnosis were identified. At diagnosis, patients had moderate to severe precapillary PH with functional and hemodynamic impairment. No other incident PH cases were exposed to other tyrosine kinase inhibitors at the time of PH diagnosis. Clinical, functional, or hemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but 1 patient. Three patients required PH treatment with endothelin receptor antagonist (n=2) or calcium channel blocker (n=1). After a median follow-up of 9 months (min-max 3–36), the majority of patients did not demonstrate complete clinical and hemodynamic recovery, and no patients reached a normal value of mean pulmonary artery pressure (≤20 mm Hg). Two patients (22%) died at follow-up (1 of unexplained sudden death and 1 of cardiac failure in the context of septicemia, respectively, 8 and 12 months after dasatinib withdrawal). The lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 0.45%.

Conclusions—Dasatinib may induce severe precapillary PH fulfilling the criteria of pulmonary arterial hypertension, thus suggesting a direct and specific effect of dasatinib on pulmonary vessels. Improvement is usually observed after withdrawal of dasatinib. (Circulation. 2012;125:2128-2137.)

Key Words: adverse drug events • pulmonary hypertension • vascular complications • chronic myeloid leukemia • dasatinib

Normal mean pulmonary artery pressure (mPAP) is 14±3 mm Hg.1 Pulmonary hypertension (PH) is defined by an increase in mPAP ≥25 mm Hg at rest.2 PH can be classified into 5 groups according to pathomechanisms and clinical management. Group 1 (pulmonary arterial hypertension, PAH) includes precapillary PH (with a normal pulmonary capillary wedge pressure [PCWP] ≤15 mm Hg) that is idiopathic, heritable, drug-induced, or associated with various conditions; group 2 corresponds to postcapillary PH; group 3 corresponds to PH due to chronic lung diseases or hypoxemia; and group 4 corresponds to chronic thromboembolic PH. In contrast, group 5 consists of several forms of PH for which no specific therapy is available.


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which the pathogenesis is unclear or multifactorial. This group includes chronic myeloproliferative disorders that can cause PH by various potential mechanisms, including high cardiac output, splenectomy, direct obstruction of pulmonary arteries, chronic thromboembolism, portal hypertension, and congestive heart failure.3,4

Chronic myelogenous leukemia (CML) is a chronic myelo proliferative disorder characterized by a translocation between chromosome 9 and 22, leading to a pathogenic tyrosine kinase signal transduction protein, breakpoint cluster region/Abelson (BCR/ABL). The prognosis of CML has been transformed by tyrosine kinase inhibitors (TKIs), which inhibit BCR/ABL kinase, such as imatinib. However, up to 20% of CML patients treated by imatinib do not achieve complete cytogenetic response. Data suggest that 2 novel TKIs, dasatinib and nilotinib, are associated with higher rates of complete cytogenetic response in imatinib-resistant and newly diagnosed chronic-phase CML.5,6 It is noteworthy that dasatinib shows greater inhibition of BCR/ABL kinase in comparison with imatinib (>300 times in vitro) and also inhibits several other kinases, including the Src family.7,8

Until recently, dasatinib was proposed as a second-line therapy for patients with CML with resistant disease or who were unable to tolerate imatinib. A randomized, controlled trial has recently demonstrated that first-line dasatinib may induce significantly higher and faster rates of complete cytogenetic response in newly diagnosed CML in comparison with imatinib, suggesting that dasatinib may become more widely used in the treatment of CML in the future.5 In addition, dasatinib is currently being tested in other malignant disorders, such as melanoma and breast, head and neck, ovarian, and non—small-cell lung cancers.9

Although TKIs are usually well tolerated, these agents are nonetheless characterized by systemic toxicity. Important side effects of imatinib include edema, musculoskeletal pains, diarrhea, nausea, rash, abdominal pain, fatigue, headache, leucopenia, neutropenia, thrombocytopenia, anemia, and elevated liver enzymes, as well. It is noteworthy that imatinib may also induce cardiac toxicity, with an estimated prevalence of congestive heart failure of 0.6%.10 Pulmonary complications, and specifically pleural effusions, have been reported more frequently with dasatinib use compared with other TKIs.11-13 In addition, some case reports have suggested that PH may be a potential specific complication of dasatinib use.14-19 By contrast, clinical and hemodynamic improvements have been reported with imatinib therapy in 2 patients with CML and coexistent severe precapillary PH.20 It was suggested that this effect could be due to inhibition of tyrosine kinase targets of imatinib such as platelet-derived growth factor receptors and c-kit.21-23 A recent randomized controlled trial has shown that PAH patients treated by imatinib demonstrate hemodynamic improvements. However, further studies are needed to better evaluate the overall risk-benefit ratio of TKIs in PAH.24

The French PH Registry involves a network of specialized pulmonary vascular centers and has facilitated the study of trends in PH at a national level.25-27 Since 2009, cases of severe precapillary PH occurring in CML patients treated with dasatinib have been reported to the Agence Francaise de Sécurité Sanitaire des Produits de Santé, the French pharmacovigilance agency, and included in the French PH Registry. This finding prompted us to assess for a potential causal link. The present report summarizes the clinical characteristics and outcomes of incident cases of dasatinib-associated PH identified from the French Registry.

Methods

We first reviewed all incident cases from the French PH Registry of confirmed precapillary PH among patients in whom a diagnosis of CML was made or who had received treatment with dasatinib, imatinib, or nilotinib. This Registry was established in accordance with French bioethics laws (Commission Nationale de l’Informatique et des Libertés), and all patients gave their informed consent. Diagnosis of precapillary PH, defined as mPAP ≥25 mm Hg with a normal PCWP ≤15 mm Hg, was confirmed in all patients by right heart catheterization. Right atrial pressure, mPAP, PCWP, and mixed venous oxygen saturation (SvO2) were recorded. Cardiac output (CO) was measured by the standard thermodilution technique. Cardiac index was calculated as CO/body surface area. Pulmonary vascular resistance (PVR) were calculated as (mPAP-PCWP)/CO, expressed in mm Hg/L per min. Acute vasodilator testing was performed during right heart catheterization by the use of inhaled nitric oxide.28 Routine evaluation at baseline included medical history, physical examination, echocardiography, contrast-enhanced computed tomography of the chest, ventilation/ perfusion lung scan, abdominal ultrasound, autoimmunity screening, and HIV serology. Age at diagnosis and clinical status as assessed by modified New York Heart Association (NYHA) functional class were recorded at diagnosis. A nonencouraged 6-minute walk test according to the American Thoracic Society recommendations was performed. Point mutations and large rearrangements in BMPR2 gene were searched as previously described29 in 7 patients (patients 1, 2, 3, 4, 5, 6, and 8) after they underwent genetic counseling and signed written informed consent.

We then estimated the total number of patients treated with imatinib, dasatinib, and nilotinib in France during the period 2006 to 2010 using data from the French pharmacovigilance agency, and the pharmaceutical companies that market dasatinib (Bristol-Myers Squib, Princeton, NJ) and imatinib and nilotinib (Novartis, Basel, Switzerland).

Results

Description of Patients Treated With Imatinib, Dasatinib, and Nilotinib for Hematologic Malignancy Identified in the French PH Registry

From the approval of dasatinib (November 2006) to September 30, 2010, 9 incident PH patients with either a diagnosis of CML or treatment with dasatinib were identified. All 9 patients were receiving dasatinib therapy at the time of PH diagnosis. Characteristics of these 9 dasatinib-treated patients are shown in Table 1. Eight of the patients were females, and median age was 51 years (min-max 17-74). Chronic thromboembolic PH was excluded on the basis of ventilation/perfusion lung scan and contrast-enhanced computed tomography of the chest. Conditions associated with PAH, such as portal hypertension, HIV infection, connective tissue diseases, or congenital heart diseases were excluded. No patient had a family history of PAH, and no other drug and toxic exposure known to induce PAH were identified. No patient had a history of left heart disease or chronic respiratory
Progressive dyspnea on exertion and had marked functional impairment (NYHA functional class II, III, and IV in 2, 4, and 3 patients, respectively). Median 6-minute walk test was 242 m (min-max 0–508). Right heart catheterization confirmed precapillary PH in all patients (median PCWP 10 mm Hg, min-max 3–13) with severe hemodynamic impairment (Table 2). Median mPAP was 46 mm Hg (min-max 30–59), median CO was 6 L/min (min-max 3.3–8.9), and median PVR was 5.9 mm Hg/L per min (min-max 3.3–12.4). At diagnosis, median transpulmonary gradient was markedly increased to 34 mm Hg (min-max 22–48). Acute vasodilator testing was performed in 7 patients. One patient showing a decrease in mPAP from 47 to 36 mm Hg associated with normal CO was considered to have an acute vasodilator response. At the time of right heart catheterization, hemoglobin level was normal or moderately reduced in the majority of patients (median hemoglobin 12.3 g/dL, min-max 77–160). Circulating brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide levels were measured in 8 patients and were increased in all cases. Diffusion lung capacity for carbon monoxide was measured in 4 patients and revealed significantly reduced values in all cases with a median value of 53% of predicted (min-max 44–63). At the time of PH diagnosis, contrast-enhanced computed tomography of the chest showed bilateral pleural effusions in 6 of 9 patients; echocardiography confirmed mild pericardial effusion in 3 patients (Table 3).

Clinical, Functional, and Hemodynamic Evolution After Withdrawal of Dasatinib
A potential causal relationship between dasatinib exposure and development of precapillary PH was suspected. Dasatinib was therefore discontinued in all patients following confirmation of the diagnosis of PH, and treatment was substituted by nilotinib in 6 patients and by hydroxy carbamide in 2 others. In addition, treatment with the endothelin receptor antagonist bosentan was initiated in 2 patients. High-dose calcium channel blocker therapy was commenced for the patient with an acute vasodilator response (patient 1). In the remaining 6 patients, treatment with specific PAH therapy was not deemed necessary.

Evaluation of Pulmonary Hypertension at Diagnosis
At PH diagnosis, all patients presented with recent and progressive dyspnea on exertion and had marked functional
All but 1 patient showed clinical, functional, and/or hemodynamic improvements following dasatinib discontinuation with a median follow-up of 15 months (min-max 8–36 months). NYHA functional class improved and, at the last evaluation, 6 patients were in functional class I, 2 patients in class II, and 1 patient in class III (Figure 1A). Evolution of 6-minute walk test (Figure 1B) was available in 6 patients and showed significant improvement (478 m, min-max 278–635) in comparison with baseline values of these patients (242 m, min-max 0–429).

Even if hemodynamic improvement was usually observed, no patient demonstrated complete normalization of pulmonary hemodynamic indices (Table 4). An invasive hemodynamic evaluation at distance of withdrawal of dasatinib was available for 8 patients after a median follow-up of 5 months (min-max 3–18). One patient (patient 8) died before hemodynamic evaluation. The last right heart catheterization showed a significant hemodynamic improvement (Figure 1C and 1D) with a decrease of mPAP from 47 mm Hg (min-max 30–59) to 28 mm Hg (min-max 25–50) and a decrease of PVR from 6.1 mm Hg/L per min (min-max 3.3–12.4) to 2.9 mm Hg/L per min (min-max 1.6–5.0). Importantly, none of our patients reached a normal hemodynamic status, and mPAP remained elevated (>25 mm Hg) in all patients, consistent with a diagnosis of persistent PH.

In some patients with long-term follow-up and sequential evaluations, there was evidence of continuing improvement in clinical and hemodynamic parameters several months after dasatinib discontinuation, even among those patients in whom specific PAH therapy had not been introduced (Table 4). Nevertheless, patient 3 who did not present initial improvement had no secondary improvement either, and died at 12 months after PH diagnosis.

### Outcomes of Patients With Dasatinib-Induced PH

Two patients (22%) died at follow-up (patients 3 and 9). Survival of patients with dasatinib-induced PH is presented in online-only Data Supplement Figure I. Patient 3 died of cardiac failure in the context of septicemia due to Candida albicans, 12 months after diagnosis of dasatinib-induced PH.

### Tables

#### Table 2. Hemodynamic Parameters at the Time of PH Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>mPAP, mm Hg</th>
<th>RAP, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>CO, L/min</th>
<th>CI, L/min per m²</th>
<th>PVR, mm Hg/L per min</th>
<th>SvO₂, %</th>
<th>Acute Vasodilator Response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>14</td>
<td>13</td>
<td>5.6</td>
<td>2.9</td>
<td>6.1</td>
<td>66</td>
<td>Yes (mPAP: 36, CI: 2.9)</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>13</td>
<td>11</td>
<td>6.5</td>
<td>4.0</td>
<td>7.4</td>
<td>63</td>
<td>No (mPAP: 59, CI: 6.4)</td>
</tr>
<tr>
<td>3†</td>
<td>30</td>
<td>5</td>
<td>8</td>
<td>6.7</td>
<td>4.7</td>
<td>3.3</td>
<td>72</td>
<td>No (mPAP: 27, CI: 6.9)</td>
</tr>
<tr>
<td>4‡</td>
<td>30</td>
<td>5</td>
<td>8</td>
<td>6.7</td>
<td>4.7</td>
<td>3.3</td>
<td>72</td>
<td>No (mPAP: 27, CI: 6.9)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>6</td>
<td>10</td>
<td>8.9</td>
<td>4.8</td>
<td>4.4</td>
<td>65</td>
<td>No (mPAP: 50, CI: 5.1)</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>24</td>
<td>8</td>
<td>3.3</td>
<td>1.8</td>
<td>12.4</td>
<td>55</td>
<td>No (mPAP: 47, CI: 2.0)</td>
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<td>7</td>
<td>38</td>
<td>6</td>
<td>11</td>
<td>4.8</td>
<td>3.2</td>
<td>5.6</td>
<td>72</td>
<td>No (mPAP: 31, CI: 2.7)</td>
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<tr>
<td>8</td>
<td>37</td>
<td>6</td>
<td>3</td>
<td>3.3</td>
<td>1.9</td>
<td>10.3</td>
<td>54</td>
<td>No (mPAP: 39, CI: 2.4)</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>4</td>
<td>10</td>
<td>6.4</td>
<td>4.0</td>
<td>5.4</td>
<td>74</td>
<td>No (mPAP: 38)</td>
</tr>
</tbody>
</table>

mPAP indicates mean pulmonary artery pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed venous oxygen saturation.

*Acute vasodilator response was defined as a decrease in mPAP of ≥10 mm Hg to reach an absolute value of <40 mm Hg, associated with no change or an increase in CO.28

†Severe clinical and hemodynamic impairment necessitated initial management in an intensive care unit with catecholamines; right heart catheterization was performed after successful weaning of catecholamines 2 weeks after withdrawal of dasatinib.

‡PH was screened by echocardiography and confirmed by right heart catheterization 6 weeks after withdrawal of dasatinib.

#### Table 3. Clinical and Functional Evaluation at the Time of PH Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>NYHA FC, I–IV</th>
<th>Pleural Effusions</th>
<th>Pericardial Effusions</th>
<th>6-MWT, m</th>
<th>BNP,* ng/L</th>
<th>PaO₂, kPa</th>
<th>DLCO, % Theo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>Bilateral</td>
<td>No</td>
<td>300</td>
<td>168</td>
<td>8.9</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>Minimal and bilateral</td>
<td>Minimal</td>
<td>345</td>
<td>424</td>
<td>8.9</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>No</td>
<td>Minimal</td>
<td>0</td>
<td>1635</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>...</td>
<td>13.2</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>III</td>
<td>Bilateral</td>
<td>No</td>
<td>183</td>
<td>128</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>IV</td>
<td>Bilateral</td>
<td>No</td>
<td>0</td>
<td>Increase of NT-proBNP</td>
<td>9.9</td>
<td>...</td>
</tr>
<tr>
<td>7</td>
<td>II</td>
<td>Bilateral</td>
<td>No</td>
<td>429</td>
<td>432</td>
<td>9.9</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
<td>Bilateral</td>
<td>Minimal</td>
<td>0</td>
<td>603</td>
<td>7.6</td>
<td>...</td>
</tr>
<tr>
<td>9</td>
<td>II</td>
<td>No</td>
<td>No</td>
<td>630</td>
<td>163</td>
<td>10.6</td>
<td>63</td>
</tr>
</tbody>
</table>

BNP indicates brain natriuretic peptide; DLCO, diffusion lung capacity for carbon monoxide; NYHA FC, New York Heart Association functional class; PaO₂, partial pressure of arterial oxygen; 6-MWT, 6-minute walk test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; % Theo, percentage of predicted theoretical value.

*Normal values of BNP are <100 ng/L.
Of note, this patient was the only case in our series who did not show improvements after withdrawal of dasatinib and had the most severe hemodynamic compromise at diagnosis requiring management in intensive care unit with catecholamines (Table 4). At last evaluation (9 months after dasatinib withdrawal), the patient was still in NYHA functional class III with signs of right heart failure, and brain natriuretic peptide levels were elevated (2134 ng/L, normal value <100 ng/L). No right heart catheterization was performed, but Doppler echocardiography showed right ventricular dilatation, paradoxical septum, and estimated systolic PAP was 70 mm Hg. Even if the cause of death was not directly related to pulmonary vascular disease, the presence of severe PH and progressive right heart failure could be at least in part involved in the fatal outcome in this patient. Eight months after dasatinib withdrawal, the second patient (patient 9) experienced sudden death a few days after long-distance airplane flight, a situation at risk in PH patients. Evolution of 6-minute walk distance was available in 6 patients and showed significant improvement in comparison with baseline values (P < 0.05). C and D, An invasive hemodynamic evaluation after withdrawal of dasatinib was available for 8 patients after a median follow-up of 5 months (min-max: 3–18), mPAP and PVR significantly decreased after dasatinib withdrawal (P < 0.05). Of note, none of our patients reached a normal hemodynamic status, and mPAP remains elevated (≥25 mm Hg) in all patients at the last hemodynamic evaluation. E and F, the 2 patients treated with endothelin receptor antagonists; A, the patient treated with calcium channel blockers. NYHA indicates New York Heart Association; 6-MWD, 6-minute walk distance; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; ERA, endothelin receptor antagonists; CCB, calcium channel blockers.

Estimates of the Numbers of Patients Exposed to Imatinib, Dasatinib, and Nilotinib in France (2006–2010)
CML is a rare disease with an incidence ranging between 1 and 1.5 cases/100 000 per year and an estimated prevalence of 1/17 000 in France. Imatinib, dasatinib, and nilotinib have been available for use in France since February 2002, November 2006, and February 2008, respectively. The present data were discussed with the Agence Française de Sécurité Sanitaire des Produits de Santé in November 2010 and estimates of TKIs prescription in France between November 1, 2006 and September 30, 2010 were provided by Novartis France and Bristol-Myers-Squibb France (both in Rueil Malmaison, France). The numbers of patients treated by imatinib, dasatinib, and nilotinib in France during this period were 8750 (69.7% of the total number of patients exposed to one of these TKIs in France), 2900 (23.1%), and 900 (7.2%), respectively. All patients with incident PH in our case series were receiving dasatinib. Importantly, 13 PH cases (including our 9 cases) were reported to the French pharmacovigilance agency during the same period (online-only Data Supplement Figure II). Thus, the lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 13 of 2900 (0.45%). In contrast, no incident cases of PH associated with imatinib or nilotinib use were reported.
during the same period. Concomitantly, 51 PH cases have been reported to the pharmacovigilance of Bristol-Myers-Squibb (including 12 cases with right heart catheterization). Based on this information, the French, European, and US drug agencies have published warnings on the risk of PH in patients treated with dasatinib in March, July, and October 2011, respectively.

**Discussion**

Since 2008, the French PH Registry has identified 9 incident cases of symptomatic precapillary PH in patients with hematologic malignancies treated with dasatinib. In these patients, no other causes or risk factors for PH were identified and there was no clinical evidence of PH when dasatinib was initiated. However most patients had severe symptoms and marked hemodynamic compromise at time of PH diagnosis. As discussed in the updated PH classification, PH with unclear or multiple causes may develop in patients with CML. One hypothesis is that PH develops merely as a consequence of the underlying hematologic disorder. However, information from the French PH Registry from 2008 to 2010 showed that all incident PH cases reported in CML patients and/or patients treated by TKIs occurred only in individuals receiving dasatinib, which was, in most cases, introduced as a second-line treatment. Another argument in favor of a potential link between PH and dasatinib therapy is the clinical and hemodynamic improvement usually observed after dasatinib was replaced by either nilotinib or hydroxy-carbamide. In the majority of cases, these improvements occurred in the absence of specific PAH therapy. The lack of CML relapse or hemodynamic deterioration following introduction of nilotinib therapy, coupled with the lack of cases of incident PH among CML patients not treated by dasatinib (>75% of CML patients in that period) is highly suggestive of a causal link between dasatinib and PH. Given the availability of alternative CML therapeutic strategies and the fact that there was evidence of at least mild persistent PH in all patients, reintroduction of dasatinib was not attempted in any of our patients.

Recent case reports have described the occurrence of PH in dasatinib-treated CML patients. The strength of our report is the availability of both a large prospective PH database that allows surveillance of national trends for PH and invasive pulmonary hemodynamic data at baseline and following dasatinib withdrawal. In recent years, this database has facilitated the study of PAH occurring in patients exposed to fenfluramine or fenfluramine derivatives such as dexfenfluramine and benfluorex. The number of patients in France treated by dasatinib was relatively small at the time of our report (<3,000). Thus, the occurrence of 9 incident cases of severe precapillary PH in dasatinib-exposed individuals between 2008 and 2010 in our registry plus 4 additional cases reported at the French pharmacovigilance level indicated that this complication may affect at least 0.45% of chronically dasatinib-exposed individuals. Our data indicate that PH...
arises as a late complication of dasatinib therapy, occurring after 8 to 48 months of exposure, in accordance with previous reports.\textsuperscript{14–18} One of the common nonhematologic side effects of dasatinib is fluid retention and pleural effusions, but the underlying mechanisms remain unclear.\textsuperscript{11–13} Interestingly, we observed bilateral pleural effusions in 6 patients; however, severe precapillary PH persisted even after resolution of pleural effusions. Although PH remains a rare complication, it is important to note that, at this time, dasatinib was licensed only as a second-line therapy. Recent data suggest that dasatinib may be used as first-line therapy in CML. Therefore, this agent is likely to become increasingly prescribed in the future, and the number of cases of dasatinib-induced PH may increase, particularly with extended duration of therapy. We therefore recommend to screen routinely for PH by echocardiography before commencing dasatinib and to perform additional diagnostic testing in patients receiving this therapy who develop dyspnea or other symptoms suggestive of PH. Where these investigations indicate possible PH, a right heart catheterization is mandatory to confirm the diagnosis of PH.\textsuperscript{2}

In series reporting dasatinib-associated pleural effusion, sex ratio was consistent with the known sex distribution of CML (55\% of cases occurring in females).\textsuperscript{11,13} In our series, dasatinib-associated PH, we observed a female predominance (8 females and 1 male), that is in keeping with the female predominance characteristic of PAH.\textsuperscript{36} Estrogen metabolism, which has been potentially implicated in the pathogenesis of PAH,\textsuperscript{37} may also be relevant in dasatinib-induced PH. Nevertheless, because only a minority of patients exposed to dasatinib will develop PH, it is likely that other cofactors are required for the development of overt disease. Multiple hits are indeed likely to trigger the onset of PH, even among patients with an obvious predisposing condition, such as \textit{BMPR2} mutations.\textsuperscript{29,38} We screened for \textit{BMPR2} mutation in 7 patients, and only 1 \textit{BMPR2} variant of unknown significance was found. In the context of cardiotoxicity induced by TKIs, preexisting cardiac conditions predispose to cardiotoxicity,\textsuperscript{10,39,40} In our series, common cardiovascular risk factors are not associated with dasatinib-induced PH, and further studies are needed to identify the potential predisposing factors that could identify patients at high risk of dasatinib-induced PH. Interestingly, clinical, functional, and hemodynamic improvements were generally observed after dasatinib withdrawal. However, 1 patient died in the context of refractory right heart failure and another unexplained sudden death was reported in our case series. In addition, all subjects remained at least mildly symptomatic and had a persistently abnormal hemodynamic pattern at last follow-up. It is noteworthy that other reports that have suggested a complete reversibility of PH have no invasive hemodynamic evaluation at follow-up.\textsuperscript{14–18} Therefore, longer-term follow-up will be required to characterize the natural history and outcomes of dasatinib-induced PH.

Imatinib, dasatinib, and nilotinib are used for the treatment of CML because of their ability to inhibit the deregulated BRC-ABL tyrosine kinase.\textsuperscript{41,42} However, the kinase target profiles of these 3 drugs are markedly different (Table 5).\textsuperscript{43} Recently, the kinase and nonkinase targets of these 3 TKIs have been characterized, showing that dasatinib displayed a less specific target profile than imatinib or nilotinib.\textsuperscript{44} Several TKIs or multiple kinase inhibitors, including imatinib, sorafenib, and sunitinib exhibit cardiotoxicity both in experimental models and in humans.\textsuperscript{39,40,45} Kerkela et al\textsuperscript{40} demonstrated that the cardiotoxicity of TKIs was an unanticipated side effect of inhibition of c-Abl, a common characteristics of TKIs used in the treatment of CML. In addition, Chintalgattu et al\textsuperscript{46} reported that cardiomyocyte platelet-derived growth factor receptor-beta is a regulator of the compensatory cardiac response to pressure overload-induced stress, suggesting that inhibition of platelet-derived growth factor pathway may be at least in part responsible for cardiotoxicity due to TKIs. Accumulated evidence indicates that receptors of tyrosine kinases (RTKs) play an important role in the pathogenesis of PAH, and inhibition of some specific RTK signaling may represent an attractive treatment for the disease. RTKs bind to their ligands with high affinity, and several members of these cell surface receptors, including receptors of platelet-derived growth factor,\textsuperscript{21,22} fibroblast growth factor,\textsuperscript{2,4,48,49} and epidermal growth factor,\textsuperscript{50} are involved in the pathogenesis of human and experimental PH. A proof-of-concept 24-week randomized, double-blind, placebo-controlled pilot study showed that, although imatinib was not associated with significant change in the primary end point (6-minute walk test), treatment conferred significant hemodynamic improvements.\textsuperscript{24} It is noteworthy that neither imatinib nor nilotinib have been associated with incident cases of PH to date, and the association with dasatinib appears unique and paradoxical because it also acts as a potent RTK inhibitor. When analyzing the complex history of our patients, one cannot exclude that previous exposure to several drugs, such as interferon α2B, hydroxycarbamide, imatinib, and other che-

\begin{table}
\centering
\caption{Targets of Tyrosine Kinases Inhibitors Approved in the Treatment of CML: Imatinib, Nilotinib, and Dasatinib}
\begin{tabular}{|c|c|c|}
\hline
Imatinib, Nilotinib & Dasatinib \\
\hline
ABL & ABL & LIMK2 \\
ARG & ARG & TXK \\
BCR-ABL & BCR-ABL & DDR1 \\
KIT & KIT & DDR2 \\
PDGFR & PDGFR & PTK6/Brk \\
SRC & SRC & RAF1 \\
YES & YES & BRAF \\
FYR & FYR & RET \\
LYN & LYN & EGFR/ERBB1 \\
HCK & HCK & RIPK2 \\
LCK & LCK & EPHA2 \\
FGR & FGR & FAH \\
FRK & FRK & GAK \\
CSK & CSK & GCK \\
TAK & TAK & HHH98/TNNI3K \\
TEC & TEC & ILK \\
BMX & BMX & LIMK1 \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Adapted from Swords et al.\textsuperscript{43}
motherapies, could have played a part in the subsequent development of PH. However, the previous drug regimen of our patients did not include the same agents before dasatinib initiation (Table 1). The rapid relief of symptoms and hemodynamic improvements after withdrawal of dasatinib are consistent with a reversible component. Nevertheless, the absence of complete resolution observed after dasatinib discontinuation suggests some degree of associated pulmonary vascular remodeling may develop. In contrast to imatinib and nilotinib, dasatinib is a potent inhibitor of additional important families of RTKs, including the Src and the Eph receptors/ephrin tyrosine kinases (Table 5).43 c-Src tyrosine kinase is abundantly expressed in vascular tissue, and activation of Src appears to play a critical role for smooth muscle cell proliferation and vasoconstriction.51 Mounting evidence suggests a crucial role of c-Src tyrosine kinase in vascular homeostasis and its direct involvement in PH (Figure 2).51,52 Thus, it would be of interest to investigate the effect on pulmonary vasculature of the inhibition of Src and on the Eph receptors/ephrin tyrosine kinases, as well, by dasatinib.

In conclusion, we report cases of severe precapillary PH fulfilling the criteria of drug-induced PAH, confirmed by complete invasive hemodynamic evaluation, that suggest a direct and specific effect of dasatinib on the pulmonary vasculature. Although clinical improvement was generally observed after withdrawal of dasatinib, some patients remained symptomatic and showed persistent hemodynamic impairment several months after discontinuation of this agent. Even if PH is a rare complication in patients treated with dasatinib, the increased use of dasatinib in the treatment of CML will certainly increase the number of patients at risk of developing PH. Physicians need to be aware of this complication to appropriately monitor and manage these patients.30–32

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Disclosures
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References

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**Figure 2.** Schematic representation of major pathways of Src kinase. This schematic representation illustrates the key functional role played by Src activation on modulation of essential signaling pathways for proliferation, vasodilatation, and vasoconstriction. Src signaling in the absence of or in the presence of parallel signaling pathways initiated by growth factor, integrin, and cytokine receptors on the surface of cells, including PDGF-R, may promote cellular proliferation via upregulation of extracellular signal-regulated kinase (ERK)1/2 activation and genes important in cell cycle progression, such as cyclin D and cyclin E. In addition, c-Src activation can trigger a signaling cascade resulting in tyrosine phosphorylation of phospholipase Cγ (PLCγ), leading to increase in intracellular levels of inositol 1,4,5-triphosphate (1,4,5-IP₃) and diacylglycerol. PKC activated via diacylglycerol and 1,4,5-IP₃ stimulates calcium release, which activates NO synthase leading to NO production. Moreover, Src-mediated tyrosine phosphorylation of eNOS at Tyr-83 modulates directly eNOS activity in endothelial cells. In contrast, Src participates in regulation of vascular tone through inhibition of voltage-dependent (including Kv1-5) and calcium-activated potassium channels. PDGF-R indicates platelet-derived growth factor receptor; PKC, phosphokinase C; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; DAG, diacylglycerol.


**CLINICAL PERSPECTIVE**

The prognosis of chronic myelogenous leukemia has been transformed by tyrosine kinase inhibitors that inhibit BCR/ABL kinase, such as imatinib, dasatinib, and nilotinib. The present report summarizes the clinical characteristics and outcomes of 9 incident cases of severe precapillary pulmonary hypertension (PH) fulfilling the criteria of pulmonary arterial hypertension induced by dasatinib use identified from the French PH registry. PH occurred after 8 to 48 months of dasatinib exposure. Most patients had severe symptoms and marked hemodynamic compromise at time of PH diagnosis. Based on our registry and data from the national pharmacovigilance agency, the lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 0.45%. Of note, clinical, functional, and hemodynamic improvements were generally observed after dasatinib withdrawal. Nevertheless, all subjects remained at least mildly symptomatic and had persistent abnormal hemodynamics. Even if PH is a rare complication in patients treated with dasatinib, the increased use of this agent in the treatment of chronic myelogenous leukemia may result in higher numbers of patients at risk of developing drug-induced pulmonary arterial hypertension. Physicians need to be aware of this complication to appropriately monitor and manage these patients. We therefore recommend screening routinely for PH by echocardiography before commencing dasatinib and performing additional diagnostic testing in patients developing dyspnea or other symptoms suggestive of PH. Where these investigations indicate possible PH, a right heart catheterization is mandatory to confirm the diagnosis and mechanisms of PH.
SUPPLEMENTARY MATERIALS

Supplementary Figure 1. Survival from dasatinib discontinuation of patients with dasatinib-induced PH.

Two patients (22%) died at follow-up (patients 3 and 9). Patient 3 died of cardiac failure in the context of septicaemia due to Candida Albicans, 12 months after diagnosis of dasatinib-induced PH. Of note, this patient was the only case of our series that did not show improvements after withdrawal of dasatinib and had the most severe hemodynamic compromise at diagnosis requiring management in intensive care unit with catecholamines. Eight months after dasatinib withdrawal, patient 9 experienced sudden death several days after long-distance airplane flight.

Supplementary Figure 2. Occurrence of incident cases of pre-capillary pulmonary hypertension in subjects treated with tyrosine kinase inhibitors in the French Registry (2002-2010)

From the approval of dasatinib (November 2006) to 30th September 2010, 9 cases from the French PH Registry were reported to the French pharmacovigilance agency. Four additional cases were reported, thus the lowest estimate of incident pre-capillary PH occurring in patients exposed to dasatinib in France was 13/2,900 (0.45%). Of note, neither imatinib nor nilotinib have been associated with incident cases of PH to date.
Supplementary Figure 1.

Supplementary Figure 2.
**Résultats tardifs de la comissurotomie mitrale percutanée à 20 ans**

**Création et validation d’un score de risque prédicant les résultats fonctionnels à long terme à partir d’une série de 912 patients**

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**Contexte**—Le suivi à long terme d’une comissurotomie mitrale percutanée permet l’identification des facteurs prédicant les résultats à long terme.

**Méthodes et résultats**—Les résultats à long terme de la comissurotomie mitrale percutanée ont été évalués chez 1 024 patients consécutifs. Pour 912 (89 %) d’entre eux, les résultats immédiats ont été jugés bons (sur la base de l’obtention d’une aire valvulaire d’au moins 1,5 cm² sans régurgitation mitrale supérieure à 2/4). Ces 912 patients ont été randomisés en deux cohortes de, respectivement, 609 et 303 sujets dont la première a été utilisée pour élaborer un système de cotation destiné à prédire les résultats fonctionnels à long terme et la seconde pour valider ce système. Au terme de 20 ans de suivi, le taux de bons résultats fonctionnels (définis par l’absence d’événement à type de décès de cause cardiovasculaire, d’intervention chirurgicale sur la valve mitrale ou de nouvelle comissurotomie mitrale percutanée, le patient se situant en classe I ou II de la New York Heart Association [NYHA]) a été de 30,2 ± 10,5 %. Les résultats tardifs de la comissurotomie mitrale percutanée dans une population de patients aux caractéristiques variées, les résultats fonctionnels demeuraient bons chez 30 % de ces individus. La possibilité de prédire les résultats fonctionnels à long terme repose sur de multiples facteurs et apparaît fortement influencée par l’âge et la qualité des résultats immédiats. Un système de cotation simple ayant fait l’objet d’une validation apparaît utile pour estimer les résultats futurs chez chaque patient. *(Traduit de l’anglais : Late Results of Percutaneous Mitral Commissurotomy up to 20 Years: Development and Validation of a Risk Score Predicting Late Functional Results From a Series of 912 Patients. Circulation. 2012;125:2119–2127.)*

**Mots clés** : dilatation par ballonnet ■ études de suivi ■ rétrécissement mitral ■ statistiques

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**L’hypertension artérielle pulmonaire chez les patients traités par le dasatinib**

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**Contexte**—Le registre français de l’hypertension artérielle pulmonaire (HTAP) permet d’observer les tendances épidémiologiques. Des cas isolés d’HTAP précapillaire ont été rapportés chez des patients atteints de leucémie myéloïde chronique traités par le dasatinib, un inhibiteur de la tyrosine kinase.

**Méthodes et résultats**—Cette étude a été menée pour examiner les cas d’HTAP secondaire à l’administration de dasatinib notifiés au registre français de l’HTAP. Entre l’autorisation de mise sur le marché du dasatinib (novembre 2006) et le 30 septembre 2010, 9 cas d’HTAP ont concerné des patients traités par ce médicament. A la date du diagnostic, ces individus présentaient une HTAP précapillaire de degré modéré à sévère ainsi que des anomalies fonctionnelles et hémodynamiques. Aucun des autres patients ayant développé une HTAP n’était traité par un autre inhibiteur de la tyrosine kinase lorsque l’affection a été diagnostiquée. Chez tous les patients sauf un, des améliorations du statut clinique, fonctionnel ou hémodynamique ont été observées dans les 4 mois ayant suivi l’arrêt du dasatinib. Pour 3 des patients, il a été nécessaire de traiter l’HTAP par l’administration d’un antagoniste des récepteurs à l’endothéline (n = 2) ou par un inhibiteur calcique (n = 1). Au terme d’une durée médiane de suivi de 9 mois (extrêmes : 3–36 mois), une majorité de patients n’avait pas encore totalement récupéré sur les plans clinique et hémodynamique et la pression artérielle pulmonaire moyenne n’avait retrouvé son niveau normal (±20 mmHg) chez aucun des sujets. Deux patients (22 %) sont décédés au cours du suivi, le premier de mort subite inexpliquée 8 mois après l’arrêt du dasatinib et le second d’insuffisance cardiaque dans un contexte de septicémie 12 mois après l’arrêt du médicament. L’estimation la plus basse de l’incidence des HTAP chez les patients traités par le dasatinib en France est de 0,45 %.


**Mots clés** : événements indésirables d’origine médicamenteuse ■ hypertension artérielle pulmonaire ■ complications vasculaires ■ leucémie myéloïde chronique ■ dasatinib