Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

Running title: *Montani et al.; Dasatinib-induced PH*

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Abstract:

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

Methods and Results - To describe incident cases of dasatanib-associated PH reported in the French PH registry. From the approval of dasatinib (November 2006) to 30th September 2010, 9 incident cases treated by dasatinib at the time of PH diagnosis were identified. At diagnosis, patients had moderate to severe pre-capillary 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 and/or haemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but one 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 failed to demonstrate complete clinical and hemodynamic recovery and no patients reached a normal value of mean pulmonary artery pressure (≤20 mmHg). Two patients (22%) died at follow-up (one of unexplained sudden death and one of cardiac failure in the context of septicaemia, 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 pre-capillary PH, suggesting a direct and specific effect of dasatinib on pulmonary vessels. Improvement is usually observed after withdrawal of dasatinib.

Key words: adverse drug events; pulmonary hypertension; vascular complications; chronic myeloid leukemia; dasatinib

Introduction

Normal mean pulmonary artery pressure (mPAP) is 14±3 mmHg[1]. Pulmonary hypertension (PH) is defined by an increase in mPAP ≥25 mmHg at rest[2]. PH can be classified into five groups according to pathomechanisms and clinical management. Group 1 (pulmonary arterial hypertension, PAH) includes pre-capillary PH [with a normal pulmonary capillary wedge pressure (PCWP) ≤15mmHg] that is idiopathic, heritable, drug-induced or associated with various conditions; group 2 corresponds to post-capillary PH; group 3 corresponds to PH due to chronic lung diseases and/or hypoxemia; and group 4 corresponds chronic thrombo-embolic PH. In contrast, group 5 consists of several forms of PH for which the etiology is unclear or multifactorial. This group includes chronic myeloproliferative disorders which 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 myeloproliferative 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 (TKI) which inhibits BCR/ABL kinase, such as imatinib. However, up to 20% of CML patients treated by imatinib fail to achieve complete cytogenetic response. Data suggest that two 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]. Of note, dasatinib shows greater inhibition of BCR/ABL kinase compared to 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 compared to 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, musculo-skeletal pains, diarrhoea, nausea, rash, abdominal pain, fatigue and headache, as well as leucopenia, neutropenia, thrombocytopenia, anemia, and elevated liver enzymes. Of note, 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 as compared to 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 two patients with CML and co-existent severe pre-capillary PH[20]. It was suggested that this effect could be due to inhibition of tyrosine kinase targets of imatinib such as PDGF 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 pre-capillary PH occurring in CML patients treated with dasatinib have been reported to the AFSSAPS (Agence Française 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 pre-capillary 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 pre-capillary PH - defined as mPAP $\geq$25 mmHg with a normal PCWP $\leq$15 mmHg - was confirmed in all patients by right-heart catheterization. Right atrial pressure (RAP), mPAP, PCWP and mixed venous oxygen saturation (SvO2) were recorded. Cardiac output (CO) was measured by the standard thermodilution technique. Cardiac index (CI) was calculated as CO/body surface area. Pulmonary vascular resistance (PVR) were calculated as (mPAP-PCWP)/CO, expressed in mmHg/L/min. Acute vasodilator testing was performed during right-heart catheterization using inhaled nitric oxide (NO)[28]. Routine evaluation at baseline included medical history, physical examination, echocardiography, contrast enhanced computed tomography of the chest, ventilation/perfusion (V/Q) lung scan, abdominal ultrasound, auto-immunity 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 non-encouraged 6-minute walk test (6-MWT) according to the

American Thoracic Society recommendations was performed. Point mutations and large rearrangements in *BMPR2* gene were searched as previously described[29], in 6 patients (patients 2, 3, 4, 5, 6, 8) after they underwent genetic counselling and signed written informed consent. We then estimated the total number of patients treated with imatinib, dasatinib and nilotinib in France during the period 2006-2010 using data from the the French Pharmacovigilance Agency, and the pharmaceutical companies that market dasatinib (Bristol-Myers-Squib, Princeton, NJ) and imatinib and nilotinib (Novartis, Basel, Switzerland).

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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 30th September 2010, 9 incident PH patients with either a diagnosis of CML and/or treatment with dasatinib were identified. All nine patients were receiving dasatinib therapy at the time of PH diagnosis. Characteristics of these nine 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 thrombo-embolic PH was excluded on the basis of V/Q 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 disease and/or hypoxaemia. Cardiovascular risk factors or comorbidities including systemic hypertension, diabetes mellitus, dyslipidemia, arrhythmia, coronary artery disease were absent in our patients, except mild systemic hypertension and coronary artery disease in one patient (patient 9).

None of the six patients tested for *BMPR2* point mutations and large rearrangements carried a deleterious mutation. Of note, patient 4 had a *BMPR2* gene polymorphism in exon 12 (c.1607G>T, pArg536Leu). This polymorphism was not previously reported in PAH patients, and concerned an amino-acid conserved in inter-species comparisons. However *in silico* analysis (Polyphen, Sift) were not in favour of a pathogenic effect of this polymorphism. Thus, in the current state of knowledge, it is not possible to conclude on the implication of this *BMPR2* polymorphism in the development of PAH.

In eight of the nine patients, second-line therapy with dasatinib was initiated because of resistance or intolerance to first-line imatinib therapy. In one patient the indication for dasatinib was acute lymphoblastic leukemia with coexisting BCR/ABL translocation. No patient had clinical evidence of PH prior to initiation of dasatinib therapy. Of note, six patients had a previous normal Doppler echocardiography before initiation of dasatinib and two of them had normal echocardiography between imatinib withdrawal and dasatinib initiation. All patients were considered to have satisfactory disease control with dasatinib therapy at time of PH diagnosis. Median delay between initiation of dasatinib and PH diagnosis was 34 months (min-max 8-48). At the time of diagnosis, the dose of dasatinib ranged from 70 to 140 mg/day (median 100 mg/day). Concomitant treatments included anagrelide in one patient. Before initiation of dasatinib, previous therapies included interferon (IFN)α2B in 6 patients, hydroxycarbamide in 6 patients, cytarabine in 3 patients and imatinib in 8 patients (**Table 1**).

Evaluation of pulmonary hypertension at diagnosis

At PH diagnosis, all patients presented with recent and progressive dyspnoea on exertion and had marked functional impairment (NYHA functional class II, III, and IV in 2, 4 and 3 patients, respectively). Median 6-MWT was 242 meters (min-max 0-508). Right-heart catheterization confirmed pre-capillary PH in all patients (median PCWP 10 mmHg, min-max 3-13) with severe hemodynamic impairment (**Table 2**). Median mPAP was 46 mmHg (min-max 30-59), median CO was 6 L/min (min-max 3·3-8·9) and median PVR was 5·9 mmHg/L/min (min-max 3·3-12·4). At diagnosis, median transpulmonary gradient was markedly increased to 34 mmHg (min-max 22-48). Acute vasodilator testing was performed in 7 patients. One patient showing a decrease in mPAP from 47 to 36 mmHg associated with normal CO was considered to have an acute vasodilator response[28]. At the time of right heart catheterization, haemoglobin was normal or moderately reduced in the majority of patients (median haemoglobin 12·3 g/dL, min-max 77-160). Circulating BNP or NT-proBNP levels were measured in 8 patients and were increased in all cases. DLCO 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 out 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 pre-capillary PH was suspected. Dasatinib was therefore discontinued in all patients following confirmation of the diagnosis of PH and treatment was substituted by nilotinib in six patients and by hydroxycarbamide in two others. In addition, treatment with the endothelin receptor antagonist bosentan was initiated in two patients. High dose calcium channel blocker therapy was commenced for the patient with an acute vasodilator response (patient 1). In the remaining six patients, treatment with specific PAH therapy was not deemed necessary.

All but one patients showed clinical, functional and/or haemodynamic 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 one patient in class III (**Figure 1A**). Evolution of 6-MWT (**Figure 1B**) was available in 6 patients and showed significant improvement (478 meters, min-max 278-635) as compared to baseline values of these patients (242 meters, 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-D**) with a decrease of mPAP from 47 mmHg (min-max 30-59) to 28 mmHg (min-max 25-50) and a decrease of PVR from 6·1 mmHg/L/min (min-max 3·3-12·4) to 2·9 L/min/m² (min-max 1·6-5·0). Importantly, none of our patients reached a normal hemodynamic status and mPAP remains elevated (≥25 mmHg) 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 of 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 **Supplemental Figure 1**. 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 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 BNP 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 70mmHg. 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[2]. At 1 month after dasatinib withdrawal, this patient had a clinical improvement (NYHA functional class I) but no hemodynamic evaluation was performed, suggesting that mildly symptomatic pre-capillary PH could have been still present in a patient who presented initially with a mean PAP of 45mmHg. As death occurred in a foreign country, no autopsy was performed and the cause of sudden death remains uncertain.

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 case/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 AFSSAPS in November 2010 and estimates of TKIs prescription in France between 1st November 2006 and 30th September 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 8,750 (69·7% of the total number of patients exposed to one of these TKIs in France), 2,900 (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 (**Supplemental Figure 2**). Thus the lowest estimate of incident PH occurring in patients exposed to dasatinib in France was 13/2,900 (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 these 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[30-32].

Discussion

Since 2008, the French PH Registry has identified 9 incident cases of symptomatic pre-capillary

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[3, 4]. One hypothesis is that PH develops merely as a consequence of the underlying hematologic disorder. However, information from the French PH Registry from 2008-2010 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 favour 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 hydroxycarbamide. 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[14-18]. 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[33-35]. The number of patients in France treated by dasatinib was relatively small at the time of our report (less than 3,000). Thus, the occurrence of 9 incident cases of severe pre-capillary PH in dasatinib-exposed individuals between 2008 and 2010 in our registry plus four additional cases reported at the French pharmacovigilance level indicated that this complication may affect at least 0·45% of chronically dasatinib-exposed 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[14-18]. One of the common non-hematologic side effects of dasatinib is fluid retention and pleural effusions, but the underlying mechanisms remain unclear[11-13]. Interestingly, we observed bilateral pleural effusions in 6 patients; however, severe pre-capillary PH persisted even after resolution of pleural effusions. Although PH remains a rare complication, it is important to note that at this period, dasatinib was licensed only as a second-line therapy. Recent data suggest that dasatinib may be employed as first line therapy in CML. Therefore, this agent is likely to become increasingly prescribed in the future and the numbers of cases of dasatinib-induced PH may increase, particularly with extended duration of therapy. We therefore recommend to screen routinely for PH by echocardiography prior to commencing dasatinib and to perform additional diagnostic testing in patients receiving this therapy who develop dyspnoea or other symptoms suggestive of PH. Where these investigations indicate possible PH, a right heart catheterization is mandatory to confirm the diagnosis of PH[2].

In series reporting dasatinib-associated pleural effusion, sex ratio was consistent with the known gender distribution of CML (55% of cases occurring in females)[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[36]. Estrogen metabolism, which has been potentially implicated in the pathogenesis of PAH[37] may also be relevant in dasatinib-induced PH. Nevertheless, since only a minority of patients exposed to dasatinib will develop PH, it is likely that other co-factors 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 *BMPR2* mutations[29, 38]. We screened for *BMPR2* mutation in six patients and only one *BMPR2* polymorphism of unknown significance was found. In the context of cardiotoxicity induced by TKIs, pre-existing cardiac conditions predispose to cardiotoxicity[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, one 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. Noteworthy, other reports that have suggested a complete reversibility of PH have no invasive hemodynamic evaluation at follow-up[14-18]. Therefore, longer-term follow-up will be required in order to characterise 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[41, 42]. However, the kinase target profiles of these 3 drugs are markedly different (**Table 5**)[43]. Recently, the kinase and non-kinase targets of these three TKIs have been characterised showing that dasatinib displayed a less specific target profile than imatinib or nilotinib[44]. Several TKIs or multiple kinase inhibitors, including imatinib, sorafenib and sunitinib exhibit cardiotoxicity both in experimental models and in humans[39,40,45]. Kerkela et al 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[40]. In addition, Chintalgattu et al reported that cardiomyocyte PDGFR-beta is a regulator of the compensatory cardiac response to pressure overload-induced stress, suggesting that inhibition of PDGF pathway may be at least in part responsible of cardiotoxicity due to TKIs[46]. Accumulated evidence indicates that receptors of tyrosine kinases (RTKs) play an important role in the pathogenesis of PAH and inhibition of some specific RTK signalling 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 PDGF[21,22], fibroblast growth factor-2 [47,48], c-kit [23] and epidermal growth factor [49,50] 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-MWT), treatment conferred significant hemodynamic improvements[24]. Of note, 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 RTKs inhibitor. When analyzing the complex history of our patients, one cannot exclude that prior exposure to several drugs such as IFNα2B, hydroxycarbamide, imatinib and other chemotherapies could have played a part in the subsequent development of PH. However, the prior drug regimen of our patients did not include the same agents prior to dasatinib initiation (**Table 1**). The rapid relief of symptoms and hemodynamic improvements after withdrawal of dasatinib are consistent with a reversible component. Nevertherless, the absence of complete resolution observed after dasatinib discontinuation suggests some degree of associated pulmonary vascular remodelling 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 plays 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 as well as the Eph receptors/ephrin tyrosine kinases by dasatinib.

In conclusion, we report cases of severe pre-capillary PH associated with dasatinib treatment, 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 numbers of patients at risk of developing PH. Physicians need to be aware of this complication in order to appropriately monitor and manage these patients[30-32].

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Table 1. Characteristics of patients with dasatinib-associated PH

	Age at diagnosis, *yrs*	Gender, *M/F*	Hematologic malignancy	Delay between initiation of dasatinib and diagnosis of PH, *months*	Dose of dasatinib at diagnosis, *mg/d*	Concomitant treatment at diagnosis of PH	Previous therapy for CML
1	74	F	CML	33	100	-	IFNα2B, hydroxycarbamide, imatinib
2	51	F	CML	30	100	Anagrelide	IFNα2B, hydroxycarbamide, mercaptopurin, imatinib
3	64	F	CML	28	140	-	Imatinib
4	28	F	CML	45	100	-	IFNα2B, cytarabine, imatinib
5	59	F	CML	45	70	-	IFNα2B, hydroxycarbamide, imatinib
6	29	F	CML	36	100	-	IFNα2B, HCM, vincristine, mercaptopurin, methotrexate, cytarabine, imatinib
7	17	F	ALL	8	100	-	Vincristine, methotrexate, adriamycin, cytarabine
8	39	F	CML	34	100	-	IFNα2B, hydroxycarbamide, imatinib
9	68	M	CML	48	80	-	hydroxycarbamide, imatinib

ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, IFN: interferon, PH: pulmonary hypertension

Table 2. Hemodynamic parameters at the time of PH diagnosis

	mPAP, *mmHg*	RAP, *mmHg*	PCWP, *mmHg*	CO, *L/min*	CI, *L/min/m²*	PVR, *mmHg/L/min*	SvO_2, *%*	Acute vasodilator response #
1	47	14	13	5.6	2·9	6·1	66	Yes *(mPAP:36, CI: 2·9)*
2	59	13	11	6·5	4·0	7·4	63	No *(mPAP:59, CI: 6·4)*
3 *	30	5	8	6·7	4·7	3·3	72	No *(mPAP:27, CI: 6·9)*
4	*PH was screened by echocardiography and confirmed by RHC 6 weeks after withdrawl of dasatinib*							
5	49	6	10	8·9	4·8	4·4	65	No *(mPAP:50, CI: 5·1)*
6	49	24	8	3·3	1·8	12·4	55	No *(mPAP:47, CI: 2·0)*
7	38	6	11	4·8	3·2	5·6	72	No *(mPAP:31, CI: 2·7)*
8	37	6	3	3·3	1·9	10·3	54	No *(mPAP:39, CI: 2·4)*
9	45	4	10	6·4	4·0	5·4	74	No *(mPAP:38)*

mPAP: mean pulmonary artery pressure, RAP: right atrial pressure, PCWP: pulmonary capillary wedge pressure, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance, SvO_2: mixed venous oxygen saturation.

* Severe clinical and hemodynamic impairment necessitated initial management in an intensive care unit with catecholamines; right-heart catherization was performed after successful weaning of catecholamines two weeks following withdrawl of dasatinib.

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

Table 3. Clinical and functional evaluation at the time of PH diagnosis

	NYHA FC, *I-IV*	**Pleural effusions**	**Pericardial effusions**	**6-MWT,** *m*	**BNP, *** *ng/L*	**PaO$_2$,** *kPa*	**DLCO, %** *theo*
1	III	Bilateral	No	300	168	8·9	-
2	III	Minimal and bilateral	Minimal	345	424	8·9	44
3	IV	No	Minimal	0	1635	-	-
4	III	No	No	-	-	13·2	59
5	III	Bilateral	No	183	128	-	-
6	IV	Bilateral	No	0	Increase of NT-proBNP	9·9	-
7	II	Bilateral	No	429	432	9·9	46
8	IV	Bilateral	Minimal	0	603	7·6	-
9	II	No	No	630	163	10·6	63

BNP: brain natriuretic peptide, DLCO: Diffusion lung capacity for carbon monoxide, NYHA FC: New York Heart Association functional class, PaO$_2$: partial pressure of arterial oxygen, 6-MWT: 6-minute walk distance

* Normal values of BNP are <100 ng/L

Table 4. Management and outcomes

	PAH therapy	Current therapy for hematologic malignancy	Short-term (<4-months) evaluation after discontinuation of dasatinib		Long-term (≥ 4months) evaluation after discontinuation of dasatinib	
1	6 months of CCB then stopped	Nilotinib	*After 3 months* NYHA FC I, 6-MWT: 320 mPAP: 42, PVR: 4·6 BNP: 30		*After 15 months* NYHA FC II, 6-MWT: 360 mPAP: 30, PVR: 2·6 echocardiography	*After 36 months* NYHA FC II, normal
2	No	Hydroxycarbamide	*After 1 month* NYHA FC II, 6-MWT: 453m mPAP: 31, PVR: 5.9 BNP: 21		*After 18 months* NYHA FC II, 6-MWT: 525m, mPAP 28, PVR 3,5 BNP: 10	
3	No	Nilotinib	*After 3 months* NYHA FC III mPAP: 35, PVR: 3·9 BNP: 715		*After 9 months* NYHA FC III Echocardiography: right ventricular dilatation, paradoxical, septum, sPAP 70mmHg BNP : 2134 **Death after 12 months**	
4	No	Nilotinib	*After 6 weeks* NYHA FC II, 6-MWT: 508 mPAP: 25, PVR:3·2 BNP >100		*After 4 months* NYHA FC I, 6-MWT: 580 BNP: 30	*After 24 months* NYHA FC I
5	No	Hydroxycarbamide	*After 3 months* NYHA FC II, 6-MWT: 265 mPAP: 26, PVR:2·5		*After 15 months* NYHA FC I, 6-MWT: 278m BNP: 11 normal echocardiography	
6	ERA	Nilotinib	*After 2 months* NYHA FC III		*After 6-months* NYHA FC II, 6-MWT: 430 mPAP: 50, PVR:5	*After 12 months* NYHA FC I
7	No	Nilotinib	*After 1 month* NYHA FC I, 6-MWT: 544 BNP:36		*After 5 months* NYHA FC I, 6-MWT: 528m mPAP: 25, PVR:2·9 BNP: 16	*After 15 months* NYHA FC I
8	ERA	None	*After 1 month* NYHA FC I	*After 3 months* NYHA FC I, 6-MWT: 635m *mPAP: 25, PVR:1•6*	*After 12 months* NYHA FC I	
9	No	Nilotinib	*After 1 month* NYHA FC I		**Sudden Death after 8 months**	

BNP: brain natriuretic peptide, CCB: calcium channel blocker, ERA: endothelin receptor antagonist, mPAP: mean pulmonary artery pressure, NYHA FC: New York Heart Association functional class, 6-MWT: 6-minute walk distance.

BNP was expressed as ng/L.

Table 5. Targets of tyrosine kinases inhibitors approved in the treatment of CML: imatinib, nilotinib and dasatinib (adapted from [43])

Imatinib Nilotinib	**Dasatinib**		
ABL	ABL	TXK	LIMK2
ARG	ARG	DDR1	MYT1
BCR-ABL	BCR-ABL	DDR2	PTK6/Brk
KIT	KIT	ACK	QIK
PDGFR	PDGFR	ACTR2B	QSK
DDR1	SRC	ACVR2	RAF1
NQO2	YES	BRAF	RET
	FYN	EGFR/ERBB1	RIPK2
	LYN	EPHA2	SLK
	HCK	EPHA3	STK36/ULK
	LCK	EPHA4	SYK
	FGR	EPHA5	TA03
	BLK	FAK	TESK2
	FRK	GAK	TYK2
	CSK	GCK	ZAK
	BTK	HH498/TNNI3K	
	TEC	ILK	
	BMX	LIMK1	

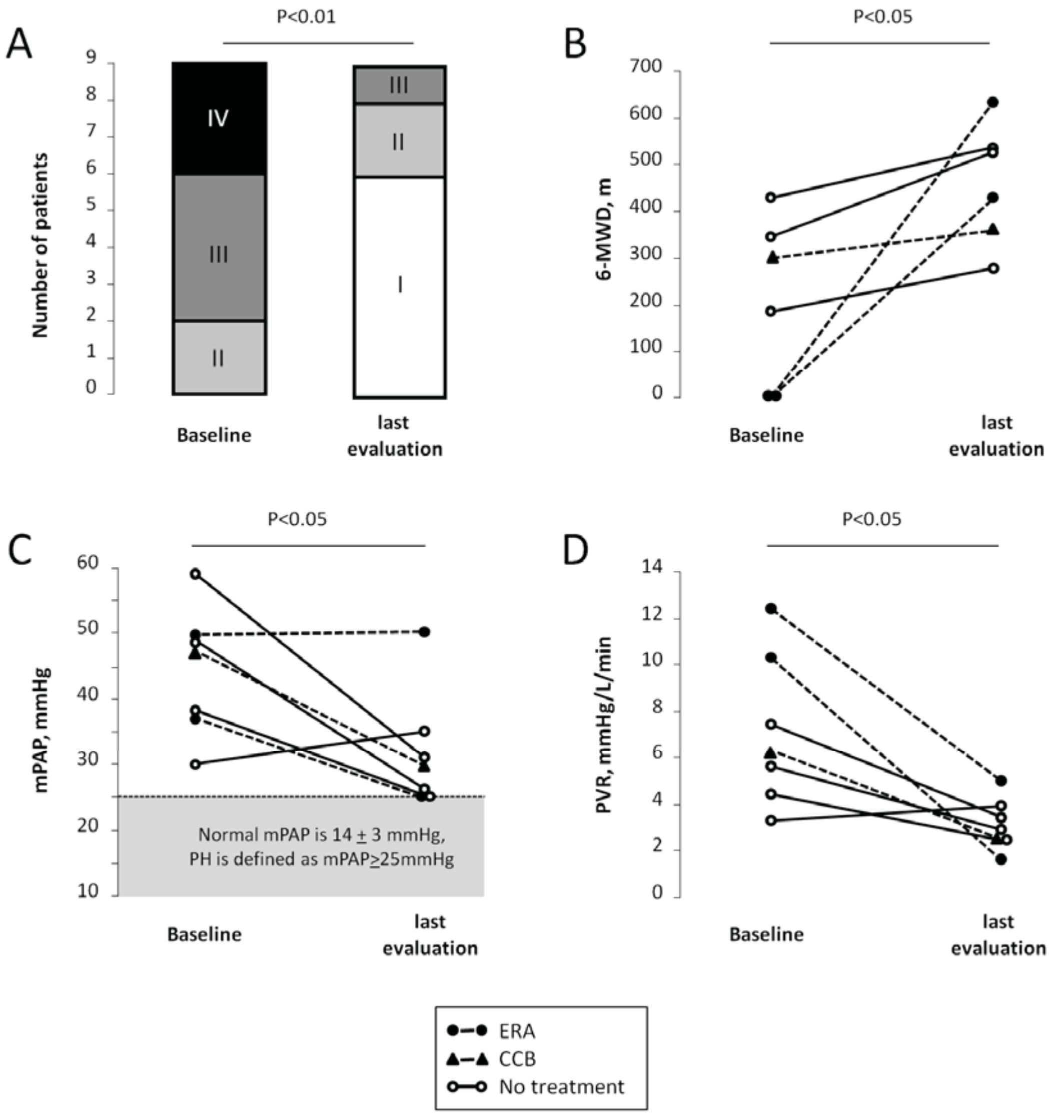
Figure Legends:

Figure 1. Evolution of clinical, functional and hemodynamic parameters after dasatinib discontinuation. **A**. After a median delay of 15 months (min-max 8-36 months) after dasatinib discontinuation, improvement of NYHA functional class was observed; however 3 patients remained symptomatic with functional class II or III symptoms at the last evaluation and 2 patients died during follow-up (after 8 and 12 months). **B.** Evolution of 6-minutes walk distance (6MWD) was available in 6 patients and showed significant improvement as compared to baseline values (P<0·05). **C, 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, mPAP remains elevated (≥25 mmHg) in all patients at the last hemodynamic evaluation.

Empty circles (○) represent spontaneous evolution of 6MWD and hemodynamic parameters after dasatinib withdrawal. Black circles (●) represent the 2 patients treated with endothelin receptor antagonists, and black triangles (▲) represent the patient treated with calcium channel blockers. *ERA: endothelin receptor antagonists, CCB: calcium channel blockers.*

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 signalling pathways for proliferation, vasodilatation and vasoconstriction. Src signalling in the absence or in the presence of parallel signalling pathways initiated by growth factor, integrin, and cytokine receptors on the surface of cells, including PDGF-R, may promote cellular proliferation via up-regulation 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 signalling cascade resulting in tyrosine phosphorylation of phospholypase Cγl (PLCγl), leading to increase in intracellular levels of inositol 1,4,5-triphosphate (1,4,5-IP_3) and diacygleroI. PKC activated via diacygleroI and 1,4,5-IP_3 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.



A
P<0.01
Number of patients
9
8
7
6
5
4
3
2
1
0
IV
III
II
III
II
I
Baseline
last evaluation
B
P<0.05
6-MWD, m
700
600
500
400
300
200
100
0
Baseline
last evaluation
C
P<0.05
mPAP, mmHg
60
50
40
30
20
10
Normal mPAP is 14 ± 3 mmHg,
PH is defined as mPAP≥25mmHg
Baseline
last evaluation
D
P<0.05
PVR, mmHg/L/min
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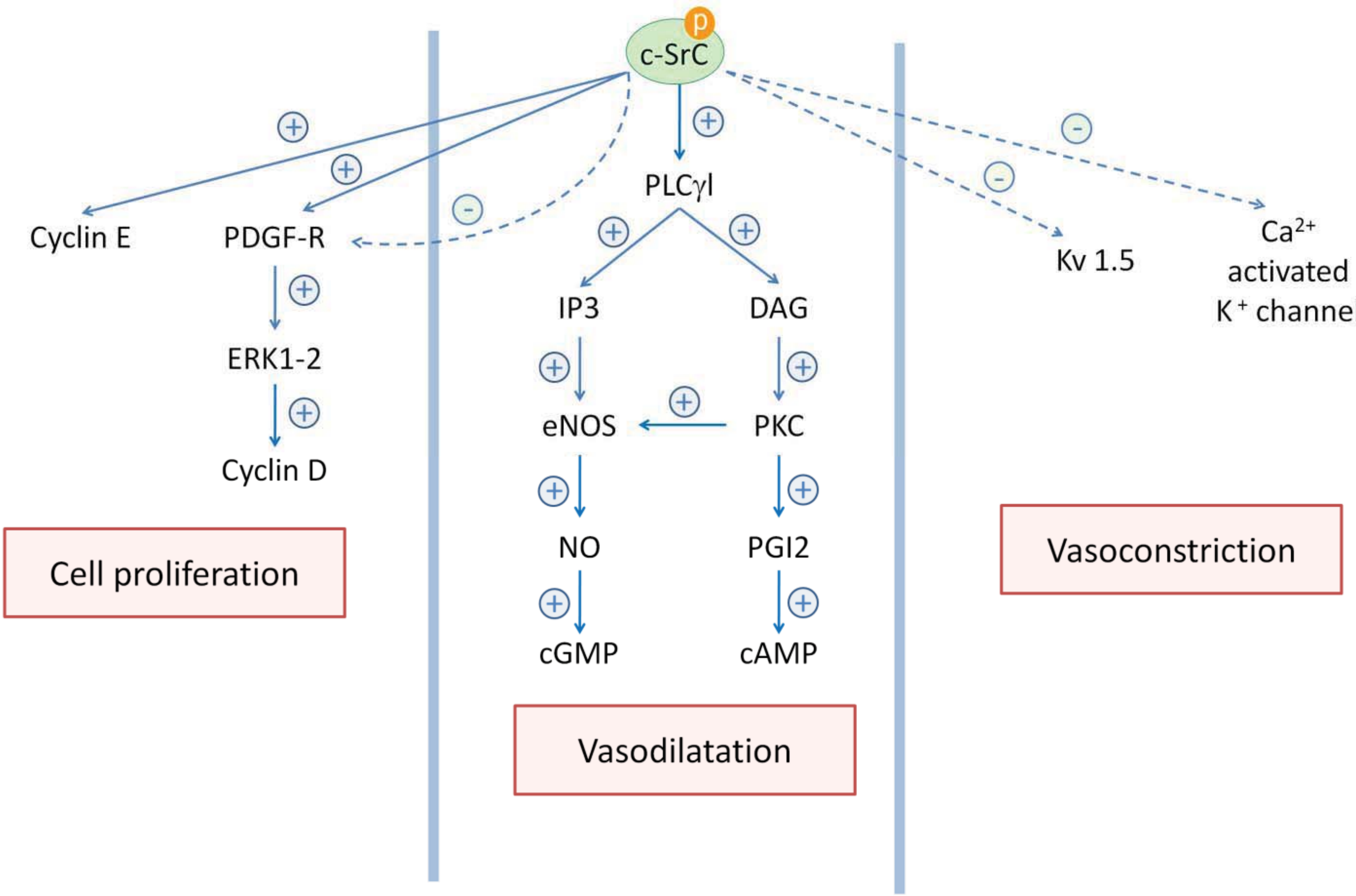
12
10
8
6
4
2
0
Baseline
last evaluation
ERA
CCB
No treatment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c-SrC
PLCγl
Cyclin E
PDGF-R
ERK1-2
Cyclin D
Cell proliferation
IP3
DAG
eNOS
PKC
NO
PGI2
cGMP
cAMP
Vasodilatation
Kv 1.5
Ca2+ activated K+ channel
Vasoconstriction

Circulation

Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

David Montani, Emmanuel Bergot, Sven Günther, Laurent Savale, Anne Bergeron, Arnaud Bourdin, Helene Bouvaist, Matthieu Canuet, Christophe Pison, Margareth Macro, Pascal Poubeau, Barbara Girerd, Delphine Natali, Christophe Guignabert, Frédéric Perros, Dermot S. O'Callaghan, Xavier Jaïs, Pascale Tubert-Bitter, Gerard Zalcman, Olivier Sitbon, Gérald Simonneau and Marc Humbert

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SUPPLEMENTARY MATERIALS

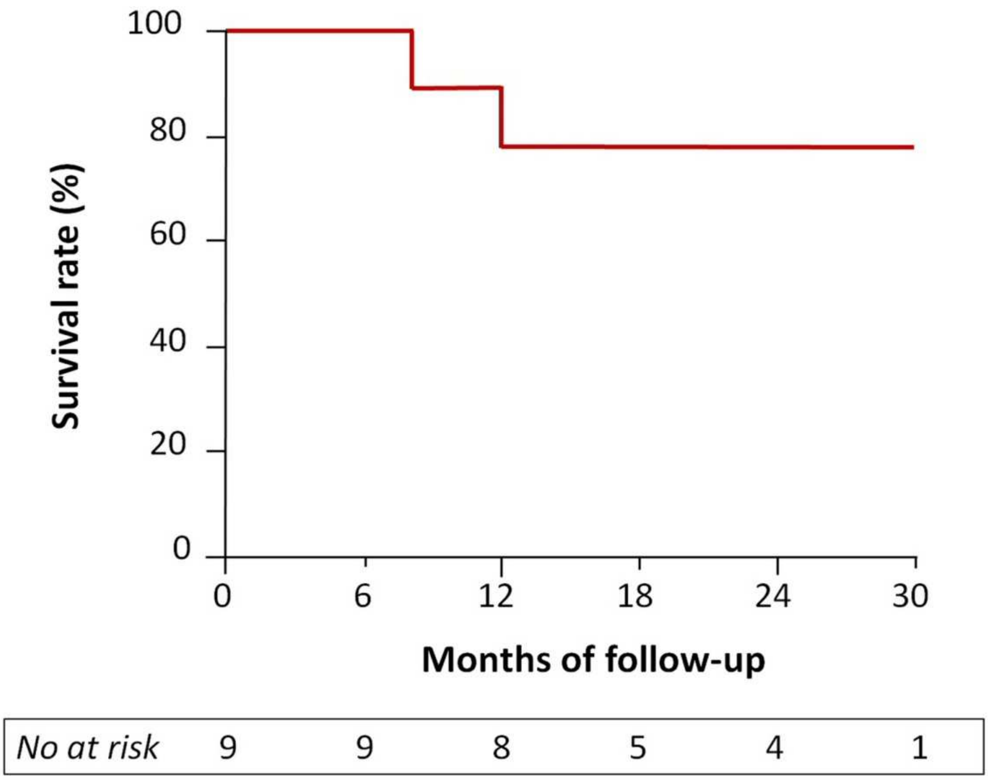
Supplementary Figure 1. Survival from dasatinib discontinuation of patients with dasatinib-induced PH.

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.

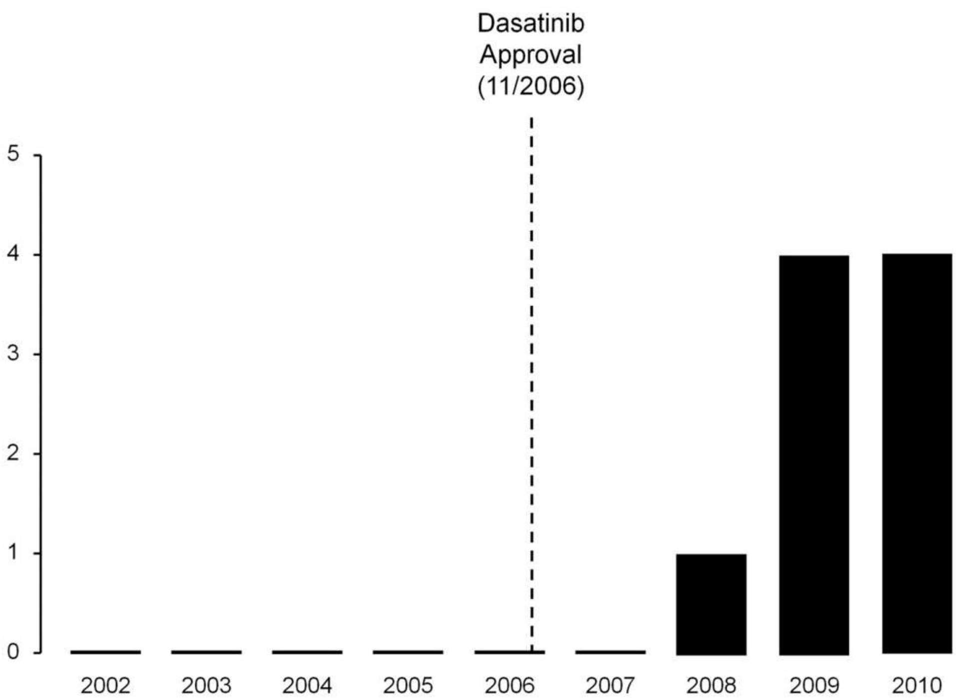
Supplementary Figure 2. Occurrence of incident cases of pre-capillary pulmonary hypertension in subjects treated with tyrosine kinase inhibitors in the French Registry (2002-2010)

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 commissurotomie mitrale percutanée à 20 ans

Création et validation d'un score de risque prédisant 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 commissurotomie mitrale percutanée permet l'identification des facteurs prédisant les résultats à long terme.

Méthodes et résultats—Les résultats à long terme de la commissurotomie 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 cm^2 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 commissurotomie mitrale percutanée, le patient se situant en classe I ou II de la New York Heart Association [NYHA]) a été de 30,2 ± 2,0 %. L'emploi d'un modèle de Cox multivarié a permis d'identifier 7 facteurs prédictifs de résultats à long terme médiocres : l'existence d'un gradient de pression final moyen augmenté ($p < 0{,}0001$) ; l'interaction entre l'âge et l'aire mitrale finale ($p < 0{,}0001$), l'âge ayant pour effet de diminuer l'influence exercée par cette dernière ; l'interaction entre le sexe et la calcification de l'appareil valvulaire ($p < 0{,}0001$), cela se traduisant par une influence plus marquée de l'anatomie mitrale chez les hommes ; et l'interaction entre le rythme cardiaque et la classe de la NYHA, celle-ci ayant une influence uniquement chez les patients en fibrillation auriculaire ($p < 0{,}0001$). Un score à 13 points a permis de définir 3 groupes à risque auxquels ont été rattachés, dans la cohorte de validation, des taux attendus de bons résultats fonctionnels à 20 ans respectivement estimés à 55,1 ; 29,1 et 10,5 %.

Conclusions—Vingt ans après la réalisation de commissurotomies mitrales percutanées 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

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 %.

Conclusions—Le dasatinib peut provoquer une HTAP précapillaire sévère répondant aux critères de l'hypertension artérielle pulmonaire, ce qui semble indiquer qu'il exercerait un effet direct et spécifique sur les vaisseaux pulmonaires. Une amélioration est généralement observée après l'arrêt du médicament. **(Traduit de l'anglais : Pulmonary Arterial Hypertension in Patients Treated by Dasatinib. *Circulation*. 2012;125:2128–2137.)**

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