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Pulmonary Hypertension Is a Frequent Event in Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors

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Abstract

Background: Tyrosine kinase inhibitors (TKI) are the current standard therapy for patients with chronic myeloid leukemia (CML). Fluid retention and pleural effusions have been reported in patients treated with TKIs, particularly with dasatinib. Although TKIs have been shown to reverse pulmonary hypertension (PH) in animal models, there have been some reports of development of reversible PH with dasatinib. **Methods:** We conducted a retrospective analysis on 401 patients diagnosed with CML in chronic phase (CP) who were treated with TKIs (imatinib, dasatinib, or nilotinib) as initial therapy for CML and had a transthoracic echocardiogram (TTE) done at some point during the course of therapy. PH was diagnosed if the patient had an estimated right ventricular systolic pressure (RVSP) of 35 mm Hg or greater. Secondary causes of PH (systolic or diastolic dysfunction on TTE, chronic obstructive pulmonary diseases [COPD], obstructive sleep apnea [OSA] and pulmonary embolism) were investigated during chart review. **Results:** Twenty (23%) out of 87 patients had evidence of PH by TTE; median age 57 years, with 46% being males. Six pts (30%) received nilotinib 400mg twice daily, 4 (20%) patients had imatinib (400mg; n=1, 600mg; n=1 and 800mg daily; n=2), and 10 (50%) patients received dasatinib (dose varied 40-140mg daily). Five (25%) patients had coronary artery disease, 9 (45%) had systemic hypertension, 2 (10%) had COPD and 3 (15%) had OSA. Thirteen pts had serial TTE to compare the progression of PH including 6 (7%) who had a TTE prior to starting TKI. Among these 13 pts with serial TTE, 7 had rising RVSP with one patient having mild global hypokinesia, another with diastolic dysfunction and another with OSA. Four of those 7 patients had normal RVSP on their TTE prior to starting therapy. Six other pts had improvement in the RVSP on serial TTE, 4 of them with systemic hypertension. Two of those 6 patients had elevated RVSP on their TTE prior to starting therapy; one pt had no change. Eleven patients had pleural effusions (7 dasatinib, 3 imatinib, 1 nilotinib) associated with PH. **Conclusions:** TKI therapy is occasionally associated with development of PH, but RVSP may improve spontaneously in some patients. A prospective study is needed to further investigate the relationship between TKIs and the development of PH.

Background

- Pulmonary hypertension (PH) is characterized by elevated pulmonary artery pressure, right ventricular hypertrophy and, eventually, right ventricular failure.
- Unexplained PH has been described in some myeloproliferative disorders, however evidence is lacking in patients with CML [1].
- There have been some reports on the occurrence of reversible PH after treatment with dasatinib[2, 3].

Objectives

- To investigate the frequency and characteristics of PH in patients with CML receiving therapy with tyrosine kinase inhibitors (TKIs).

Patients and Methods

- Chart review of patients with CML treated with TKIs at MDACC between 2000 and 2009.
- Included patients with CML in chronic phase (CP) enrolled in several studies using imatinib (800 mg orally daily), nilotinib (400 mg BID) or dasatinib (100mg orally daily) as frontline therapy who had at least one trans-thoracic echocardiogram (TTE) done at baseline or during the course of therapy.
- Patients with CML CP who had received prior therapies were excluded.

Results

- Of 401 patients with CML treated with TKI as initial therapy, 87 had at least one TTE done
- Among 28 patients with pre-therapy (baseline) TTE, 8 (29%) patients had an elevated right ventricular systolic pressure (RVSP) at baseline.
- Elevated RVSP suggesting pulmonary hypertension during therapy occurred in 20 (23%) of 87 patients.
- Elevated RVSP was seen most commonly in patients treated with dasatinib (occurring in 10 of 19 patients [53%]) [mean 36 mmHg, range 35-50 mmHg] and nilotinib (seen on 6 of 14 patients [43%]) [mean 36 mmHg, range 31-50 mmHg] (Table 2).
- LVEF remained normal in 18 (90%) of the 20 patients with elevated RVSP, suggesting that PH could possibly be related to the use of TKIs.
- 70% of patients with elevated RVSP while on therapy with dasatinib had evidence of concomitant pleural effusions.
- Only 4 of 54 (8%) patients treated with imatinib had evidence of elevated RVSP (2 had other possible etiologies).

Results

- Of the patients that had elevated RVSP (suggesting PH), 13 patients had serial TTE during therapy (figure 1).
  - 7 patients experienced worsening PH (receiving Dasatinib n=2, Imatinib n=2, Nilotinib n= 3)
  - 4 had resolution (receiving imatinib n=2, dasatinib n=3, nilotinib n=1) while on therapy. The improvement in RVSP was seen after switching from the TKI to another agent (Dasatinib n=2, nilotinib n=1) or reducing the dose of dasatinib by 50% (N=1).
  - 2 of 3 patients with elevated RVSP at baseline normalized after starting therapy with nilotinib.
- Pleural effusion was identified in 11 patients (55%) with elevated RVSP (Table 3).
- Pleural effusion occurred most frequently among patients on dasatinib (70%).

Table 1. Patient's Characteristics

	Median (range)	N° (%)
Age (y)	56 (30-82)	
Males		11 (55)
Median follow-up (months)	16 (2-54)	17 (51)
Median WBC (x10^9/L)	27.2 (2.7-156.5)	
Platelets (x10^9/L)	228 (70-599)	
Hemoglobin (g/dl)	12.2 (6.2-14.1)	
Splenomegaly		2 (10)
Sokal score		
High		3 (15)
Intermediate		5 (25)
Low		12 (60)
Medical History		
Pleural effusion during TKI		11 (55)
Systemic Hypertension		9 (45)
Tobacco smoking		8 (40)
Coronary artery disease		5 (25)
Diastolic heart failure		4 (20)
Atrial Fibrillation		3 (15)
Obstructive sleep Apnea		3 (15)
COPD		2 (10)
Systolic heart failure		2 (10)

WBC= White blood cell, COPD= Chronic Obstructive Pulmonary Disease., y= years

Figure 1. Algorithm of Patients with elevated RVSP who had serial TTE

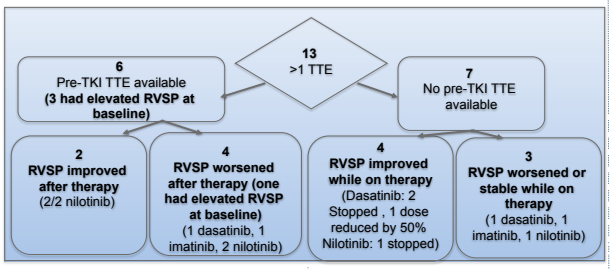

Table 2. TTE evidence of PH by therapy

TKI	N TTE Available	N Elevated RVSP on TTE (%)	N Possible secondary cause of elevated RVSP
Imatinib	54	4 (8)	2 had ischemic CAD with low EF that worsened after starting TKI
Dasatinib	19	10 (53)	2 had COPD, 1 had OSA
Nilotinib	14	6 (43)	2 had OSA (with normal RVSP prior to starting TKI)

TKI, tyrosine kinase inhibitor; TTT, transthoracic echocardiogram; RVSP, right ventricle systolic pressure; CAD, coronary artery disease; EF ejection fraction; COPD, chronic obstructive pulmonary disease.

Table 3. Incidence of pleural effusion

TKI used	N Concomitant PE and elevated RVSP	N of patients with SOB
Imatinib	3 of 4 (75%)	1
Dasatinib	7 of 10 (70%)	4
Nilotinib	1 of 6 (17%)	0

TKI, tyrosine kinase inhibitor; RSVP, right ventricle systolic pressure, PE= Pleural Effusion

Conclusions

- PH occurs in some patients with CML in chronic phase at baseline while in others it appears during therapy with TKI
- PH is seen less commonly in patients on imatinib compared to dasatinib or nilotinib.
- Concomitant pleural effusion and PH occurred more frequently in patients receiving dasatinib.
- Unclear whether there is a causal relationship between TKI and PH.
- A larger prospective study is needed to further investigate the relationship between TKIs and the development of PH.

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