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Pulmonary hypertension in patients with chronic myeloid leukemia

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Abstract

Dasatinib, a tyrosine kinase inhibitor (TKI), induces pulmonary hypertension (PH) in patients with chronic myeloid leukemia (CML). However, information on other TKIs is limited.

We retrospectively analyzed PH prevalence by reviewing transthoracic echocardiography (TTE) findings in a population of Korean CML patients treated with TKI at a single hospital between 2003 and 2020. PH was defined as a high PH probability according to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.

Of the 189 patients treated with TKI(s) during the study period, 112 (59.3%) underwent TTE. Among the 112 patients treated with a TKI for a median of 40.4 months (range: 1.1–167.2 months), PH was found in 12 (10.7%), most frequently in those treated with dasatinib (ie, in 3 [7.5%] of 40 of those treated with imatinib, 1 [3.1%] of 32 of those treated with nilotinib, and 8 [21.6%] of 37 of those treated with dasatinib). PH resolved in 4 (50.0%) of the 8 dasatinib-treated patients after discontinuation of the agent. One nilotinib-treated and all three imatinib-treated patients recovered from PH. In multivariate analyses, age >60 years, dasatinib treatment, and positive cardiopulmonary symptoms/signs at the time of transthoracic echocardiography were statistically significant risk factors for developing PH.

These results show that PH is induced not only by dasatinib, but also by imatinib and nilotinib. Careful screening for PH during any TKI treatment may thus be warranted in patients with CML.

Abbreviations: CI = confidence interval, CML = chronic myeloid leukemia, ELTS = EUTOS long-term score, LDH = lactate dehydrogenase, MPN = myeloproliferative neoplasm, MR = molecular response, OR = odds ratio, PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, TKI = tyrosine kinase inhibitor, TRPG = tricuspid regurgitation peak gradient, TRV = tricuspid regurgitation velocity, TTE = transthoracic echocardiography, WBC = white blood cell.

Keywords: chronic myeloid leukemia, dasatinib, imatinib, nilotinib, pulmonary hypertension

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) characterized by a marked increase in granulocytic lineage cells and the presence of the Philadelphia chromosome. The introduction of tyrosine kinase inhibitors (TKIs) into the clinic has markedly changed the treatment paradigm and outcomes for this disorder. Today, the overall survival of CML patients treated with TKIs is very close to that of the healthy population.[1] Accordingly, the adverse effects of long-term TKI treatment have received widespread attention and a treatment-free remission trial is recommended for patients who maintain a deep molecular response for years.[2,3]

Pulmonary hypertension (PH) is a progressive disease that often leads to premature death.[4,5] PH is divided into 5 types according to its etiology.[6] The first type is pulmonary arterial hypertension (PAH), which consists of a diverse range of diseases that cause similar pathological changes within the pulmonary vasculature, including idiopathic, familial, drug-, and toxin-induced PAH and associated forms of PAH-like systemic sclerosis, portal hypertension, congenital heart disease, and human immunodeficiency virus (HIV)-induced PAH. The remaining 4 groups of PH occur secondary to other conditions and are usually referred to as secondary PH.

A fifth type of PH is caused by MPN.[7] Many reports have described PH in patients with Philadelphia chromosome-negative

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MPN (Ph^- MPN).[8–13] By contrast, there have been few reports on PH in newly diagnosed CML patients. Dasatinib, a dual Src and BCR-ABL TKI, is associated with PAH in patients with CML.[14–21] There have been some reports of PH in CML patients treated with TKIs other than dasatinib.[10–12,22] However, data on other TKIs, such as imatinib and nilotinib, are still limited. In this study, we analyzed the prevalence of PH and its clinical implications in TKI-treated patients with CML.

2. Patients and methods

2.1. Patients

The medical records of patients with CML who were diagnosed and treated with one or more TKI(s) at Chungnam National University Hospital, Daejeon, Korea, between July 2003 and June 2020 were reviewed retrospectively. CML patients who underwent transthoracic echocardiographic examination (TTE) during TKI treatment were enrolled. TTE was performed before 2017 in a group of study patients who complained of relevant symptoms or signs. Thereafter, TTE was included as part of the follow-up evaluation on a clinical practice basis. Beginning in 2017, TKI-related cardiovascular events became a growing concern,[23,24] which coincided with a report of PH in patients treated with TKIs other than dasatinib.[22] Thus, the decision was made to perform TTE at least once in patients on TKI treatment, irrespective of cardiopulmonary symptoms and the duration of treatment.

During the study period, 189 CML patients were treated with one or more TKIs. Of the 189 patients, 112 (58.3%) underwent TTE and were therefore enrolled in the study. These 112 patients had been treated with TKI(s) for a median of 40.4 months (range 1.1–167.2 months). Their median age was 54 years (range 13–81 years), and 66 (58.9%) patients were male. Of the 112 patients, 92 (82.1%) underwent TTE between January 2017 and June 2020. Nearly all, (110/112, 98.2%) of the patients had chronic disease; according to the Sokal score,[25] Hasford score,[26] and EUTOS long-term score (ELTS),[27] 34 (30.4%), 20 (17.9%), and 4 (3.6%) were identified as high risk, respectively. Of the 112 patients, 40 (35.7%), 32 (28.6%), and 37 (33.0%) were being treated with imatinib, nilotinib, and dasatinib; 86 (76.8%), 32 (28.6%), and 7 (6.2%) were on first, second, and third or higher-line TKI treatment, respectively, at the time of their TTE examination. TTE was performed to evaluate cardiopulmonary symptoms in 11 (9.8%) patients, for PH screening in 91 (81.3%) patients, and for other reasons in 10 (8.9%) patients (Table 1).

Table 1

Patient characteristics (N = 112).

Age, y, median (range)	54 (13–81)
Male, N (%)	66 (58.9)
Year of CML diagnosis, N (%)	
2003–2016	79 (70.5)
2017–2020	33 (29.5)
Year of TTE examined, N (%)	
2003–2016	20 (17.9)
2017–2020	92 (82.1)
Phase, N (%)	
Chronic	110 (98.2)
Accelerated	2 (1.8)
Blastic	0 (0.0)
Hematologic indices at diagnosis	
WBC ($\times 10^9$/L)	140.2 ± 108.8
Hemoglobin, g/dL	10.8 ± 2.3
Platelet ($\times 10^9$/L)	606.9 ± 501.9
Palpable splenomegaly at diagnosis, N (%)	48 (42.9)
Sokal score, N (%)	
Low risk	30 (26.8)
Intermediate risk	48 (42.8)
High risk	34 (30.4)
Hasford score, N (%)	
Low risk	28 (25.0)
Intermediate risk	64 (57.1)
High risk	20 (17.9)
ELTS, N (%)	
Low risk	98 (87.5)
Intermediate risk	10 (8.9)
High risk	4 (3.6)
TKI treatment at the time of TTE examined, N (%)	
Imatinib	40 (35.7)
Nilotinib	32 (28.6)
Dasatinib	37 (33.0)
Radotinib	2 (1.8)
Ponatinib	1 (0.9)
Line of TKI at the time of TTE examined, N (%)	
First	86 (76.8)
Second	19 (17.0)
Third	6 (5.3)
Fourth or more	1 (0.9)
Time receiving any TKI(s), mo, median (range)	40.4 (1.1–167.2)
Comorbidity, N (%)	
Diabetes mellitus	28 (25.0)
Hypertension	27 (24.1)
Smoking	17 (15.1)
Ischemic heart disease	3 (2.7)
Chronic kidney disease	23 (20.5)
Reason for undergoing TTE, N (%)	
Cardiopulmonary symptoms/signs	11 (9.8)
Screening for PH	91 (81.3)
Others	10 (8.9)

CML = chronic myeloid leukemia, ELTS = EUTOS long-term survival score, PH = pulmonary hypertension, TKI = tyrosine kinase inhibitor, TTE = transthoracic echocardiography.

2.2. Diagnosis of PH

Echocardiographic results were reviewed by two cardiologists, and a diagnosis of PH was made when the PH probability was "high" according to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.[28] Briefly, PH probability was defined as "high" when the tricuspid regurgitation velocity (TRV) was >3.4 m/s, or when a TRV of 2.9 to 3.4 m/s was accompanied by certain other features. Patients with PH associated with left heart failure or chronic obstructive lung disease were excluded.

2.3. Statistical analysis

Descriptive data were analyzed using Student's t test or the χ^2 test (Fisher's exact test) and are presented as the mean±standard deviation (SD), median (range), or percentage. Risk factors for PH were analyzed using binary logistic regression analyses. Statistical analyses were performed using SPSS software (ver. 24.0; SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was used to indicate statistical significance.

2.4. Ethics

This study was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH 2020–09–029).

Table 2

Prevalence of pulmonary hypertension during tyrosine kinase inhibitor treatment in patients with chronic myeloid leukemia (N = 112).

	CML-associated PH, N (%)	Heart failure-associated PH, N (%)
Phase		
Chronic	11/110 (10.0)	2/110 (1.8)
Accelerated	1/2 (50.0)	0/2 (0.0)
Total	12/112 (10.7)	2/112 (1.8)
TKI treated at the time of TTE examined		
Imatinib	3/40 (7.5)	2/40 (5.0)
First line	3/39 (7.7)	2/39 (5.1)
Second or higher line	0/1 (0.0)	0/1 (0.0)
Nilotinib	1/32 (3.1)	1/32 (3.1)
First line	0/18 (0.0)	0/18 (0.0)
Second or higher line	1/14 (7.1)	0/14 (0.0)
Dasatinib	8/37 (21.6)	0/37 (0.0)
First line	6/28 (21.4)	0/37 (0.0)
Second or higher line	2/9 (22.2)	0/37 (0.0)
Radotinib	0/2 (0.0)	0/2 (0.0)
First line	0/1 (0.0)	0/1 (0.0)
Second or higher line	0/1 (0.0)	0/1 (0.0)
Ponatinib	0/1 (0.0)	0/1 (0.0)
Year of TTE examined,		
2003–2016	7/20 (35.0)	1/20 (5.0)
2017–2020	5/92 (5.4)	1/92 (1.1)

CML = chronic myeloid leukemia, PH = pulmonary hypertension, TKI = tyrosine kinase inhibitor, TTE = transthoracic echocardiography.

3. Results

3.1. Pulmonary hypertension in TKI-treated CML patients

Of the 112 patients undergoing TTE during TKI treatment, 12 (10.7%) had PH of indeterminate etiology (6.3% among the overall population of 189 TKI-treated patients), and were therefore diagnosed with TKI treatment-related PH. Two (1.8%) patients with left heart failure-associated PH were excluded from the analyses. There were no cases of chronic obstructive lung disease-associated PH in either group. PH was most frequently observed in patients on dasatinib (8 [21.6%] of 37 patients), followed by imatinib (3 [7.5%] of 40 patients), and nilotinib (1 [3.1%] of 32 patients). Of the 20 patients who underwent TTE between 2003 and 2016, 7 (35.0%) had PH; of the 92 patients who underwent TTE between 2017 and 2020, 5 (5.4%) had PH (Table 2).

3.2. Characteristic and clinical features of TKI-treated patients with PH

Characteristics and clinical features were compared between TKI-treated patients with (n = 12) and without PH (n = 100). Patients with PH were older than those without PH (median of 66.5 years [range 58–78] vs median of 57.5 years [range 13–81], $P = .001$). No differences were observed in the sex ratio, frequency of palpable splenomegaly and chronic phase, hematologic indices at CML diagnosis, Sokal score, Hasford score, and ELTS. More patients with PH were on dasatinib at the time of TTE treatment (8 [66.7%] of 12 patients vs 29 [29.0%] of 100 patients, $P = .009$). The line and duration of total TKI treatment did not differ between the 2 groups. Chronic kidney disease was more frequently observed in patients with PH (7 [58.3%] of 12 patients vs 16 [16.0%] of 100 patients, $P = .003$). Cardiopulmonary symptoms/signs, such as dyspnea, chest discomfort, cough, and pleural effusion, were more common in patients with PH (7 [58.3%] of 12 patients vs 3 [3.0%] of 100 patients, $P = .001$) (Table 3). PH resolved in 4 (50.0%) of the 8 dasatinib-treated patients after discontinuation of the agent. However, it persisted in 4 patients: in one since CML diagnosis and in one despite discontinuing dasatinib; the latter patient had exertional dyspnea. All 3 imatinib-treated patients recovered from PH: 1 after the TKI was changed and 2 despite continuing imatinib. One nilotinib-treated patient also recovered from PH after the TKI was changed (Supplementary Table 1, http://links.lww.com/MD/G376).

3.3. Risk factors for developing PH during TKI treatment

In univariate logistic regression analyses, old age (>60 years), dasatinib treatment, hypertension, chronic kidney disease, and cardiopulmonary symptoms/signs at the time of undergoing TTE were identified as risk factors for developing PH during TKI treatment. In multivariate analyses, age >60 years (odds ratio [OR], 12.3; 95% confidence interval [CI], 1.1–142.1, $P = .04$), dasatinib treatment (OR, 8.2; 95% CI, 1.3–50.6, $P = .03$), and cardiopulmonary symptoms/signs (OR, 36.1; 95% CI, 5.3–247.3, $P = .001$) were statistically significant risk factors for developing PH (Table 4).

4. Discussion

In this study, we investigated the prevalence of PH in TKI-treated CML patients. Overall, 10.7% of the 112 patients undergoing TTE had PH. This was equivalent to 6.3% among the whole population of 189 patients treated with TKI during the study period, including those not undergoing TTE. Both prevalences were much higher than expected in the general population.[29,30] In a study based on the nationwide health insurance system database, the prevalence of PH in Korea was 0.002%.[29] Given that the standard diagnostic tool is right heart catheterization, diagnosis of PH based on TTE alone may overestimate the incidence. PH could have been present before CML diagnosis. In addition, because this was not a prospective study and 60% of TKI-treated patients underwent TTE, the prevalence may not have been determined accurately. Despite these limitations, our results suggest a risk of PH in patients treated with TKIs other than dasatinib.

Quintas-Cardama et al[31] suggested a possible relationship between dasatinib and PH in a study on dasatinib-induced pleural effusion in CML patients. They examined TTE in 18 patients with pleural effusion treated with dasatinib and coincidentally found that right ventricular pressure increased from a median 29 (range 25–75) mmHg at baseline to median 42 (range 25–75) mmHg at the onset of pleural effusion, with a return to baseline levels after discontinuation of the agent. Many reports have described how dasatinib induces PH, which is reversible with drug discontinuation. However, most of those studies were case reports or case series.[14–21] In an effort to determine whether other TKIs induce PH, Mianmi et al[22] performed a cross-sectional study on PH in TKI-treated CML patients. They used TTE to assess the incidence of PH in 96 CML patients treated with imatinib, nilotinib, or dasatinib. The mean tricuspid regurgitation peak gradient (TRPG), which reflects pulmonary arterial pressure, was 22.7 mmHg in the imatinib

Table 3

Characteristics of tyrosine kinase inhibitor-treated patients with and without pulmonary hypertension.

	With PH (N=12)	Without PH (N=100)	P*
Age, y, median (range)	66.5 (58−78)	57.5 (13−81)	.001
Female, N (%)	5 (41.7)	41 (41.0)	1.00
Palpable splenomegaly at CML diagnosis, N (%)	4 (33.3)	36 (36.0)	1.00
Hematologic indices at CML diagnosis			
WBC ($\times 10^9$/L)	113.8±101.3	143.2±109.7	.40
Hemoglobin (g/dL)	11.3±2.0	10.8±2.3	.48
Platelet ($\times 10^9$/L)	761.6±853.0	589.0±448.1	.28
Phase at the time of TTE examined, N (%)			.80
Chronic phase	11 (91.7)	99 (99.0)	
Accelerated phase	1 (8.3)	1 (1.0)	
Sokal score, N (%)			.71
Low risk	2 (16.7)	28 (28.0)	
Intermediate risk	5 (41.7)	43 (43.0)	
High risk	5 (41.7)	29 (29.0)	
Hasford score, N (%)			.24
Low risk	0 (0.0)	28 (28.0)	
Intermediate risk	8 (66.7)	56 (56.0)	
High risk	4 (33.3)	16 (16.0)	
ETLS, N (%)			.93
Low risk	10 (83.3)	88 (88.0)	
Intermediate risk	2 (16.7)	11 (11.0)	
High risk	0 (0.0)	1 (1.0)	
TKI treated at the time of TTE examined, N (%)			
Imatinib	3 (25.0)	37 (37.0)	.53
Nilotinib	1 (8.3)	34 (34.0)	.10
Dasatinib	8 (66.7)	29 (29.0)	.01
Line of TKI at the time of TTE examined, N (%)			.27
First	9 (75.0)	77 (77.0)	
Second	1 (8.6)	18 (18.0)	
Third	2 (16.7)	4 (4.0)	
Fourth or more	0 (0.0)	1 (1.0)	
Time receiving any TKI(s) (months)	40.0±36.1	48.2±36.0	.40
Comorbidity, N (%)			
Diabetes mellitus	4 (66.7)	14 (14.0)	.10
Hypertension	6 (50.0)	22 (22.0)	.07
Smoking	2 (16.7)	15 (15.0)	.81
Ischemic heart disease	1 (8.7)	2 (2.0)	.33
Chronic kidney disease	7 (58.3)	16 (16.0)	.003
Reason for undergoing TTE, N (%)			.001
Cardiopulmonary symptoms or signs	7 (58.3)	3 (3.0)	
Screening for PH	5 (41.7)	87 (87.0)	
Others	0 (0.0)	10 (10.0)	

ETLS = EUTOS long-term survival score, PH = pulmonary hypertension, TKI = tyrosine kinase inhibitor, TTE = transthoracic echocardiography.

* χ^2 Test, Fisher exact test, or student t test.

group, 23.1 mmHg in the nilotinib group, and 23.4 mmHg in the dasatinib group. All of these values are higher than the 19.0 mmHg observed in newly diagnosed CML patients. TRPG > 31 mmHg, a marker of PH onset, was detected in 9 (9.4%) of 96 patients: 1 (2.7%) of 37 treated with imatinib, 3 (10.0%) of 30 with nilotinib, and 5 (13.2%) of 38 with dasatinib. The prevalence of PH has varied among reports. Venton et al and Kim et al reported PH using TTE in 3 (18.8%) of 28 and 30 (36.6%) of 82 CML patients treated with TKI, respectively. These studies recruited more Ph^- MPN patients and did not discriminate according to the type of TKI used. All of these points make it challenging to interpret PH prevalence. In a study based on an adverse event reporting system, PH was reported in 127 (3.2%) of 3930 CML patients treated with TKI.[32]

In the study cited above, three patients complained of dyspnea, whereas the other 6 were asymptomatic.[22] In the present study, we found PH in 12 (10.7%) of the 112 TKI-treated patients: 3 (7.5%) of 40 treated with imatinib, 1 (3.1%) of 32 with nilotinib, and 8 (21.6%) of 37 with dasatinib. Only 1 patient had exertional dyspnea, which is related to PH. Again, some selection bias might have affected the prevalence, as TTE was performed in a few patients before 2017. Nevertheless, these findings indicate that TKIs other than dasatinib are associated with subclinical PH. PH prevalence in imatinib- and nilotinib-treated patients; however, is lower than that in dasatinib-treated patients. PH resolved in four of eight patients after discontinuation of dasatinib, whereas it persisted in four patients for years despite drug discontinuation. One of the patients was symptomatic and required treatment. It is unclear whether the persistent PH is truly associated with dasatinib, because 1 patient had PH at the time of CML diagnosis, and the other 2 patients did not undergo TTE at the time of diagnosis.

Table 4

Logistic regression analysis on risk factors for developing non-cardiogenic pulmonary hypertension during tyrosine kinase inhibitor treatment.

	Univariate analysis		Multivariate analysis	
Factors	**Odds ratio (95% CI)**	***P***	**Odds ratio (95% CI)**	***P***
Old age (>60 y)	15.8 (2.0–127.4)	.01	12.3 (1.1–142.1)	.04
Gender, female	1.0 (0.3–3.7)	.97	—	—
Sokal score, high	1.7 (0.5–6.0)	.37	—	—
Hasford score, high	0.4 (0.1–1.5)	.18	—	—
Dasatinib treatment	4.9 (1.4–17.5)	.02	8.2 (1.3–50.6)	.03
Second or higher line TKI	1.1 (0.3–4.5)	.88	—	—
Long TKI treatment (>5 y)	0.7 (0.2–2.7)	.58	—	—
Diabetes mellitus	3.1 (0.9–11.6)	.10	—	—
Hypertension	5.6 (1.6–19.5)	.01	2.0 (0.2–16.6)	0.50
Chronic kidney disease	7.4 (2.1–26.1)	.002	1.6 (0.2–14.5)	0.70
Cardiopulmonary symptoms	45.2 (8.9–229.6)	.001	36.1 (5.3–247.3)	0.001

CI = confidence interval, TKI = tyrosine kinase inhibitor.

In the study cited above, a correlation trend for TRPG values and age or TKI treatment duration was noted,[22] whereas other studies found that PH was more common in high-risk patients.[31] In the present study, we identified older age, dasatinib treatment, and cardiopulmonary symptoms/signs, but not high-risk score or duration of TKI treatment, as independent risk factors for developing PH during TKI treatment based in multivariate logistic regression analyses. As TKI treatment duration was arbitrarily determined, it may be inappropriate to address its implications in PH development. Pleural effusion induced by dasatinib has previously been reported to be associated with PH.[31] We also detected 3 PH patients with pleural effusion induced by dasatinib. Collectively, TTE should be performed for any patients with cardiopulmonary symptoms and/or signs, including pleural effusion, during TKI treatment and regular TTE screening is warranted in elderly CML patients treated with dasatinib.

In conclusion, PH is common in CML patients treated with dasatinib; however, it is also observed in patients treated with imatinib or nilotinib. Although patients with PH may be asymptomatic, careful screening for PH during any TKI treatment may nonetheless be warranted in patients with CML.

Author contributions

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