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【 ORIGINAL ARTICLE 】

Relationship between Dasatinib-induced Pulmonary Hypertension and Drug Dose

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Abstract:

Objective Dasatinib, a second-generation tyrosine kinase inhibitor, is used for chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). It reportedly causes pulmonary arterial hypertension (PAH) and the dose-dependent induction of apoptosis in pulmonary endothelial cells. However, no report has yet discussed the relationship between dasatinib-induced PAH and drug dose. We therefore investigated the incidence of dasatinib-induced PAH and the relationship between dasatinib-PAH and drug dose in consecutive patients with CML and Ph+ ALL who took dasatinib.

Methods The clinical data of 128 patients with CML (94 patients) and Ph+ ALL (34 patients) were retrospectively analyzed.

Patients All patients (>17 years old) who received dasatinib from January 2009 to March 2020 at Jichi Medical University (Tochigi, Japan) were included. Patients who transferred within one month of starting dasatinib administration were excluded.

Results Four (4.3%) and three (8.8%) patients developed pulmonary hypertension (PH), which was considered present when the transtricuspid pressure gradient was ≥40 mmHg, in the CML and ALL groups, respectively. No significant difference was observed between the PH onset and the administration period, cumulative dose, or daily dose of dasatinib. PH occurred in seven patients (5.5%), and the period from the start of dasatinib administration to the PH onset ranged from 7 to 39 (median: 28) months. No patients died from PH in either group.

Conclusion Dasatinib-induced PAH does not occur time- or dose-dependently. When administering dasatinib, cardiovascular diagnostic modalities should be routinely checked, and PAH occurrence should be promptly detected.

Key words: dasatinib, pulmonary arterial hypertension, tyrosine kinase inhibitor, chronic myelogenous leukemia, acute lymphoblastic leukemia

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Introduction

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) that was introduced to the market after imatinib and targets breakpoint cluster region (BCR)/Abelson murine leukaemia (ABL) kinase, Src family kinases, c-kit, and PDGFRβ. It is widely used as a first-line therapy for chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Recently, the rate of cardiovascular events and pleural effusion (PE) has been reported to be higher with newer TKIs than with the first-generation TKI imatinib (1).

Pulmonary arterial hypertension (PAH) is an uncommon but serious complication and is known to have various causes, such as heredity, shunt disease, and collagen disease.

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Drug-induced PAH is a type of PAH that has been found to be caused by various drugs. In recent years, a considerable number of studies have been made on dasatinib-induced PAH, and dasatinib was classified as "likely" in the European Society of Cardiology guideline of 2015 (2). Thereafter, based on accumulated evidence, the Sixth World Symposium on Pulmonary Hypertension in 2018 was published and clearly demonstrated the relationship between dasatinib and PAH (3).

Several previous reports have demonstrated that dasatinib is associated with an increased risk of PE, with approximately 30% of patients experiencing PE in large cohorts, while generally tolerating it well. The exact mechanism underlying PE remains to be elucidated; however, it has been suggested that immune mechanisms can play a role, based on reports of its association with lymphocytosis and the presence of lymphocyte-dominant exudates and chyle accumulation (4). Regarding the mechanism underlying dasatinib-induced PAH, Phan et al. reported that dasatinib altered the pulmonary endothelial permeability in a reactive oxygen species-dependent manner *in vitro* and *in vivo*, leading to PE (5). In addition, dasatinib caused the rapid dose-dependent induction of apoptosis in the pulmonary endothelial cells of rats, and this injury and dysfunction of the pulmonary endothelial cells was suggested to cause PAH (6). Therefore, we hypothesized that dasatinib-induced PAH is caused dose-dependently in clinical practice.

We analyzed 94 consecutive CML patients and 34 Ph+ ALL patients who received dasatinib at Jichi Medical University and investigated the incidence of dasatinib-induced PAH and the relationship between dasatinib-PAH and drug dose in Japanese clinical practice. In addition, we report two representative cases of dasatinib-induced PAH.

Materials and Methods

Patients

All patients (>17 years old) who received dasatinib from January 2009 to March 2020 at Jichi Medical University (Tochigi, Japan) were included. Patients were identified from their prescription histories, and their hospital records were examined. This was a retrospective analysis of data collected for routine clinical care and was approved by the ethics committee of Jichi Medical University. Because of the retrospective observational design, the outline of the study was published on the website, and consent from the patients was obtained by providing an opportunity to refuse and opt out. We excluded patients who transferred within one month from the start of the oral administration of dasatinib. Since the three patients with CML lived far from our hospital, their stable condition was immediately confirmed after the start of the treatment, and they were transitioned to outpatient treatment at a nearby doctor. One patient with ALL was transferred to another university hospital, as the patient had moved to another region in Japan.

Data collected included sex, age at dasatinib initiation, body mass index, estimated glomerular filtration rate, administration period, cumulative dose and daily dose of dasatinib, history of TKI treatment, and date of the last follow-up. In patients with pulmonary hypertension (PH) or PE, the administration period was from the initiation of dasatinib to the onset of complications, and the cumulative dose was calculated from this period. The daily dose was calculated as the cumulative dose divided by the administration period. In patients who did not have pulmonary circulatory complications, if dasatinib was continuously administered during the observation period, the observation was continued until the end of the period; however, if dasatinib was discontinued because of other complications or insufficient effect, the observation was terminated at that point.

The cardiac evaluation

Patients were referred to the cardiology department when they had cough, shortness of breath, or PE on chest radiography during treatment in the hematology branch. For these patients, echocardiography was first performed as a screening test, and we designated a transtricuspid pressure gradient (TRPG) of ≥40 mmHg as PH. Cardiac catheterization was performed on the basis of the cardiologist's decision. In this article, according to the European Society of Cardiology guideline of 2015 (2), patients with a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg, a pulmonary capillary wedge pressure of ≤15 mmHg, and a pulmonary vascular resistance of >3 Wood units by right heart catheterization (RHC), in the absence of other causes of precapillary PH, were considered to have PAH.

Statistical analyses

Data are expressed as medians [interquartile range (IQR), 25-75th percentile] or percentages. Continuous and categorical variables were compared between the two groups using Student's *t*-test and the chi-squared test, respectively. All statistical analyses were performed using the SPSS Statistics software program, version 25.0 (IBM; Armonk, USA), and time-to-event curves were plotted using EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (7). p values <0.05 were considered significant for all tests.

Results

Patients' characteristics

Patients' characteristics are summarized in Tables 1 and 2. Between January 2009 and March 2020, 94 CML patients and 34 Ph+ ALL patients received chemotherapy including dasatinib. The majority of CML patients underwent outpatient treatment only. Therefore, some lacked sufficient data to calculate the body mass index or estimated glomerular filtration rate. Among the CML patients, four patients (4.3%) developed PH. No significant difference was observed be-

Table 1. CML Patient's Characteristics.

	PH, n=4	Non PH, n=90	p value
Age, years	56.0 (35.1-65.8)	52.8 (38.4-67.4)	0.963
Male, % (n)	75.0 (3)	60.0 (56)	0.485
Follow up period, day	583.0 (245.3-836.8)	608.0 (122.5-1,528.5)	0.456
Dasatinib			
Administration period, days	583.0 (232.5-831.5)	551.5 (118.5-1,386.5)	0.490
Cumulative dose, g	37.6 (23.2-93.6)	45.8 (9.1-121.5)	0.570
Dose/day, mg	100.0 (62.5-125.2)	100.0 (84.2-100.0)	0.666
Preceding TKI			
Imatinib, % (n)	50.0 (2)	34.4 (31)	0.439
Nilotinib, % (n)	0	7.8 (7)	0.730
Bosutinib, % (n)	0	3.3 (3)	0.876

Data are median (IQR, 25-75th percentile) or percentage. CML: chronic myeloid leukemia, PH: pulmonary hypertension, PE: pleural effusion, BMI: body mass index, eGFR: estimated glomerular filtration rate, TKI: tyrosine kinase inhibitor

Table 2. ALL Patient's Characteristics.

	PH, n=3	Non PH, n=31	p value
Age, years	29.1 (28.5-43.7)	53.5 (43.4-61.8)	0.217
Male, % (n)	0	61.3 (19)	0.076
BMI, kg/m^2	20.3 (18.1-22.0)	22.0 (19.3-23.8)	0.422
eGFR, mL/min/1.73m^2	100.0 (94.0-111.0)	75.0 (65.0-92.0)	0.306
Follow up period, day	960.0 (727.0-1,070.5)	162.0 (100.0-345.0)	0.066
Dasatinib			
Administration period, days	829.0 (597.5-981.5)	131.0 (75.8-329.0)	0.148
Cumulative dose, g	41.6 (38.1-63.5)	15.2 (7.8-30.0)	0.507
Dose/day, mg	75.3 (62.8-85.0)	110.0 (97.4-120.9)	0.019
Preceding TKI			
Imatinib, % (n)	0	61.3 (19)	0.257
Nilotinib, % (n)	0	-	-
Bosutinib, % (n)	0	-	-

Data are median (IQR, 25-75th percentile) or percentage. ALL: acute lymphocytic leukemia, PH: pulmonary hypertension, PE: pleural effusion, BMI: body mass index, eGFR: estimated glomerular filtration rate, TKI: tyrosine kinase inhibitor

tween PH and the administration period, cumulative dose, and daily dose of dasatinib (Fig. 1A-C). Among the ALL patients, three patients (8.8%) developed PH, during the period. Among the ALL patients, as with the CML patients, there was no clear difference in the incidence PH according to the administration period or cumulative dose of dasatinib (Fig. 2A, B). However, the patients with PH received significantly lower daily doses of dasatinib than the patients with no PH (Fig. 2C).

Outcome of dasatinib therapy

Table 3 shows the outcome of dasatinib therapy among CML and ALL patients. Twenty CML patients (21.2%) were still taking dasatinib at the end of the observational period, while 57 CML patients (60.6%) discontinued dasatinib. PH developed in four patients (4.2%), and PE was detected in 28 patients (29.7%). Other side effects mainly included cytopenia and gastrointestinal bleeding. Nine patients (9.5%) switched from dasatinib to another TKI because of inadequate efficacy against CML. Three patients (3.1%) received transplantation. One discontinued dasatinib successfully because of treatment-free remission. During the period, there were two deaths (2.1%) due to blast crisis in CML. Twenty-five patients with ALL (73.5%) discontinued dasatinib. Although PH developed in three patients (8.8%), the incidence of PE was only 8.8%, which was lower than that in CML patients. Furthermore, nine patients underwent hematopoietic stem cell transplantation (26.5%), and three patients died due to deterioration of ALL during the observation period (12.1±16.5 months). Therefore, compared to the general outcome of ALL, the low percentage of ALL patients who underwent transplantation or died may be due to dasatinib being discontinued because of other reasons, such as inadequate efficacy and cytopenia, and many patients dropped out of the study before receiving transplantation or died. For both CML and ALL patients, PH occurred in seven patients (5.5%), and no patients died from PH.

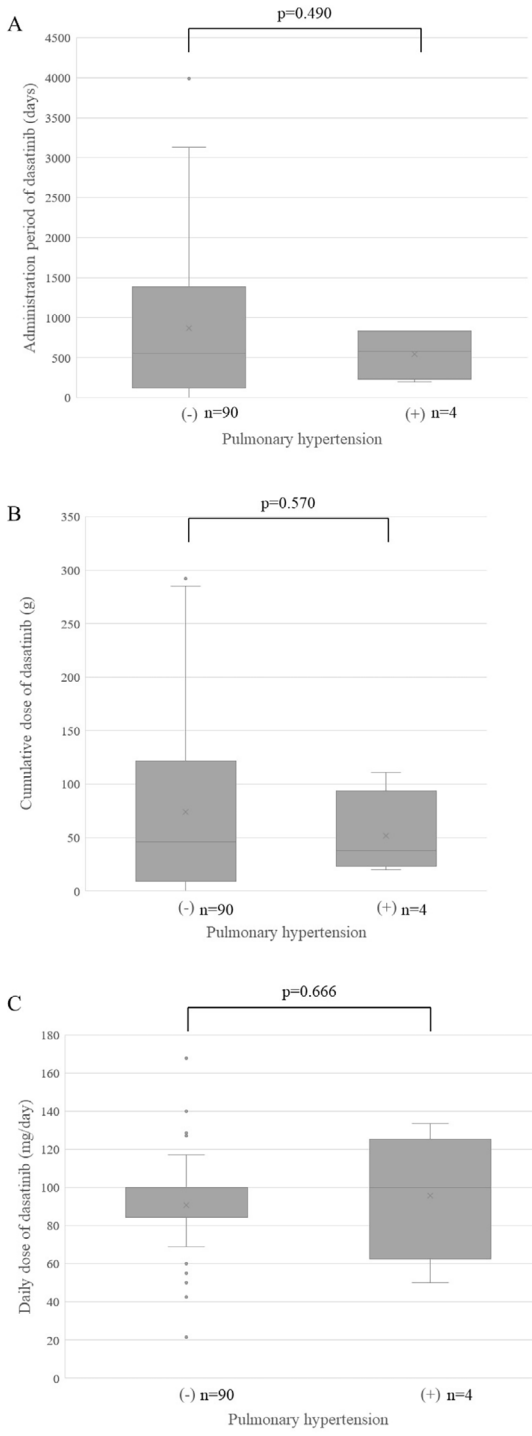

Figure 1. **(A) Relationship between pulmonary hypertension and the administration period of dasatinib in the CML patients. (B) Relationship between pulmonary hypertension and cumulative dose of dasatinib in the CML patients. (C) Relationship between pulmonary hypertension and daily dose of dasatinib in the CML patients.**

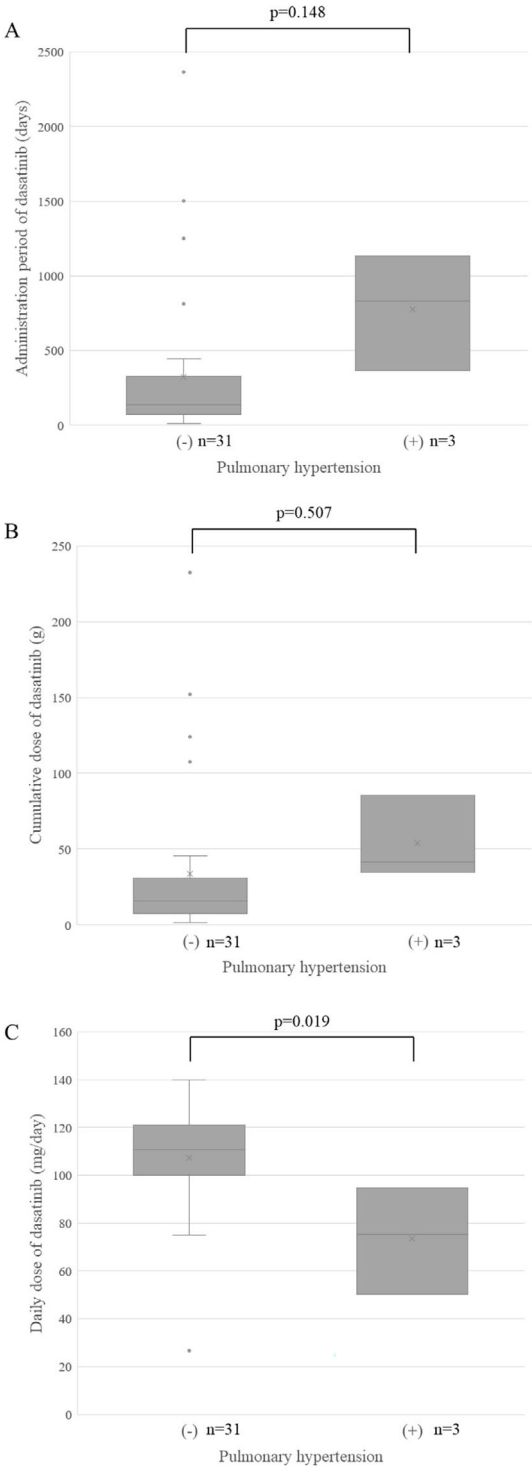

Figure 2. **(A) Relationship between pulmonary hypertension and the administration period of dasatinib in the ALL patients. (B) Relationship between pulmonary hypertension and cumulative dose of dasatinib in the ALL patients. (C) Relationship between pulmonary hypertension and daily dose of dasatinib in the ALL patients.**

Cumulative incidence of PH

Fig. 3 describes the cumulative incidence of PH. There were 4 CML patients and 3 ALL patients who developed PH, and their period from initiation of dasatinib to the onset of PH ranged from 7 to 39 (median: 28) months. In both the CML and ALL groups, the cumulative incidence of PH did not increase in a time-dependent manner. Although the presence of several cases of withdrawal means we cannot make a definitive conclusion, there were some cases in which dasatinib was taken for a long period of 10 years or more

Table 3. Outcome of Dasatinib.

	CML	ALL
Number	94	34
Continue, number (%)	20 (21.2)	4 (11.8)
Discontinue, number (%)	57 (60.6)	25 (73.5)
PH, number (%)	4 (4.2)	3 (8.8)
PE, number (%)	28 (29.7)	3 (8.8)
Other side effects, number (%)	14 (14.8)	4 (11.8)
Insufficient outcome, number (%)	9 (9.5)	6 (17.6)
Transplantation, number (%)	3 (3.1)	9 (26.5)
Complete treatment, number (%)	1 (1.0)	0
Hospital transfer, number (%)	13 (13.8)	2 (5.9)
Death, number (%)	2 (2.1)	3 (8.8)
No data	1 (1.0)	0

Data are number and percentage. CML: chronic myeloid leukemia, ALL: acute lymphocytic leukemia, PH: pulmonary hypertension, PE: pleural effusion

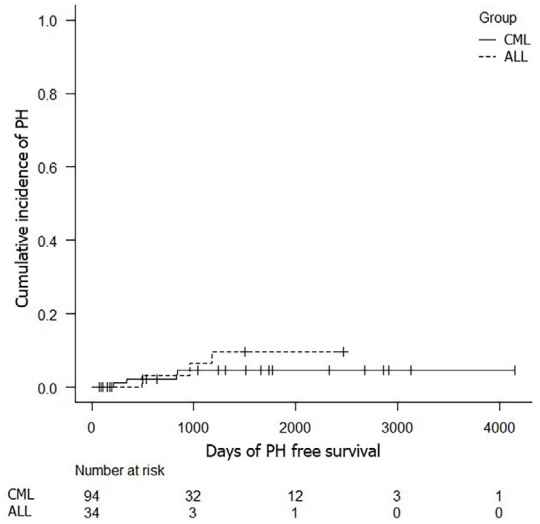

Figure 3. Cumulative incidence of pulmonary hypertension. ALL: acute lymphocytic leukemia, CML: chronic myeloid leukemia, PH: pulmonary hypertension

without complications.

Characteristics of PH patients

Table 4 shows the characteristics of PH patients. Cases 1-3 were referred to the Department of Cardiovascular Medicine for PAH treatment and underwent cardiac catheterization. Cases 1 and 2 are described in detail below as representative cases. Case 3 received induction therapy including dasatinib; however, her bone marrow findings did not improve, and allogeneic bone marrow stem cell transplantation was performed one year after the diagnosis. Dasatinib (120 mg/day) was continued even after transplantation, and PAH occurred 14 months later. Soon after dasatinib was discontinued, her hemodynamics improved immediately. Although a lower dose of bosutinib (200 mg/day) was started two weeks after discontinuing dasatinib, she ultimately died of ALL recurrence one month later. In cases 4-6, outpatient echocardiography was performed because of dyspnea, and a slightly high TRPG level was noted. As only a brief echocardiographic report remained, detailed findings suggestive of increased pulmonary vascular resistance (PVR), such as septal flattening and changes on right ventricular outflow tract blood flow Doppler imaging, could not be confirmed. These patients improved with dasatinib discontinuation alone. In case 4, echocardiography performed 2 months after discontinuation of dasatinib confirmed a decrease in the TRPG level to 21 mmHg. In cases 5 and 6, it was confirmed that significant tricuspid valve regurgitation had disappeared on echocardiography just one month later, and the TRPG level had decreased beyond measurement. Case 7 had a high TRPG level of 65 mmHg; however, this was improved by dasatinib discontinuation and outpatient administration of diuretics. Eleven months later, echocardiography demonstrated a TRPG level of 31 mmHg.

Representative cases

- **Case 1**

A 32-year-old man had a 1-month history of cough and a 2-week history of exertional dyspnea [World Health Organization functional class (WHO-FC) II]. Although he had been diagnosed with CML four years prior, he had not been followed up thereafter. Two years after the diagnosis, he developed blast crisis and was treated with eight cycles of hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine, combined with dasatinib. Because the number of copies of major BCR-ABL mRNA on quantitative polymerase chain reaction remained high after chemotherapy, dasatinib was increased to the maximal dose of 180 mg, and he returned to the second chronic phase. At 22 months after starting dasatinib monotherapy, he complained of cough.

Upon admission, a physical examination showed a regular heart rate of 100 bpm, a blood pressure of 124/80 mmHg, and oxygen saturation of 97% on room air. His brain natriuretic peptide level increased to 180.0 pg/mL, and on echocardiography, his TRPG level increased to 96 mmHg, and flattening of the left ventricle due to elevated right ventricular pressure was observed. Initial RHC showed elevation of the PAP (mPAP=43 mmHg) and PVR (671 dyn•s•cm^{-5}). His pulmonary capillary wedge pressure was 10 mmHg, and his cardiac index (CI) decreased to 2.3 L/min/m^2. Connective tissue disease, congenital heart disease, respiratory disease, and chronic thromboembolic pulmonary hypertension were ruled out by further examinations. Finally, he was diagnosed with dasatinib-induced PAH.

Nine days after discontinuation of dasatinib, his TRPG level declined promptly to 60 mmHg on echocardiography. Despite not using a pulmonary vasodilator, his hemodynamics were normalized (mPAP, 16 mmHg), which was con-

Table 4. Characteristics of Dasatinib-induced PH Patients.

Case	Diagnosis	Sex	Age, year	TRPG, mmHg	mPAP, mmHg	Administration period, day	Cumulative dose, g	Dose/day, mg	Preceding imatinib	Transplantation	Therapy for PH	Outcome
1	CML	M	32	96	43	833	111.3	133.6	-	-	Discontinuation of dasatinib	Improve
2	ALL	F	31	74	54	829	41.6	50.2	-	+	Discontinuation of dasatinib, masitentan, tadalafil, iroprost	Improve
3	ALL	F	30	40	26	366	34.6	94.8	-	+	Discontinuation of dasatinib	Died of ALL
4	CML	F	69	42	-	827	41.3	50	+	-	Discontinuation of dasatinib	Improve
5	CML	M	50	44	-	197	19.7	100	-	+	Discontinuation of dasatinib	Improve
6	CML	M	63	47	-	339	33.9	100	+	-	Discontinuation of dasatinib	Improve
7	ALL	F	62	65	-	1,134	85.4	75.3	-	-	Discontinuation of dasatinib, diuretics	Improve
Mean±SD			55.3±13.0		646±319	52.5±30.5	86.3±27.8					

PH: pulmonary hypertension, CML: chronic myeloid leukemia, ALL: acute lymphocytic leukemia, TRPG: transtricuspid pressure gradient, mPAP: mean pulmonary arterial pressure

firmed by RHC 6 months later. As the number of copies of major BCR-ABL mRNA quantitated with an Amp-CML kit was increased again two months later, nilotinib was introduced. His tumor markers declined quickly, and there was no recurrence of PAH and CML.

- **Case 2**

A 31-year-old woman had a 2-week history of cough and exertional dyspnea (WHO-FC III). She had been diagnosed with Ph+ ALL 2 years prior and received combination chemotherapy, which consisted of 60 mg/m^2 prednisolone daily for 3 weeks and 140 mg/body dasatinib daily for 6 weeks as induction, following hyper-CVAD alternating with high-dose methotrexate and cytarabine, combined with dasatinib as consolidation. After a continuous daily dose of 100 mg dasatinib, she underwent allogeneic hematopoietic stem cell transplantation from a human leukocyte antigen-identical sibling donor 5 months after her diagnosis. To prevent relapse, 40 mg daily dasatinib was restarted, although this was interrupted with thrombocytopenia. At 24 months after restarting dasatinib, she complained of dyspnea.

Upon admission, a physical examination showed a regular heart rate of 113 bpm, blood pressure of 103/80 mmHg, and oxygen saturation of 99% on room air. Her brain natriuretic peptide level increased to 974.6 pg/mL, and echocardiography revealed enlargement of the right atrium and ventricle, severe tricuspid valve regurgitation, and a TRPG level of 74 mmHg. Initial RHC showed elevation of the mean PAP (54 mmHg) and pulmonary vascular resistance (1,857 dyn•s•cm^{-5}). Her pulmonary capillary wedge pressure was 5 mmHg, and the CI was 1.6 L/min/m^2. No other causative disease of PAH was observed, so she was diagnosed with dasatinib-induced PAH.

Given that discontinuation of dasatinib did not improve her dyspnea after seven days and that her CI was lower than that of the patient in Case 1, we started pulmonary vasodilators after eight days. Although 10 mg/day macitentan and 40 mg/day tadalafil were administered sequentially, her TRPG level did not improve completely; therefore, iloprost inhalation and home oxygen therapy were added. Imatinib 100 mg was introduced as an alternative to dasatinib for patients with ALL. After 3 months, her TRPG and brain natriuretic peptide levels decreased to 20 mmHg and 19 pg/mL, respectively. Iloprost inhalation was reduced gradually and discontinued one year later. She is still continuing her intake of macitentan and tadalafil and has not experienced recurrence of PAH or ALL.

Discussion

The main findings of the present study can be summarized as follows: 1) PH occurred in 7 of 128 patients (5.4%), and no patients died of PH in our institute. 2) Dasatinib-induced PAH does not occur time- or dose-dependently.

TKIs are used as the first-line drug treatment for CML and Ph+ ALL. Especially in chronic-phase CML, because of the introduction of second-generation dasatinib and nilotinib following the first-generation drug imatinib, the 10-year survival rate has improved to 80-90%, and it has become a drug-controllable tumor (8). In recent years, bosutinib and the third-generation drug ponatinib were also introduced; thus, treatment with newer TKIs has significantly improved the major molecular response and increased the rate of a complete molecular response in CML patients (1). Furthermore, the introduction of these drugs has also led to incremental improvements in the outcomes of patients with Ph+ ALL (9, 10). However, the rates of cardiovascular events and PE are reportedly higher with these newer TKIs than

with imatinib (1).

Dasatinib inhibits BCR-ABL, c-Kit, and the platelet-derived growth factor receptor more potently than does imatinib, and it also inhibits Src family kinases (11). Based on accumulated evidence, the Sixth World Symposium on Pulmonary Hypertension in 2018 has thus now classified the association of dasatinib with PH as definite (3). Montani et al. showed that there was an interval of 8 to 48 (median 34) months from the initiation of dasatinib administration to the onset of PAH (12). Similarly, our current study showed an interval of 7 to 39 (median 28) months to the onset of PH. Although improvements in clinical symptoms, exercise tolerance, and hemodynamics were observed after four months of discontinuation, it was also revealed that mPAP was not completely normalized in most cases (12). Of the three PAH cases that underwent cardiac catheterization in our current study, cases 1 and 3 achieved complete hemodynamic improvement; while case 2 has been using pulmonary vasodilators, the exercise tolerance has not yet normalized. Thus, the differences between these cases may be related to the degree of pulmonary artery remodeling, although this point has not yet been clarified.

The efficacy of dasatinib is currently being tested in other malignancies, including melanoma and breast, lung, ovarian, and head and neck cancers (13). It should be noted that the number of patients with dasatinib-induced PAH is expected to increase in the future as the indication of dasatinib expands.

In addition, it is necessary to pay attention to the effects of other TKIs on the pulmonary artery. We changed dasatinib to nilotinib in case 1 and to bosutinib in case 3. Recently, however, it was reported that PAH is caused by bosutinib and ponatinib (14, 15). Therefore, when selecting a treatment for CML or Ph+ ALL, it is important to be aware of the characteristics of different TKIs.

The true incidence and prevalence of dasatinib-induced PAH have been challenging to estimate. Montani et al. first reported the lowest estimate of incident PAH occurring in patients exposed to dasatinib in France as 0.45% (12). Since then, several reports have described the incidence of dasatinib-induced PAH as ranging from 0.2% to 5% (16-18). El-Dabh et al. pointed out the following four reasons for these discrepancies: 1) many of the studies are case reports or series that do not report the total number of patients receiving dasatinib at those institutions during that time period; 2) large-scale formal echocardiographic screening studies for asymptomatic PH have not been performed; 3) suspected cases have not uniformly been confirmed with catheterization; and 4) symptoms of PH may overlap with other, more common complications of dasatinib, such as PE (13). The slightly increased incidence rate at our facility was 5.5%, possibly because we defined PH in cases with a TRPG level of ≥40 mmHg. Some suspected cases may have been determined not to be PAH by cardiac catheterization.

Several previous reports have demonstrated that dasatinib is associated with an increased risk of PE, with approximately 30% of patients experiencing PE in large cohorts, while generally tolerating it well. The exact mechanism underlying PE remains to be elucidated; however, it has been suggested that immune mechanisms may play a role, based on reports of an association with lymphocytosis and the presence of lymphocyte-dominant exudates and chyle accumulation (4).

Phan et al. reported that dasatinib altered the pulmonary endothelial permeability *in vitro* and *in vivo* leading to PE (5). Guignabert et al. subsequently demonstrated that dasatinib causes the rapid, dose-dependent induction of apoptosis in pulmonary endothelial cells of rats and suggested that PAH was caused by injury and dysfunction of pulmonary endothelial cells (6). Fig. 2C shows that patients with PH received significantly lower daily doses of dasatinib than the patients with no PH. This may have been due to a statistical error, owing to the small number of patients with PH (n=3) and the difference was not clinically meaningful. Thus, in the current study, no clinically significant difference was observed in the incidence of PH according to the cumulative or daily dose of dasatinib. As mentioned earlier, only three of the seven PH patients received RHC and were diagnosed with PAH; however, even if all seven had PAH, no difference was noted in the incidence of PAH according to the cumulative or daily dose of dasatinib. Furthermore, the current study revealed no clear difference in the incidence of PH or PAH according to the duration of dasatinib administration. As shown in Fig. 3, PH did not develop immediately after the start of dasatinib, and the seven patients developed PH 7 to 39 months after the initiation of dasatinib. Thus, cardiovascular evaluations should be performed continuously in patients who start taking dasatinib.

Guignabert et al. also showed that PAH is more likely to develop because of other environmental risk factors, such as hypoxia or certain other toxins, in addition to the administration of dasatinib (6). Phan et al. further revealed that pulmonary endothelial permeability was altered by dasatinib in a reactive oxygen species-dependent manner (5). In addition to these environmental risk factors, our results may have been influenced by racial differences between Japanese people and Caucasians. When administering dasatinib, it is necessary to keep in mind that pulmonary circulatory complications may not occur time- or dose-dependently and always be alert for fatal complications, such as PAH.

We analyzed the CML and ALL patients separately in the present study. In both the CML and ALL patients, dasatinib was used as a therapeutic drug. However, CML and ALL are originally diseases with completely different pathological conditions, concomitant drugs, and indications for bone marrow transplantation. These factors may thus have contributed to the differences in the results between the CML and ALL patients.

Of note, the efficacy of and need for PAH-specific therapy for dasatinib-induced PAH remains inconclusive. Some reports have suggested that dasatinib-induced PAH is alleviated by PAH-specific therapy, and others have mentioned

that the hemodynamics improved with discontinuation of dasatinib alone, without using a pulmonary vasodilator (19, 20). When the case 1 patient was hospitalized, there were no data showing that PAH-specific treatments were effective for dasatinib-induced PAH; therefore, we simply discontinued dasatinib. Weatherald et al. analyzed 19 patients with dasatinib-induced PAH (21). Nine patients received PAH-specific therapy, two patients received calcium channel blockers, and dasatinib was discontinued in ten patients. After a median clinical follow-up of 24 (1-81) months, similar clinical and hemodynamic outcomes in the treated and non-treated patients were observed. However, this study's results might have been influenced by the possibility that exercise tolerance and the CI at the diagnosis in the treated group were worse than in the non-treated group, and a beneficial effect of PAH-specific therapy in the most severe patients cannot be excluded. Even in our case 1, the patient's CI had declined to 2.3 L/min/m^2. However, the fact that exercise tolerance was relatively well maintained (WHO-FC II) may be because of his good clinical course. In contrast, case 2 had more severe dyspnea (WHO-FC III), and her CI had dropped to 1.6 L/min/m^2. Therefore, we chose PAH-specific therapy. When treating dasatinib-induced PAH, it is necessary to consider disease severity in each patient.

There are few aggregate reports on the long-term prognosis of dasatinib-induced PAH (12, 21, 22). In eight of nine patients, clinical, functional, or hemodynamic improvements were observed within four months. However, no patients reached a normal value of mPAP (<20 mmHg), and two patients died (one had heart failure) (12). In the 19 cases reported by Weatherald et al., PAH persisted in the long term in 37%, and four patients died (one had heart failure in the context of septicemia, and one had sudden death after a long-distance flight; no information was available for the other two patients) (21). Although rare, death due to right heart failure despite PAH-specific therapy has been reported in a 36-year-old woman from Japan (22). There were no deaths due to PH in the present study.

Several limitations associated with the present study warrant mention. First, our data are limited by the retrospective study design. Second, the number of subjects in the present analysis was small. Third, as we did not perform RHC for all patients in whom PH was suspected, PH may have been caused by other factors aside from those discussed in the three cases diagnosed with PAH by RHC. Of note, we were unable to rule out the involvement of pulmonary thromboembolism in three of the seven PH cases. We performed lung perfusion scintigraphy or contrast-enhanced computed tomography for the three patients with PAH. However, only one patient was confirmed to have a D-dimer level below the reference value. Fourth, echocardiography prior to dasatinib administration was not performed in some of the patients suspected of having PH, so whether or not PH was absent prior to dasatinib could not be determined. However, since all seven patients with PH underwent echocardiography when symptoms such as shortness of breath appeared, it was considered unlikely that PH had existed before the administration of dasatinib. Furthermore, since PE was a side effect of dasatinib that had been recognized since the clinical trial stage, in mild PE cases, there were some instances in which the dose of dasatinib was reduced or combined with diuretics without performing echocardiography. Thus, because not all patients with PE underwent echocardiography, not all patients could be conclusively diagnosed with PH. Nevertheless, we believe that our group of patients is representative of a contemporary Japanese regional core hospital.

In conclusion, our study demonstrated that dasatinib-induced PAH does not occur time- or dose-dependently. Therefore, when administering dasatinib, clinicians should routinely check cardiovascular diagnostic modalities and detect the occurrence of fatal complications, such as PAH, at the earliest possible stage. Furthermore, when choosing the treatment for CML and ALL, it is necessary to be familiar with the characteristics of each TKI. Many aspects of the clinical picture of dasatinib-induced PAH remain unknown, and the further accumulation of cases is warranted in the future.

The authors state that they have no Conflict of Interest (COI).

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