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ORIGINAL PAPER

Computed tomography-measured pulmonary artery to aorta ratio and EUTOS score for detecting dasatinib-induced pulmonary arterial hypertension

Takumi Toya[1] · Yuji Nagatomo[1] · Kazuki Kagami[1] · Midori Yukino[1] · Risako Yasuda[1] · Takayuki Namba[1] · Yasuo Ido[1] · Shinichi Kobayashi[2] · Nobuyuki Masaki[1] · Hirotaka Yada[1] · Fumihiko Kimura[2] · Takeshi Adachi[1]

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Abstract

Background Periodic echo-based screening to detect early stages of a rare complication of dasatinib, pulmonary arterial hypertension (PAH), is inefficient and weakens the potential benefit of dasatinib as a potent drug for chronic myelogenous leukemia (CML). This study aimed to identify the predisposing factors of DASA-PAH to stratify high-risk patients for dasatinib-induced PAH (DASA-PAH).

Methods Sixty consecutive adult patients who received dasatinib were enrolled in this case-control study. We defined DASA-PAH when at least one of the following four criteria was met: (1) recent electrocardiographic changes indicating right ventricular pressure overload, (2) estimated systolic pulmonary arterial pressure > 40 mmHg measured by Doppler echocardiography; (3) computed tomography (CT)-measured pulmonary artery to aorta diameter (PaD/AoD) ratio > 1; and (4) mean pulmonary arterial pressure > 25 mmHg and pulmonary artery wedge pressure < 15 mmHg measured by right heart catheterization.

Results We identified 13 patients with DASA-PAH among 59 patients analyzed. Baseline PaD/AoD ratios of patients who developed DASA-PAH (PH group) were significantly larger than those who did not (NPH group). A dramatic rise in PaD/AoD ratio after dasatinib treatment was observed. Interestingly, the EUTOS score and spleen size were significantly smaller in the PH than in the NPH group.

Conclusion High baseline PaD/AoD ratio and low EUTOS score were associated with DASA-PAH development. The spleen might play a protective role against DASA-PAH.

Keywords CT · Dasatinib · EUTOS score · Pulmonary arterial hypertension

Abbreviations

AoD	Aortic diameter
CML	Chronic myelogenous leukemia
CT	Computed tomography
DASA	Dasatinib
DASA-PAH	Dasatinib-induced pulmonary arterial hypertension
ECG	Electrocardiography
LA	Left atrium
LVEF	Left ventricular ejection fraction
MPAP	Mean pulmonary arterial pressure
PaD	Pulmonary artery diameter
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
SPAP	Systolic pulmonary arterial pressure
TKI	Tyrosine kinase inhibitor
TTE	Transthoracic echocardiography
WU	Wood units

✉ Takumi Toya
tyt0725@gmail.com

[1] Division of Cardiology, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan

[2] Division of Hematology, National Defense Medical College, 3-2 Namiki, Tokorozawa 359-8513, Japan

Introduction

Dasatinib (DASA), which is 325-fold more potent than first-generation tyrosine kinase inhibitor (TKI) imatinib, can inhibit BCR-ABL tyrosine kinase whose aberrant activation is a causative factor of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoid leukemia (Ph + ALL) [1]. DASA has been used as the second-line treatment for patients with imatinib-resistant CML or Ph + ALL as well as the first-line treatment because of its potent effect against BCR-ABL tyrosine kinase [2].

On the contrary, DASA can cause various side effects. Pleural effusion can be observed in approximately one-third of patients treated with DASA [3], but the etiology of DASA-related pleural effusion is poorly understood. The finding of a high lymphocyte counts in pleural effusion gave us the hypothesis that DASA-related pleural effusion is immune-mediated, but not cardiovascular-related [4]. Growing evidence suggests that DASA can also elicit rare complication of pulmonary arterial hypertension (PAH), leading to nonspecific symptoms including dyspnea and easy fatigability with more frequent side effects of DASA such as pleural effusion and anemia. It is difficult to differentiate PAH from pleural effusion or anemia as a primary cause of symptoms without further investigations via transthoracic echocardiography (TTE) and right heart catheterization (RHC) as a gold standard to confirm PAH [5]. Recently, we reported an extreme case of DASA-induced pulmonary arterial hypertension (DASA-PAH) with the mean pulmonary arterial pressure (MPAP) of 67 mmHg and pulmonary vascular resistance (PVR) of 23.5 wood units (WU) at the first diagnosis of DASA-PAH. The patient was successfully treated with DASA withdrawal and a triple combination of pulmonary vasodilators, showing the difficulty of diagnosis (*EHJ Case Reports*; in press). Although a complete molecular response of CML has been induced under the treatment with DASA in this patient, the Philadelphia chromosome was shown to be present after 4-month cessation of DASA. The survival rate of patients with CML under a complete cytogenetic response is equivalent to that of age-matched controls; thus, it is crucial not to halt CML treatment because of the side effects of TKIs [6]. Few reports exist regarding the predisposing factors to DASA-PAH development. Therefore, a screening method to identify high-risk patients for DASA-PAH deserves further investigation.

Recently, published report of long-term outcomes of 21 RHC-confirmed DASA-PAH showed a prompt functional and hemodynamic improvement after DASA withdrawal, but PAH persisted in 37% of the patients [7]. Consistent data were shown in a previous report of 41 patients with RHC-confirmed DASA-PAH, but only 58% of the patients achieved complete resolution [8]. These data indicated the existence of underlying abnormality in DASA-PAH development, although it is unclear whether this abnormality is systemic or localized in the pulmonary vasculature. Interestingly, DASA administration to control rats did not induce PAH-related hemodynamic, structural, or molecular changes in the pulmonary artery. Furthermore, both DASA and imatinib increased nitric oxide and decreased endothelin-1 protein and mRNA in the pulmonary artery endothelial cells and smooth muscle cells co-culture model [9]. Comparable results showed that DASA did not induce PAH in control animals, but exacerbated PAH in a rodent model of PAH induced by monocrotaline or hypoxia, suggesting a two-hit theory in the underlying pathophysiology of DASA-PAH [10].

The European Society of Cardiology recommended TTE surveillance every 3 months during DASA treatment, but an optimal interval between TTE surveillances is not based on previous data [11]. Stratifying the risk for DASA-PAH could lead us to a more efficient screening strategy for affected patients.

Given the above data, we performed this study to identify the predisposing factors to predict the development of DASA-PAH and to investigate which method can easily stratify patients at a high risk for DASA-PAH development.

Methods

Study design

This single-center case-control study investigated contributing factors that may predict DASA-PAH development. This study complies with the Declaration of Helsinki, and our institutional ethics committee approved the protocol. Written informed consent was obtained from all patients prior to inclusion in this study.

Patients

We enrolled 60 consecutive adult patients age > 18 years who received DASA in our facility from April 2009 to December 2017. We excluded one patient because of insufficient data for analysis.

Definition of DASA-PAH

DASA-PAH was defined when at least one of the four following criteria was met:

1. Recent electrocardiographic (ECG) changes indicating right ventricular pressure overload during the follow-up period
2. Estimated systolic PAP > 40 mmHg measured by Doppler echocardiography
3. Pulmonary artery diameter (PaD)/ascending aortic diameter (AoD) ratio measured by CT > 1, or if baseline PaD/AoD ratio is > 1, > 1.1 times increase in PaD/AoD ratio
4. Mean pulmonary arterial pressure (MPAP) > 25 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and PVR > 3 WU measured by RHC.

ECG

A 12-lead standard ECG (10 mm = 1 mV, 50 mm/s) was obtained in supine position during quiet respiration. We identified right ventricular hypertrophy and right atrium enlargement with ECG criteria including P > 0.25 mV in lead II, qR pattern in lead V1, rSR' pattern in lead V1, R in lead aVR > 0.5 mV, R:S > 1 in lead V1 with R > 0.5 mV, R in lead V1 + S in lead V5 > 1 mV, R:S < 1 in lead V5 or V6, S in lead V5 or V6 ≥ 0.7 mV, inverted T wave in V1–V3, and QRS axis > 110° [12–14].

TTE

Echocardiographic parameters measured were the diameter of the left atrium (LA) and left ventricular ejection fraction (LVEF). We also recorded the estimated pulmonary artery systolic pressure (SPAP), mitral valve inflow pattern (E and A velocity), early diastolic mean velocity of the mitral annulus (mean e′), and the ratio of the early diastolic velocity of the mitral inflow to e′ (mean E/e′). The maximum peak tricuspid regurgitation velocity using continuous-wave Doppler recorded from any view and estimated right atrium pressure assumed from the inferior vena cava diameter and collapsibility were used to determine the estimated SPAP [15]. The estimated SPAP > 40 mmHg was used to determine the development of DASA-PAH [16]. Experienced, certified ultrasonographers or physicians performed the TTE.

CT measurement

Previous reports demonstrated that a PaD/AoD ratio > 1 suggests MPAP > 25 mmHg [17, 18] and > 1.1 times increase in PaD/AoD ratio suggests significant increase in PAP [19]. PaD was measured at its widest transverse diameter manually at the level of the bifurcation of the main pulmonary artery, and the AoD was averaged from two perpendicular measurements taken from the same level [20]. The observer was blinded to any clinical information of the patients during CT measurement.

RHC

A 5F Swan-Ganz catheter was inserted from the jugular vein. Cardiac output (CO) and cardiac index were calculated by Fick's method. PAWP and MPAP were measured at breath-hold. PVR was derived from the following equation: PVR = (MPAP − PAWP)/CO.

Statistical analysis

All numerical values are expressed as means ± standard error. Patients' demographic characteristics and clinical parameters were compared according to the presence or absence of DASA-PAH using a Wilcoxon rank sum test for non-parametric variables and Chi square test for categorical data. A P-value < 0.05 was considered statistically significant. The demographic and clinical variables significantly associated with DASA-PAH development were entered into a logistic regression model to assess relative contributions. All statistical analyses were performed in JMP version 13.0.0 (SAS Institute, Inc., Cary, North Carolina).

Results

Demographic characteristics

Among 59 patients analyzed, we identified 13 patients who developed DASA-PAH based on our criteria. Only one patient was confirmed to have DASA-PAH by the RHC criteria. This patient fulfilled all four criteria. The other 12 patients were diagnosed with DASA-PAH with one or two criteria of ECG, TTE, or CT. We compared baseline characteristics between patients who developed DASA-PAH (PH group) and those who did not (NPH group) (Table 1). Baseline characteristics, e.g., age, sex, smoking history, and comorbidities, such as hypertension, hyperlipidemia, and diabetes mellitus, did not differ between the two groups. The rate of previous cancer therapy was comparable between the two groups. Baseline BNP value was not significantly different between the two groups, but the highest BNP value during CML treatment was significantly higher in the PH group (P = 0.015). The initial dose of DASA was similar between the two groups, but the final dose of DASA was substantially lower in the PH group (P = 0.009).

TTE and CT

We compared the baseline echocardiographic and CT parameters between the two groups (Table 2). LVEF, E/e′, E/A, LA size, and estimated SPAP were not significantly different between the two groups. CT showed that the baseline AoD was similar between the two groups, but the baseline

Table 1 Baseline characteristics of patients

	NPH n = 46	PH n = 13	P value
Age, years	60.9 ± 2.4	67.8 ± 4.8	NS
Male	33 (71.7)	7 (53.9)	NS
Hypertension	11 (23.9)	6 (46.1)	NS
Hyperlipidemia	9 (19.6)	1 (7.7)	NS
Diabetes Mellitus	8 (17.4)	2 (15.4)	NS
Hyperuricemia	12 (26.1)	2 (15.4)	NS
Smoking Hx	4 (8.7)	1 (7.7)	NS
COPD/ILD	3 (6.5)	2 (15.4)	NS
Connective tissue disease	2 (4.4)	2 (15.4)	NS
Ischemic heart disease	5 (10.9)	1 (7.7)	NS
Heart failure	1 (2.2)	2 (15.4)	NS
Hx of Chemotherapy	9 (19.6)	2(15.4)	NS
eGFR, ml/min/1.73 m^2	68.7 ± 2.7	71.5 ± 7.8	NS
BNP, pg/ml			
Baseline	32.9 ± 11.2	61.2 ± 20.5	NS
Maximum value during treatment	69.4 ± 20.7	261.7 ± 37.4	0.015
Dasatinib dose, mg			
Initial	92.6 ± 3.4	90.8 ± 5.0	NS
Final	85.0 ± 4.1	60.8 ± 8.7	0.01
Sokal score	0.97 ± 0.05	0.90 ± 0.25	NS
Hasford score	937 ± 41	841 ± 184	NS
EUTOS score	55.8 ± 4.7	33.6 ± 9.9	0.04
4 × spleen size, cm	13.1 ± 3.2	0.0 ± 0.0	< 0.0001
7 × basophil, %	34.4 ± 3.6	35.7 ± 3.6	NS

Data are presented as no. (%) or mean ± SE

BNP brain natriuretic peptide, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *Hx* history, *ILD* interstitial lung disease, *NPH* non-pulmonary hypertension group, *PH* pulmonary hypertension group

Table 2 Baseline echocardiographic and CT parameters

	NPH n = 46	PH n = 13	P value
Baseline echocardiographic parameters			
LVEF, %	68.8 ± 1.5	67.0 ± 4.0	NS
E/e′	9.1 ± 1.4	11.5 ± 3.2	NS
E/A	1.18 ± 0.15	0.78 ± 0.1	NS
LAD, cm	3.5 ± 0.1	4.2 ± 0.3	NS
SPAP, mmHg	18 ± 3.6	24 ± 10.2	NS
Baseline CT parameters			
AoD, cm	31.6 ± 1.0	30.5 ± 0.7	NS
PaD, cm	26.3 ± 0.9	30.0 ± 1.5	0.044
PaD/AoD ratio	0.83 ± 0.02	0.98 ± 0.04	0.004

Data are presented as mean ± SE

AoD aortic diameter, *LA* left atrium diameter, *LVEF* left ventricular ejection fraction, *NPH* non-pulmonary hypertension group, *PaD* pulmonary artery diameter, *PH* pulmonary hypertension group, *SPAP* systolic pulmonary artery pressure

PaD diameter was significantly larger in the PH group (P = 0.044), and baseline PaD/AoD ratio was significantly higher in the PH group than in the NPH group (P = 0.004). The PaD/AoD ratio of the PH group showed a dramatic increase after DASA treatment (P = 0.009), whereas no significant increase in PaD/AoD ratio was observed in the NPH group (Fig. 1). Absolute change in PaD/AoD ratio was significantly higher in the PH group than in the NPH group (P = 0.02) (Fig. 2). When we divided patients into two groups according to baseline PaD/AoD ratio by its median, patients with higher PaD/AoD ratio at baseline tended to have a higher risk to develop DASA-PAH than patients with lower PaD/AoD (P = 0.089) (Fig. 3).

EUTOS score and spleen size

Interestingly, the EUTOS score, a prognostic indicator of CML, was significantly lower in the PH group than in the NPH group (P = 0.04) (Table 1), whereas other prognostic indicators of CML such as Sokal score and Hasford score did not differ between the two groups. Considering the breakdown of the EUTOS score [calculated as 4 × spleen size (under left costal margin [cm]) + 7 × basophil count (%)], 4 × spleen size (under left costal margin) was significantly smaller in the PH group (P < 0.001), whereas 7 × basophil count did not differ between the two groups (Table 1).

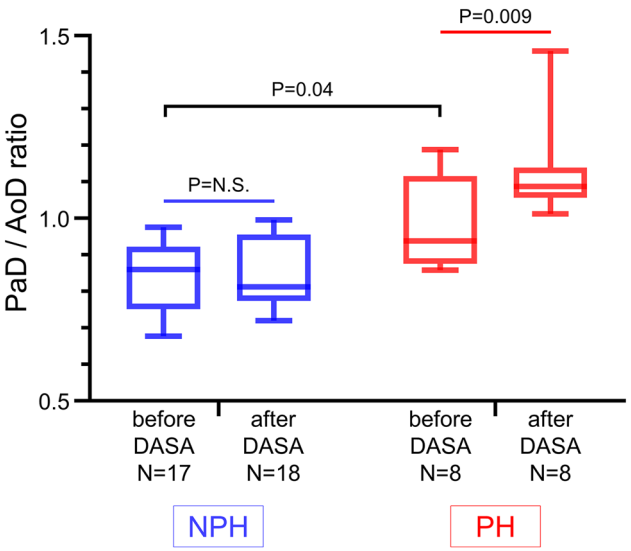

Fig. 1 Comparison of PaD/AoD ratio by dasatinib treatment. A boxplot shows PaD/AoD ratio before and after dasatinib treatment. PaD/AoD ratio was significantly higher in the PH group than the NPH group at baseline (P = 0.04). PaD/AoD ratio did not alter by dasatinib treatment in NPH group, whereas PaD/AoD ratio significantly increased after dasatinib treatment in the PH group (P = 0.009). Data are shown as median and interquartile range. *AoD* aortic diameter, *DASA* dasatinib, *NPH* non-pulmonary hypertension group, *PaD* pulmonary artery diameter, *PH* pulmonary hypertension group

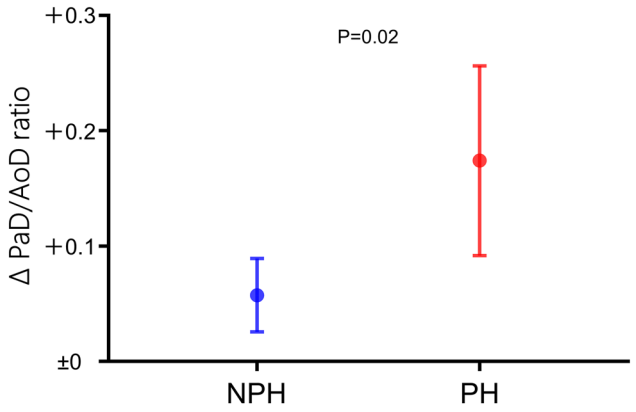

Fig. 2 Absolute change in PaD/AoD ratio by dasatinib treatment. An absolute change in PaD/AoD ratio induced by dasatinib treatment was significantly higher in the PH group than in the NPH group (P = 0.02). Data are shown as mean ± SD. *AoD* aortic diameter, *DASA* dasatinib, *NPH* non-pulmonary hypertension group, *PaD* pulmonary artery diameter, *PH* pulmonary hypertension group

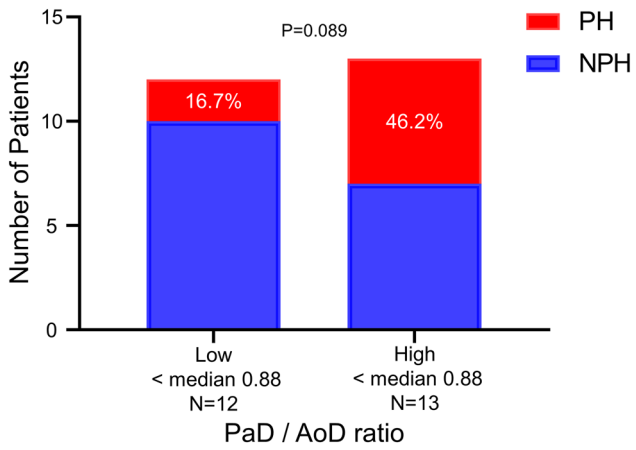

Fig. 3 Prevalence of DASA-PAH according to low and high PaD/AoD ratio. Patients were divided into two groups by median PaD/AoD value. The prevalence of DASA-PAH in high PaD/AoD ratio group was higher than that in the low PaD/AoD ratio group (P = 0.089). *AoD* aortic diameter, *DASA-PAH* dasatinib-induced pulmonary arterial hypertension, *PaD* pulmonary artery diameter

Univariate logistic regression analysis

On univariate logistic regression analysis, the odds ratio for baseline PaD, baseline PaD/AoD %, and EUTOS score was 1.24 (95% CI 0.99–1.55; P = 0.059), 1.16 (95% CI 1.01–1.32; P = 0.034), and 0.97 (95% CI 0.94–0.99, P = 0.046), respectively (Table 3).

Table 3 Relationship between baseline variables and the development of DASA-PAH by univariate logistic regression analysis

	Odds ratio	95% confidence interval	P
Baseline PaD	1.24	0.99–1.55	0.059
Baseline PaD/AoD %	1.16	1.01–1.32	0.034
EUTOS score	0.97	0.94–0.99	0.046

A relative contribution of baseline PaD, baseline PaD/AoD, and EUTOS score was analyzed by univariate logistic regression analysis

AoD aortic diameter, *PaD* pulmonary artery diameter

Discussion

Although the prevalence of clinically significant DASA-PAH confirmed by RHC was speculated to be as low as 0.45% [21], reported cases confirmed by RHC were considered to have moderate to severe DASA-PAH. In fact, an average MPAP of reported cases of DASA-PAH confirmed by RHC was 47.2 ± 10.3 (mean ± SD) mmHg [8, 21]. Therefore, it is anticipated that substantial cases with mild to moderate DASA-PAH were underrecognized by a conventional screening method. To screen early cases of DASA-PAH, we diagnosed DASA-PAH with multiple modalities in this case-control study. We reported that baseline PaD/AoD ratio and EUTOS score might be useful to predict DASA-PAH.

DASA is considered a likely cause of drug-induced PAH [22]. In addition, BCR-ABL TKI such as bosutinib and ponatinib are thought to be a possible cause [23, 24], whereas imatinib might have a protective effect on PAH because of its antiproliferative effect [25]. The different effects of each BCR-ABL TKI on multiple tyrosine kinases might be one of the primary causes of the above-mentioned inconsistent effect against PAH [5]. DASA inhibits Src kinase 20 times more potently than does imatinib [26]. Src kinase activation triggers vasodilatation through tyrosine phosphorylation of phospholipase C, which leads to an increase in intracellular cyclic guanosine monophosphate and cyclic adenosine monophosphate. Furthermore, Src kinase activation results in tyrosine phosphorylation of eNOS at tyrosine-83, thereby modulating eNOS function in endothelial cells. A possibility that Src kinase inhibition might be involved in DASA-PAH has been discussed in previous papers [21]. However, Guignabert et al. reported that DASA treatment induced pulmonary endothelial cell apoptosis in a dose-dependent manner and endothelial dysfunction via increased production of reactive oxygen species, which was independent of Src kinases [10]. The authors also demonstrated that DASA developed PAH in a rodent model of PAH induced by monocrotaline or hypoxia, but not in control animals, suggesting a two-hit theory in the underlying pathophysiology of DASA-PAH.

In our patients, we could not find associations between common cardiovascular risk factors and DASA-PAH development. In only one patient, comorbid scleroderma was suspected as a predisposing factor to DASA-PAH development, indicating a two-hit theory. However, a relative risk of connective tissue disease to develop DASA-PAH was 3.5 (95% CI 0.55–22.7), requiring further accumulation of comparable cases to confirm this finding.

Significant correlation of CT-derived PaD/AoD ratio with RHC-determined PAP has been described previously [17]. The change in PaD/AoD ratio is mainly induced by the change in PaD. Theoretically, pulmonary arterial distensibility [27], redistribution of blood volume [28], left ventricular systolic, or diastolic dysfunction [29] can affect PaD. In our patients, baseline echocardiographic parameters did not differ statistically, but there was a tendency of increased LAD and E/e′ and decreased E/A, indicating the reduced diastolic function in the PH group. Increased right ventricular pressure might have affected the left ventricle through interventricular interaction, but Anand et al. reported that PaD/AoD ratio correlated significantly with RHC-measured systolic PAP, MPAP, and PVR, but did not correlate with right or left ventricular pressure, PAWP, and cardiac index, supporting the utility of PaD/AoD ratio as a marker of pulmonary hypertension [17]. Taken together, our data indicating an association between increased baseline PaD/AoD ratio and a higher risk of DASA-PAH is consistent with the two-hit hypothesis of DASA-PAH development.

Interestingly, we found that the spleen size was inversely associated with DASA-PAH development in this population. There were no previous reports regarding the protective effect of splenomegaly against PAH. On the contrary, pulmonary hypertension following splenectomy has been well described, and it is classified as group 5 pulmonary hypertension in the latest guideline [22]. The reported prevalence of pulmonary hypertension following splenectomy varies because of underlying diseases necessitating splenectomy [30]. The incidence of pulmonary hypertension following splenectomy in thalassemia was reported to reach as high as 70%, but approximately 30% in sickle cell disease [31, 32], although these results need to be interpreted with caution because pulmonary hypertension was not confirmed by standardized methods. Hypercoagulant state following splenectomy is considered to cause thrombotic obstruction in the pulmonary vasculature, resulting in chronic thromboembolic pulmonary hypertension (CTEPH) without a definite history of venous thromboembolism. The circulating level of procoagulant microparticles was shown to be elevated after splenectomy for hematologic disorders, suggesting that splenectomy unveils the prothrombotic state caused by underlying hematologic disorders [33, 34]. However, reported cases of CTEPH after splenectomy for traumatic indication without any thrombotic risk factors indicated that splenectomy itself could be contributory to the thrombotic state [35]. Furthermore, other mechanisms except CTEPH causing pulmonary hypertension should be discussed because our patient with RHC-confirmed DASA-PAH showed no evidence of segmental mismatch in perfusion-ventilation scintigraphy. Histological examination of three cases with post-splenectomy pulmonary hypertension revealed intimal fibrosis and plexiform lesions as well as thrombotic occlusion, indicating the presence of a common underlying pathophysiology with PAH [36]. As these data indicate a causative link between splenectomy and pulmonary hypertension through various mechanisms, we could speculate that splenomegaly can conversely play a protective role against pulmonary hypertension. However, it remains a matter of speculation and we need to perform further investigations to determine whether splenomegaly protected patients from DASA toxicity.

Study limitations

Our study has some limitations. First, we employed a case-control design; thus, the presence of some bias cannot be ignored. Our hospital is a central medical institution in the region, treating complicated patients. A possible consideration is receiving patients who developed side effects during DASA treatment from other institutions. If the EUTOS score of those patients were low, overestimation of the prevalence of DASA-PAH in patients with low EUTOS scores might have occurred. However, regarding CML patients, most of the referred patients came to our hospital with suspected diagnosis of CML before the first-line treatment, not because of the side effects of the CML treatment. Second, we could obtain only five follow-up TTE data among 13 patients whose baseline TTE data were available; thus, we could not perform statistical analysis using TTE data. Moreover, we could not compare SPAP measured by TTE with PaD/AoD ratio measured by CT in the current data. Thus, we could not conclude if a PaD/AoD ratio measured by CT could add any clinical implication on the TTE-based screening of DASA-PAH recommended by the current European guideline [22]. However, if we have previous CT data prior to starting DASA treatment, baseline PaD/AoD ratio can be used as an easy tool to stratify patients at high risk for DASA-PAH requiring frequent TTE follow-up. We cannot tell the best approach to evaluate PaD/AoD ratio for the screening purpose from this study. CT images can be easily analyzed to measure PaD/AoD ratio, but potential risks of radiation exposure should be carefully weighed against the benefits when we use them for all eligible patients before dasatinib administration. To limit radiation exposure, echo can be an alternative way to measure PaD/AoD ratio, but again, further study is necessary to conclude it. Third, we confirmed PAH by RHC only in one case. Therefore,

we could not investigate the association of our criteria of DASA-PAH and RHC data, which is the current golden standard of PAH diagnosis. However, the maximum brain-type natriuretic peptide value during DASA treatment was significantly higher in the PH group than in the NPH group, and the administration dose of DASA at the final follow-up was significantly lower in the PH group than in the NPH group, indicating the presence of hemodynamic changes in the PH group and PAH-related symptoms or events that made physicians to reduce the prescribed dose of DASA.

Conclusions

In this study, high baseline PaD/AoD ratio and low EUTOS score were associated with DASA-PAH development. Our findings could be applied to a new screening method to stratify patients at high risk for DASA-PAH. However, it is not proven yet and a validation study is necessary to identify these factors to facilitate accurate stratification of high-risk patients and early detection of DASA-PAH in another cohort. Moreover, a mechanistic study on the protective role of splenomegaly against DASA-PAH is warranted.

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Author contributions TT designed the study, analyzed data, and drafted the paper. YN and YI helped the statistical analysis and manuscript editing. KK and MY helped the data collection. RY and TN performed echo and CT measurement. NM, SK, HY, FK, and TA supported manuscript and figure editing.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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