Dasatinib-induced pulmonary arterial hypertension in pediatric acute lymphoblastic leukemia with Philadelphia chromosome: A report of two cases

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Abstract

Background: Long-term oral dasatinib administration can induce pulmonary arterial hypertension (PAH) in pediatric patients with Philadelphia chromosome-positive (Ph $^+$) acute lymphoblastic leukemia (ALL). We describe the findings in two pediatric cases involving Ph $^+$ ALL patients who developed cardiovascular events such as PAH after dasatinib treatment, and present a review of the related literature. **Case presentation:** Two pediatric patients diagnosed with B-cell ALL (*BCR-ABL* P190 fusion gene positive) received conventional chemotherapy and imatinib simultaneously, which was then changed to dasatinib because of a partial response. The two patients developed PAH after 18 months and 6 years of dasatinib therapy. All signs and symptoms improved after immediate discontinuation of dasatinib and symptomatic treatment. **Conclusions:** Pediatric Ph $^+$ ALL patients receiving dasatinib should be carefully monitored for serious cardiopulmonary and vascular events such as PAH. Development of adverse reactions should be followed by immediate and permanent discontinuation of oral dasatinib. Dynamic monitoring by echocardiography is recommended when administering dasatinib for maintenance therapy.

Dasatinib-induced pulmonary arterial hypertension in pediatric acute lymphoblastic leukemia with Philadelphia chromosome: A report of two cases

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Abbreviations

PAH	pulmonary arterial hypertension
Ph^+ ALL	Philadelphia chromosome-positive acute lymphoblastic leukemia
OS	overall survival rate
EFS	event-free survival rate
TKI	tyrosine kinase inhibitor
CML	chronic myeloid leukemia
FISH	fluorescence in situ hybridization
PASP	pulmonary artery systolic pressure
LV	left ventricle
LA	left atrium
RA	right atrium
PA	pulmonary artery
AA	aortic arch
FS	fractional shortening
EF	ejection fraction
NA	not available
RT-PCR	reverse transcription polymerase chain reaction
allo-HSCT	allogeneic hematopoietic stem cell transplantation
VEGF	vascular endothelial growth factor
CR	Complete remission

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Abstract

Background: Long-term oral dasatinib administration can induce pulmonary arterial hypertension (PAH) in pediatric patients with Philadelphia chromosome-positive (Ph^+) acute lymphoblastic leukemia (ALL). We describe the findings in two pediatric cases involving Ph^+ ALL patients who developed cardiovascular events such as PAH after dasatinib treatment, and present a review of the related literature.

Case presentation: Two pediatric patients diagnosed with B-cell ALL (*BCR-ABL* P190 fusion gene positive) received conventional chemotherapy and imatinib simultaneously, which was then changed to dasatinib because of a partial response. The two patients developed PAH after 18 months and 6 years of dasatinib therapy. All signs and symptoms improved after immediate discontinuation of dasatinib and symptomatic treatment.

Conclusions: Pediatric Ph^+ ALL patients receiving dasatinib should be carefully monitored for serious cardiopulmonary and vascular events such as PAH. Development of adverse reactions should be followed by immediate and permanent discontinuation of oral dasatinib. Dynamic monitoring by echocardiography is recommended when administering dasatinib for maintenance therapy.

Keywords: Dasatinib, pulmonary arterial hypertension, acute lymphoblastic leukemia, Philadelphia chromosome, childhood

Background

Acute lymphoblastic leukemia (ALL) is a malignant blood disorder with a high prevalence in childhood, particularly in pediatric patients with B-cell ALL (B-ALL)[1]. Due to the continuous improvement in MICM precise staging and multi-drug combination chemotherapy regimens, the 5-year overall survival rate (OS) of pediatric patients with ALL has reached over 90% and the 5-year event-free survival rate (EFS) has reached 80%[2]. However, conventional chemotherapy has been shown to be ineffective for very high-risk pediatric patients. Philadelphia chromosome (Ph)-positive ALL was historically associated with very poor outcomes before the advent of tyrosine kinase inhibitors (TKIs)[3]. The long-term survival of pediatric patients with Ph^+ ALL has significantly improved with the use of regimens combining TKI with chemotherapy. The CCCG-ALL-2015 study showed that the 4-year EFS and OS were 71.0% and 88.4%, respectively, for pediatric Ph^+ ALL patients treated with TKI[4]. Nevertheless, while severe and life-threatening cardiovascular events, such as pulmonary arterial hypertension (PAH), have been reported in adults with chronic myeloid leukemia (CML) and Ph^+ B-ALL patients receiving long-term TKI therapy[5], they have been rarely reported in pediatric patients. This study reports the clinical findings for two pediatric Ph^+ ALL patients who showed PAH as a result of long-term dasatinib therapy at our department, and also reviews the relevant literature on the incidence of PAH during the course of dasatinib treatment.

Case presentation

Case 1

A male pediatric patient aged 6 years and 4 months was admitted for "coughing for more than half a month" in April 2014. The bone marrow aspirate was verified as showing B-ALL by flow cytometry. The*BCR-ABL* fusion gene was shown to be positive by fluorescence*in situ* hybridization (FISH). *BCR-ABL* (P190) was quantified as 76%; karyotype analysis revealed chromosomal translocation with t(9; 22) (q34;q11) [20]. Therefore, the MICM diagnosis was Ph^+ B-ALL. In accordance with the CCLG-ALL-2008 protocol, DVLDex regimen chemotherapy combined with oral imatinib was administered. After 9 months (June 2015) of treatment, the patient's *BCR-ABL* (P190) decreased to 0.048%, as detected in the bone marrow, and the TKI treatment was changed to dasatinib. In March 2016, the bone marrow *BCR-ABL* fusion gene copy number was below the detection limit, and the peripheral blood *BCR-ABL* fusion gene copy number remained below the detection limit in the subsequent reexamination. The pediatric patient was treated with sequential chemotherapy until 2017, and then continued to take dasatinib without regular follow-up after completion of chemotherapy.

On September 11, 2021 (after treatment with dasatinib for more than 6 years), the patient was hospitalized again for paroxysmal cough, sustained fatigue, and shortness of breath after activity. Chest radiography demonstrated pulmonary infection and pleural effusion. Echocardiography showed enlargement of the right cardiac cavities, widening of the pulmonary artery, moderate to severe tricuspid regurgitation, pulmonary hypertension (136 mmHg; the normal pulmonary artery systolic pressure [PASP] was $<$25 mmHg and $>$18 mmHg) and massive pericardial effusions. The patient was told to discontinue oral dasatinib immediately,

underwent pericardial drainage on September 11, 2021, and then received captopril, plavix, and sildenafil orally to treat PAH. Doppler echocardiography revealed that the cardiac function had returned to normal and the PASP was not further aggravated during the treatment period. The patient was prescribed symptomatic treatment for PAH with continued oral bosentan, sildenafil tablets, and poliovel after hospital discharge on October 14, 2021, and the TKI treatment was changed to oral nilotinib on December 23, 2021. Cardiac ultrasound showed that the cardiac structure had returned to normal, and the PASP had decreased to 22 mmHg after discontinuation of dasatinib for four months (January 2021). Subsequently, the PASP remained normal at scheduled reexaminations (Table 1 and Figure 1), and the patient no longer experienced fatigue and shortness of breath.

Table 1 List of dynamic changes in echocardiographic parameters after discontinuation of dasatinib and treatment in the patient in case 1

Date	**2021/9/11 (D1)**	**2021/9/13 (D3)**	**2021/9/21 (D11)**	**2021/9/27 (D17)**	**2021/10/6 (D26)**	**2021/11/11 (2 m)**	**2021/12/23 (3 m)**	**2022/1/13 (4 m)**	**20 (6**
LV (mm)	33	32	35	38	39	44	44	46	47
LA (mm)	22	NA	NA	NA	NA	NA	21	Normal	No
RA (mm)	45	NA	NA	52	48	38	33	Normal	No
RV (mm)	42	42	46	41	40	34	28	32	No
PA (mm)	29	34	28	28	27	22	23	22	23
AA (mm)	16	17	17	17	17	17	21	20	21
FS (%)	40	38	37	36	35	35	33	33	34
EF (%)	70	68	67	66	65	64	63	61	64
PASP (mmHg)	136	103	82	79	87	39	36	22	28

Abbreviations: LV: left ventricle; LA: left atrium; RA; right atrium; RV: right ventricle; PA: pulmonary artery; AA: aortic arch; FS: fractional shortening; EF: ejection fraction; PASP: pulmonary artery systolic pressure; NA: not available.

Case 2

A female pediatric patient aged 3 years and 7 months was hospitalized after intermittent fever for 10 days in May 2020. TDT, CD10, CD19, CD22, CD34, HLA-DR, and Ccd79a expressions were identified in bone marrow aspirate by flow cytometry. The *BCR-ABL* fusion gene was shown to be positive by FISH and reverse transcription polymerase chain reaction (RT-PCR). Karyotype analysis of the pediatric patient revealed chromosomal translocation with t(9;22) (q34; q11), and the diagnosis was Ph^+ B-ALL. A chemotherapy regimen combined with oral imatinib was administered according to the CCLG-ALL-2018 protocol[6]. After 1 month of treatment,*BCR-ABL* was quantified as 2.9%, and the results for minimal residual disease in the bone marrow were negative, so the TKI regimen was changed to oral dasatinib. The *BCR-ABL* fusion gene in the patient's bone marrow did not show complete remission after 5 months of sequential chemotherapy. The patient underwent related-donor haploid allogeneic hematopoietic stem cell transplantation, with the donor being the patient's biological father. The bone marrow reconstitution was successful after the allo-HSCT, and the patient continued to take dasatinib orally for maintenance therapy. Periodic routine examination

indicated negative results for the *BCR-ABL* fusion gene and minimal residual disease in the bone marrow, and the results of cardiac ultrasound during the therapy period were normal.

Nevertheless, the patient's echocardiography showed enlargement of the right cardiac cavities, widening of the pulmonary artery, moderate to severe tricuspid regurgitation, and pulmonary hypertension in January 2022 (after treatment with dasatinib for 18 months). Dasatinib was promptly discontinued, and oral captopril was simultaneously started for treating the PAH. Echocardiography reexaminations demonstrated slightly expanded right cardiac cavities, a slightly widened pulmonary artery, moderate tricuspid regurgitation, and a PASP of 28 mmHg (Table 2 and Figure 1). The patient is currently receiving oral consolidation therapy with captopril, and echocardiography showed that the PASP was not elevated.

Table 2 List of dynamic changes in echocardiographic parameters

after discontinuation of dasatinib and treatment in the patient in case 2

Date	2022/1/24 (D1)	2022/1/28 (D5)	2022/2/4 (D12)	2022/2/18 (D26)	2022/3/12 (D48)	2022/5/3 (3 m)
LV (mm)	20	20	20	20	21	20
LA (mm)	33	33	33	33	35	34
RV (mm)	30	33	33	28	28	32
RV (mm)	29	32	29	27	27	30
PA (mm)	22	22	21	19	20	19
AA (mm)	15	15	14	15	15	15
FS (%)	34	32	38	32	32	35
EF (%)	64	62	69	62	65	65
PASP (mmHg)	62	58	65	28	43	29

Abbreviations: LV: left ventricle; LA: left atrium; RA; right atrium; RV: right ventricle; PA: pulmonary artery; AA: aortic arch; FS: fractional shortening; EF: ejection fraction; PASP: pulmonary artery systolic pressure; NA: not available.

Figure 1 Trend of pulmonary artery systolic pressure after discontinuation of dasatinib and symptomatic treatment in the patient in case 1 and case 2

Abbreviations: PASP: pulmonary artery systolic pressure;NPASP: Normal pulmonary artery systolic pressure

Discussion and Conclusions

Approximately 3%–5% of the cases of childhood ALL show a t(9;22) (q34;q11)/Ph^+ status[7]. In comparison with Ph^- ALL, Ph^+ ALL cases show a higher degree of malignancy and a poor response to conventional chemotherapy with lower rates of survival. TKIs can inhibit tyrosine kinase activation by competitively binding to the active site of tyrosine kinase, thereby impeding leukemia cell proliferation. The long-term survival of pediatric patients with Ph^+ ALL has improved significantly since the advent of TKIs[4]. In one study of 30 pediatric patients with Ph^+ ALL who received TKI treatment in combination with induction chemotherapy at the early stage of treatment, the postinduction complete remission rate was 96.7%, complete remission rate was 100%, and the 3-year OS was nearly 80%[3]. However, relapse and drug resistance were relatively frequent events in Ph^+ ALL patients treated with the first-generation TKI imatinib. The second-generation TKI dasatinib is more clinically potent in inhibiting multiple tyrosine kinases, including Src family tyrosine kinase, *BCR-ABL* kinase, and C-Kit. Additionally, dasatinib also shows higher selectivity and affinity to the BCR/ABL kinase domain than imatinib, and dasatinib can cross the blood–brain barrier to prevent and eradicate central nervous system leukemia. It is used to treat patients with imatinib resistance or relapse while receiving imatinib[8]. According to the Chinese Children's Cancer Group study ALL-2015

(CCCG-ALL-2015), patients treated with dasatinib had significantly higher rates of 4-year EFS (71.0% vs 48.9%) and OS (88.4% vs 69.2%) and lower relapse rates (19.8% vs 34.4%) than the 97 patients treated with imatinib[4]. Therefore, dasatinib in combination with conventional chemotherapy is currently more recommended for pediatric Ph^+ ALL patients.

PAH is a severe disease characterized by elevated pulmonary arterial pressure and pulmonary vascular resistance, resulting in right ventricular failure and even death. Changes in pulmonary vascular structure or function have been attributed to multiple etiologies and various distinctive pathogeneses. PAH is a rare adverse reaction of dasatinib, and the mechanisms underlying the occurrence of PAH in patients receiving dasatinib are unclear. In addition to inhibiting BCR/ABL kinase activity, dasatinib can also inhibit the activity of normal Src family tyrosine kinase and platelet-derived growth factor. This may be one of the factors associated with the occurrence of PAH, since normal Src family tyrosine kinase is widely expressed in endothelial cells of blood vessels and promotes proliferation of vascular smooth muscle cells and vasoconstriction. In addition, the occurrence of PAH may involve changes in vascular permeability related to the expression of vascular endothelial growth factor (VEGF), since inhibition of VEGF expression by dasatinib may induce PAH and secondary multiplasmic effusion[9].

After nine cases of dasatinib-induced PAH were reported by the French PAH Registry in 2008, 29 cases of dasatinib-induced PAH (including the two pediatric patients of this study) have been reported in subsequent studies (Table 3). Of the 29 patients aged 5 to 73 years (24 cases involved CML, while the remaining five involved ALL), 19 were male and 10 were female. The present study is the first to describe the findings for pediatric patients. Most of these patients had already developed associated clinical symptoms before receiving a definitive diagnosis. Although elevated pulmonary arterial pressure was observed in only one patient (case 2 of this study) during the routine echocardiography reexaminations, she did not develop meaningful clinical manifestations of PAH. Twenty-two of the 29 patients showed different degrees of comorbid pleural effusion, and 13 had comorbid pericardial effusion. All of the 29 patients immediately discontinued oral dasatinib and received symptomatic treatment after the diagnosis of PAH. Subsequently, the clinical symptoms were alleviated, and the PASP was progressively restored to normal levels in all patients.

For the two pediatric patients in this study, oral dasatinib was discontinued immediately after a diagnosis of PAH, and oral captopril was simultaneously administered to treat PAH. The subsequent reexaminations using echocardiography demonstrated that the PASP progressively improved to normal levels. After discontinuation of oral dasatinib in these 29 patients, five received oral imatinib, two received oral bosutinib, one received ponatinib, 14 received nilotinib, and seven did not receive other TKIs. Only one patient who changed to bosutinib subsequently showed aggregated PAH, while the condition of the remaining patients improved. Consequently, close monitoring is still necessary to avoid the reoccurrence of PAH when altering to other TKIs for therapy.

In summary, Ph^+ pediatric ALL patients receiving dasatinib for maintenance therapy should be closely monitored for the potential adverse effects of dasatinib administration. In patients who show these adverse effects, dasatinib should be discontinued immediately and active treatment for complications such as PAH and multiple-cavity effusion should be administered. Determination of the long-term quality of life of these patients requires multicenter studies with large sample sizes.

Abbreviations

ALL Acute lymphoblastic leukemia

CML Chronic myeloid leukemia

CR Complete remission

EFS Event-free survival

FISH Fluorescence in situ hybridization

OS Overall survival

PAH Pulmonary arterial hypertension

PASP Pulmonary artery systolic pressure

TKI Tyrosine kinase inhibitor

VEGF Vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SJT and HX designed the study. SJT, ZC and HX acquired and analyzed the data. SJT, HX, ZC and LY discussed the results. SJT, HX, ZC, LY and MS wrote the manuscript. HX and ZC reviewed and supervised the work. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Table 3 Summary of the cases of dasatinib-associated pulmonary arterial hypertension

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	R s
1[10]	Male	41	140	140	Dyspnea, cough, edema	NA	+	-	26	Discontinuation + glucocorticoids + diuretics, replacement of oral nilotinib treatment	2.5	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	R s
2[11]	Male	48	140-50	140-50	Dyspnea, jugular vein dilation, edema, hepatosplenomegaly	61	+	+	21	Discontinuation + diuretic + glucocorticoids, dasatinib reduction therapy, discontinuation after exacerbation	12	I
3[12]	Male	70	140	140	Dyspnea	NA	+	-	32	Discontinued + Sildenafil	7	I
4[13]	Female	53	100-70	100-70	Dyspnea, edema, hepatosplenomegaly	65-70	-	-	31	Discontinuation + sildenafil + diuretic, replacement of oral nilotinib treatment	2	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	R s
5[14]	Male	47	140-100	140-100	Dyspnea, jugular vein dilation, edema, hepatosplenomegaly	61	+	+	39	Discontinuation + sildenafil and replace oral nilotinib treatment	6	I
6[15]	Female	61	140-70	140-70	Dyspnea	NA	+	+	27	Discontinuation + sildenafil and replace oral nilotinib treatment	4	I
7[16]	Male	57	70	70	Dyspnea, edema	elevated	-	-	37	Sildenafil + diuretic, discontinuation and replacement with nilotinib treatment	3	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	Evaluation results
8[17]	Female	23	140	140	Dyspnea	114	+	+	35	Discontinuation + prostaglandin + diuretic, replacement of oral nilotinib treatment	9	I
9[18]	Male	33	100	100	Dyspnea	105	-	-	63	Discontinuation + sildenafil and replace oral nilotinib treatment	3	I
10[19]	Male	50	100	100	Dyspnea, cough, chest pain	60	+	-	48	Discontinuation + sildenafil and replace oral nilotinib treatment	22	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	E r s
11[20]	Male	43	140	140	Dyspnea	90	+	+	69	Discontinuation + sildenafil + calcium channel blocker + diuretic, switch to oral treatment with Ponatinib	1	I
12[20]	Male	52	140	140	Dyspnea	75	+	+	38	Discontinuation + sildenafil and replace oral nilotinib treatment	3	I
13[21]	Male	55	100	100	Chest tightness, fatigue, edema	115	+	+	36	Discontinuation + diuresis with intermittent oral dasatinib treatment	36	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	E r s
14[9]	Female	61	140	140	Dyspnea, cough	NA	+	-	26	Discontinuation + tadalafil + ambrisentan + diuretic, replacement of oral treatment with nilotinib	4	I
15[22]	Male	52	NA	NA	Dyspnea	NA	-	-	48	Discontinuation + Ambrisentan, replacement of oral bosutinib treatment	NA	N
16[8]	Female	46	70	70	Dyspnea	98	+	+	144	Discontinuation + Tadalafil + Ambrisentan	2	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	R s
17[23]	Male	67	100	100	Dyspnea, edema	NA	+	-	42	Discontinuation + sildenafil and replace oral imatinib treatment	1	I
18[24]	Male	24	100	100	Dyspnea, edema	NA	+	-	48	Discontinuation + sildenafil + bosentan + diuretic, replacement of bosutinib treatment	6	I
19[25]	Female	46	140	140	Dyspnea, chest tightness	78	+	+	59	Discontinuation + tadalafil + bosentan, replacement of oral imatinib treatment	3	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	E r s
20[26]	Male	63	140-50	140-50	Dyspnea, jugular vein dilation, hepatosplenomegaly	NA	-	-	60	Discontinuation + tadalafil + macitentan + sellepag and replacement of oral imatinib treatment	12	I
21[27]	Female	73	NA	NA	Dyspnea	NA	+	-	9	Discontinuation, replacement of oral imatinib treatment	12	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	R s
22[28]	Female	59	140	140	Dyspnea, chest pain	100	-	+	54	Discontinuation + tadalafil + macitentan + diuretic + bronchodilator, replacement of nilotinib treatment	1	I
23[29]	Male	38	NA	NA	Dyspnea, chest pain, cough, syncope	57	+	-	18	Discontinuation + Anrisentan + Diuretic	6	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment	Evaluation time (months)	E r s
24[5]	Male	56	100	100	Chest tightness, shortness of breath	117	+	+	47	Discontinued + liothyronine + diuretic, resumed dasatinib treatment, replaced nilotinib + bosentan + sildenafil after exacerbation	14	I
25[30]	Male	24	140	140	Dyspnea, jugular vein dilation	67	+	-	10d	Discontinued the drug	1W	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	E r s
26[31]	Male	50	140	140	Dyspnea, jugular vein dilation, edema, hepatosplenomegaly	70	+	-	24	Discontinuation + bosentan + glucocorticoids + diuretics, replacement of nilotinib treatment	9	I
27[32]	Female	47	100	100	Dyspnea, chest tightness	80	+	+	15	Discontinuation + sildenafil + glucocorticoids + diuretics + tigecycline	4	I

Serial number	Sex	Age (years)	Age (years)	Dasatinib dose (mg/d)	Clinical presentation	PASP (mmHg)	Pleural effusion	Pericardial effusion	PAH appearance time (months)	Treatment plan	Evaluation time (months)	R s
28	Male	13	60	60	Cough, fatigue,shortness of breath	137	+	+	75	Discontinuation + diuretic + digitalis + bosentan + poliovir + sildenafil + captopril, replacement of nilotinib treatment	3	I
29	Female	5	40-50	40-50	With no clinical manifestation	65	-	-	6	Discontinuation + captopril + ryanodine, replacement of imatinib treatment	1	I

PASP: pulmonary artery systolic pressure; PAH: pulmonary artery hypertension; NA: not available

Patients 1 to 24 had CML, while patients 25 to 29 had ALL (patients 28 and 29 were the two pediatric patients in this case report

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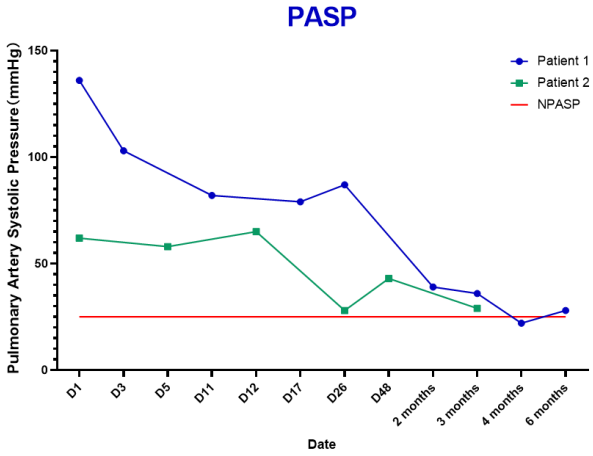

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`Table 1 and 2.docx` available at https://authorea.com/users/511348/articles/607482-dasatinib-induced-pulmonary-arterial-hypertension-in-pediatric-acute-lymphoblastic-leukemia-with-philadelphia-chromosome-a-report-of-two-cases