

# Successful treatment of pulmonary hypertension following hematopoietic stem cell transplant with a single oral tadalafil: a case report

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## Abstract

A 46-year-old man who had undergone hematopoietic stem cell transplant twice because of acute lymphoblastic leukemia with recurrence presented with dyspnea, leading to a diagnosis of pulmonary arterial hypertension which was quickly and effectively treated with the phosphodiesterase type 5 inhibitor tadalafil. To our knowledge, pulmonary arterial hypertension related to hematologic malignancies requiring hematopoietic stem cell transplant is rarely reported. Importantly, the present case suggests that early diagnosis and treatment with a pulmonary vasodilator, such as tadalafil, can greatly decrease pulmonary vascular resistance in patients with severe pulmonary arterial hypertension after hematopoietic stem cell transplant and can then improve other symptoms. Accordingly, pulmonary vascular disease should be considered if respiratory symptoms develop following hematopoietic stem cell transplant, because treatment with pulmonary vasodilator may lead to significant improvement in pulmonary arterial hypertension.

## Keywords

pulmonary hypertension, pulmonary arterial hypertension, hematopoietic stem cell transplant, phosphodiesterase type 5 inhibitor

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## Case description

A 46-year-old Japanese man diagnosed with T-lymphoblastic leukemia with complex karyotype (without Philadelphia chromosome) underwent hematopoietic stem cell transplant (HSCT) using a total body irradiation (TBI) containing conditioning regimen in January 2015, but the disease relapsed in October 2018. Fortunately, a second complete remission was achieved with salvage chemotherapy of clofarabine, etoposide, and cyclophosphamide. To prevent leukemia recurrence, a second HSCT was planned. Prior to that, a baseline transthoracic echocardiogram demonstrated normal heart size with normal estimated pulmonary artery systolic pressure (PASP), right atrial (RA) size, right ventricular (RV) size, and RV function. We performed a second allogeneic cord blood transplantation using non-TBI regimen, which consisted of fludarabine, melphalan, and busulfan in December 2018. To prevent graft-versus-host disease,

tacrolimus was administered. After a few months, he recovered and was discharged to home in late March 2019.

In April 2019, the patient developed dyspnea with WHO functional Class III limitations and was evaluated at the department of hematology. A chest CT showed significant cardiomegaly and pericardial effusion, and the patient was referred to the Department of Cardiology. When seen, he complained of weakness and shortness of breath. His blood pressure was 122/80 mm Hg, heart rate was 109 beats per minute, and oxygen saturation was 95% on room air. On physical examination, he had a loud P2 heart sound, jugular

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venous distension, and peripheral edema. An ECG demonstrated a sinus rhythm with late R/S transition but was otherwise unremarkable. A chest X-ray revealed bilateral enlargement of pulmonary artery with mild cardiomegaly (Fig. 1a). A repeat transthoracic echocardiogram now showed RA and RV enlargement. The estimated PASP was now 55–60 mm Hg (Fig. 1c and e). The tricuspid annular plane of systolic excursion was 15 mm demonstrating RV dysfunction. A moderately large pericardial effusion was also present. A pulmonary function test revealed low diffusing capacity with a diffusing capacity of the lungs for carbon monoxide of 35.2%, compared with 84.2% immediately following the first HSCT (Table 1).

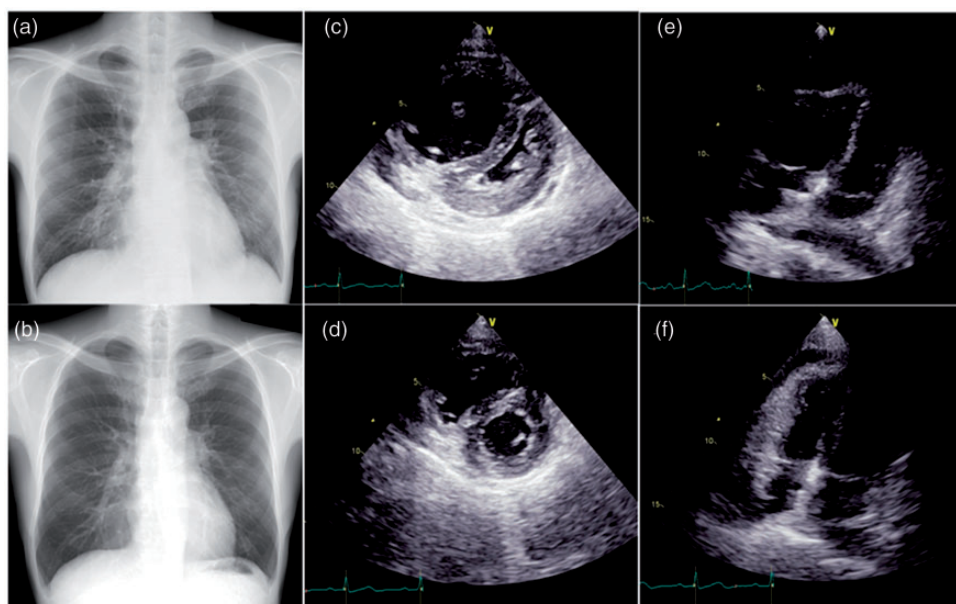
Hematological studies showed no evidence of connective tissue disease or human immunodeficiency virus infection. A lung ventilation perfusion scan did not demonstrate segmental/subsegmental perfusion defects. A contrasted chest CT scan was also negative for evidence of pulmonary thromboembolism and also revealed bilateral pleural effusions and a pericardial effusion. A separate high-resolution chest CT (HRCT) demonstrated mild bilateral lower lobe interlobular septal thickening, but no mediastinal lymph node enlargement or ground glass opacity. Due to severity of his dyspnea, the patient was unable to perform a six-minute walk test. A right heart catheterization was performed which demonstrated hemodynamics consistent with group 1 pulmonary arterial hypertension (PAH) (Table 1). Because the clinical suspicion for idiopathic/hereditary PAH was low at the time of the procedure, a vaso-reactivity test was not performed.

While we felt the diagnosis was consistent with PAH after HSCT, the interlobular septal thickening raised concerns for pulmonary veno-occlusive disease (PVOD), thus we decided to cautiously start treatment with the phosphodiesterase type 5 (PDE-5) inhibitor tadalafil with the expectation that if he tolerated it but remained symptomatic, we would include additional pulmonary vasodilator therapy.

**Table 1.** Comparison of key hemodynamics with tadalafil therapy.

	Before treatment	After treatment (eight weeks)
WHO classification	III	I
Right heart catheterization		
RAP (mmHg)	4	2
PAP (mmHg)	62/27 (mean 41)	27/12 (mean 18)
PCWP (mmHg)	4	8
PA saturation (%)	69	76
PVR (Wood Units)	8.0	1.3
CO	4.6	5.3
CI	3.3	3.8
BNP (<18.4 pg/ml)	77.9	14.6
DLCO (80–120%)	35.2	45.2

RAP: right atrial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PA saturation: pulmonary arterial saturation; PVR: pulmonary vascular resistance; CO: cardiac output; CI: cardiac index; BNP: brain natriuretic peptide; DLCO: diffusing capacity of the lungs for carbon monoxide.



**Fig. 1.** The findings of chest X-ray (CXR) and transthoracic echocardiogram (TTE) before and four weeks after tadalafil treatment. CXR on admission (Panel a) demonstrated cardiomegaly with pulmonary congestion. CXR after treatment (Panel b) demonstrated no cardiomegaly. The parasternal short axis and apical view of TTE before treatment (Panel c and e) showed severe enlargement of RV with a RVEDA of 15.3 cm<sup>2</sup> and RVESA of 10.6 cm<sup>2</sup>, with an interventricular septum (IVS) bowing. TTE after treatment (Panel d and f) showed a mild enlargement of RV with a RVEDA of 11.9 cm<sup>2</sup> and RVESA of 6.8 cm<sup>2</sup>, without IVS bowing or flattening.

With oral tadalafil, which he tolerated without any side effects or exacerbation of symptoms, his shortness of breath and fatigue improved. A repeat transthoracic echocardiogram showed that the estimated PASP had decreased to 40–45 mm Hg with improvement in the RA and RV sizes as well as RV function (Fig. 1d and f). A repeat chest X-ray revealed no cardiomegaly or pulmonary edema (Fig. 1b). Subsequently, the patient was discharged in a month. Eight weeks after discharge, right heart catheterization was performed to evaluate the efficacy of tadalafil and revealed now normalized hemodynamics (Table 1). Now, two years later, the patient has been stable with WHO functional class I symptoms (none to minimal) with routine physical activity; as he has tolerated the medication well, we have elected to continue him on tadalafil to prevent recurrence of pulmonary hypertension (PH).

## Discussion

In this case, a middle-aged Japanese man who had undergone HSCT twice because of acute lymphoblastic leukemia with recurrence presented with dyspnea, leading to a diagnosis of PAH which was quickly and effectively treated with the monotherapy of PDE-5 inhibitor tadalafil. To our knowledge, PAH related to hematologic malignancies requiring HSCT is rarely reported. This case represents an even more unusual case of either successful treatment with tadalafil or eventual resolution over time.

Hematopoietic stem cell transplantation is a viable treatment for many patients with various hematologic diseases. However, several toxicities associated with HSCT limit its widespread use. A case of HSCT-related PH complication was first reported in 1984 in a 12-year-old boy who had undergone HSCT for acute lymphoblastic leukemia.<sup>1</sup> However, because few cases of PH following HSCT have been reported, much remains unclear about the cause, incidence, and risk factors. The types of PH most commonly reported after HSCT are PAH and PVOD, depending on the location of vascular injury.<sup>2</sup>

According to European Society of Cardiology and European Respiratory Society guidelines, in the present case, the hemodynamic findings on right heart catheterization were consistent with group 1 PAH.<sup>3</sup> Theoretically, PVOD and PAH cannot be differentiated on the basis of only clinical symptoms or the results of cardiac catheterization. While adverse events to pulmonary vasodilator (e.g. acute pulmonary edema, worsened dyspnea) may suggest PVOD as opposed to pre-capillary disease, definitive diagnosis of PVOD requires a wedge resection lung biopsy. However, due to the morbidity of wedge resection lung biopsy and because the chest HRCT was not highly suggestive of PVOD, empiric treatment and close monitoring with a single pulmonary vasodilator, the PDE-5 inhibitor tadalafil, was the decided course in this case. Evidence for the medical treatment of HSCT-PAH is limited to a few case reports. These cases reported a favorable outcome of

HSCT-PAH with oral therapeutic regimens consisting of either PDE-5 inhibitor with inhaled and oral prostacyclin analogues<sup>4</sup> or endothelin receptor antagonist with steroid therapies.<sup>5</sup> Our case differs from these two prior reports in our decision to initiate monotherapeutic pulmonary vasodilator therapy with tadalafil alone due to worries that interlobular septal thickening might represent a variant of PVOD. Not only did he tolerate the tadalafil monotherapy but there was a rapid clinical improvement in hemodynamics and clinical course. Thromboembolic disease was ruled out by imaging studies. PVOD more frequently takes a progressive course, and ultimately it was felt that this patient's PAH was caused by a pre-capillary abnormality following HSCT.

Most reported cases of PH complicating HSCT have occurred in children, but under reporting of cases in adults may be a factor of under recognition in adults or reporting bias favoring pediatric cases. With the case series of PH after HSCT in children, the findings emphasized the importance of the early diagnosis of HSCT-PAH because aggressive and timely treatment improves the likelihood of hemodynamic normalization and survival.<sup>6</sup> When PH has occurred in older adults, the presentation and mechanisms of PH seem to differ from those in children and younger adults.<sup>2</sup> Because of these possible differences, we conducted and summarized a literature search for reported cases of PH, including PVOD<sup>7–13</sup> and PAH,<sup>4,5,14</sup> in adults (20 years and older) after HSCT (Table 2). With respect to the onset of PAH, except for a case related to graft-versus-host disease, the present case is consistent with other cases occurring within four months after HSCT. Of note, the prognosis differs significantly between patients with PVOD and PAH following HSCT. Regardless of the small number of patients, all four patients (including ours) developing PAH were alive after treatment and four out of seven patients developing PVOD died (one due to relapse of their hematologic malignancy). This finding is consistent with a previously reported one-year mortality rate in cases of PVOD of as high as 70%.<sup>15</sup> As PH is a severe complication after HSCT, early accurate diagnosis and subsequent prompt treatment is important to ensure a favorable outcome.

Concerning medical treatment, our patient has remained clinically well with normalization of his hemodynamics and continued relief of exertional dyspnea on tadalafil monotherapy over the past two years. Compared to other reported pulmonary vasodilator regimens (Table 2), tadalafil monotherapy is generally well tolerated without need for monthly liver function test (LFT) monitoring (as in the case of bosentan), reduced side effect profiles compared to prostacyclin analogues (as in the case of beraprost), and also less costly compared to the other reported pulmonary vasodilator treatment regimens. Based on this clinical context, the decision was made to continue tadalafil for a longer time

**Table 2.** Cases of PH, including PVOD and PAH, in adults (20 years and older) after HSCT.

References	Age at HSCT (years)	Sex	Diagnosis	Pre-transplant therapy	Transplant conditioning therapy	Onset of PVOD	Diagnosis modality	Treatment	Outcome
<b>PVOD after HSCT</b>									
Salzman et al.	39	M	NHL	CY, doxorubicin, vincristine, PSL, AraC, etoposide, cisplatin	CY, etoposide, BCNU, dacarbazine	Day 52	Surgical lung bx, Autopsy	Steroids	Deceased
Williams et al.	24	M	ALL	CY, doxorubicin, MTX, AraC, PSL, CSA, dactinomycin, vincristine, BCNU, 6MP, asparaginase	NR	Day 180	Surgical lung bx,	Steroids, heparin	Alive at day 360
Or et al.	36	F	ALL	Daunorubicin	CY, TBI, TLI, MEL, etoposide	Day 6	Clinical	Oxygen, supportive care	Alive at day 27
Seguchi et al.	20	M	NHL	CY, doxorubicin, vincristine, PSL, carboplatin, AraC, mitoxantrone	CY, TBI, AraC	Day 73	Surgical lung bx negative, autopsy positive	Steroids	Deceased
Mukai et al.	49	F	CML	Interferon-alpha	CY, TBI	Day 223	Clinical	Steroids	Deceased
Malhotra et al.	48	M	MM	Vincristine, doxorubicin, PSL	MEL	Day 11	Clinical	None	Alive at day 19
Hosokawa et al.	21	M	AML	Idarubicin, AraC	FLU, MEL	Day 35	Clinical, CT, TTE	Steroids	Recovered at day 164, but deceased due to relapse
<b>PAH after HSCT</b>									
Grigg et al.	36	F	CML	Hydroxyurea	BU, CY	12.5 mo	CT, TEE, PFT, open lung bx,	Bosentan, Steroid	Alive at 29 mo
Limsuwan et al.	20	F	CML	Imatinib	AraC, CY, TBI	4 mo	CT, TTE, RHC	Sildenafil, Beraprost	Alive at 30 mo
Nakaoka et al.	35	F	AML	Unknown	BU, CY	Day 94	TTE, RHC	Beraprost, Warfarin	Alive at 1yr
Present case	46	M	ALL	Clofarabine, etoposide, CY	FLU, BU, MEL	3 mo	CT, TTE, RHC	Tadalafil	Alive at 2yr

NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; MM: multiple myeloma; AML: acute myeloid leukemia; CY: cyclophosphamide; PSL: prednisolone; AraC: cytosine arabinoside; BCNU: 1,3-bis-(2 chloroethyl)-1-nitrosourea; FLU: fludarabine; MEL: melphalan; MTX: methotrexate; BU: busulphan; TBI: total body irradiation; TLI: total lymphoid irradiation; TTE: thoracic echocardiogram; TEE: trans-esophageal echocardiogram; RHC: right heart catheterization; PFT: pulmonary function test; NR: not reported; mo: month; yr: year; bx: biopsy; HSCT: hematopoietic stem cell transplant; PVOD: pulmonary veno-occlusive disease; CSA: cyclosporin A; 6MP: 6-mercaptopurine.

period in the case that tadalafil itself was likely the reason for the improvement of pulmonary vascular disease/dysfunction.

In this present report as well as the prior reported cases, the exact mechanisms by which PH develops after HSCT is unknown and the possible diagnosis of drug-induced PAH and PVOD cannot be excluded. While it is impossible to completely exclude the possibility of chemotherapy-induced damage to the pulmonary vascular endothelium in our case, his chemotherapeutic regimen (busulphan–melphalan–fludarabine) is a widely used conditioning regimen and was not previously used in the reported cases of HSCT-associated PAH (Table 2). Furthermore, our patient did not manifest other evidence of endothelial damage such as veno-occlusive disease or microangiopathy. While our present case suggests that early diagnosis and treatment with a pulmonary vasodilator, such as tadalafil, can improve the hemodynamics and symptoms in patients with severe PAH after HSCT, we caution that this is still an isolated case. By reporting it, we hope to add to the existing body of cumulative case reports from which future clinicians can base their clinical judgment as the paucity of cases makes treatment trials unlikely. Moreover, because pulmonary complications after HSCT are common and have various causes, PH should not be overlooked. Accordingly, PH should be considered if respiratory symptoms develop following HSCT, and careful diagnostic work-up to diagnosis and differentiate PAH from PVOD should be taken because treatment with pulmonary vasodilator may lead to significant clinical improvement in PAH.

### Consent

Informed consent was obtained to publish.

### Author contributions

T.D.T.: study conception, design, analysis, interpretation of data, and drafting of manuscript; D.C.I. and T.S.: edition of manuscript and critical revision; A.Y.: acquisition of data; and M.Y.: critical revision.

### Conflict of interest

The author(s) declare that there is no conflict of interest.

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