ABSTRACT

Characteristics of Imaging Findings in Patients with Pulmonary Veno-Occlusive Disease

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Pulmonary veno-occlusive disease (PVOD) is one of the rare diseases that cause pulmonary artery hypertension (PAH). Diagnosis of PVOD is confirmed by histopathological examination. However, early diagnosis with other medical tests is difficult, and many patients with PVOD have been diagnosed at autopsy. I discuss the relevant characteristics of PVOD that might be observed in images obtained using chest radiography, computed tomography (CT), and lung perfusion scintigraphy, and how these findings differ from other PAH diseases. In chest radiographs and conventional CT scans, cardiomegaly and pulmonary artery dilatation, which are reflections of right heart overload due to pulmonary hypertension, are often observed. Furthermore, in patients with PVOD, a high-resolution CT (HRCT) scan often reveals ground glass opacity with a centrilobular distribution and interlobular septal thickening, findings that are less frequently observed in cases of idiopathic PAH (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH). In lung perfusion scintigraphy scans, a general heterogeneity of count distribution and upper lobe hypoperfusion are frequently observed in cases of PVOD, but the degree of count distribution heterogeneity is less than that seen in patients with IPAH (e. g., mottled pattern). Although PVOD has few disease-specific characteristics that can be observed with imaging modalities, a consideration of the image findings mentioned above might facilitate early diagnosis of PVOD.

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●一般演題 9（Session 5）

結合組織病性肺動脈性肺高血圧症の剖検肺における病理組織学的検討

—特に肺静脈閉塞性病変合併の有無に関して—

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はじめに

結合組織病に伴う肺動脈性肺高血圧症（pulmonary arterial hypertension associated with connective tissue disease：CTD-PAH）は，特発性 PAH と比較しても予後が悪いことが知られている[1)]。また PAH 特異的治療に対し抵抗性を示す症例があり，CT 上小葉間隔壁肥厚や運動時の著明な低酸素など肺静脈閉塞性疾患（pulmonary veno-occlusive disease：PVOD）様病態の存在を疑う例が存在する。PVOD は原因不明の肺静脈・細静脈閉塞から進行性の肺高血圧症をきたす治療抵抗性で非常に予後不良のまれな疾患であり，特発性，家族性などのほか，CTD 合併例の症例報告もある[2)]。従来，CTD-PAH の肺血管病変は動脈病変を特徴とする特発性 PAH と同様と考えられてきたが，自己免疫・炎症機序により，肺動脈のみならず肺静脈も血管炎や内皮傷害から閉塞をきたした結果 PVOD 様病態を併発し，治療抵抗性・予後不良の一因となっている可能性がある。

そこで本研究の目的は，CTD-PAH の剖検肺において肺動脈病変に加え特に肺静脈閉塞性病変の合併の有無について組織学的検討を行うこととした。

1　対象と方法

当院の過去の剖検例（1982 年 1 月～2011 年 6 月の 2900 例）中，CTD を合併した PAH の 10 剖検例を抽出し対象とした。ホルマリン固定パラフィン包埋された肺組織（各肺葉より少なくとも 2 ブロックずつ切り出し）を薄切し，ヘマトキシリンエオジン染色，マッソントリクローム染色，エラスティカワンギーソン染色を施して，肺動脈および肺静脈病変の組織学的評価を行った。

2　結　　果

CTD-PAH 10 例の臨床的背景と肺血管病変の組織学的所見を**表 1** に示す。10 例の平均年齢は 48±13 歳で全例女性であった。基礎疾患の内訳は強皮症（systemic sclerosis：SSc）1 例，SSc と混合性結合組織病（mixed connective tissue disease：MCTD）の合併 1 例，MCTD 3 例，全身性エリテマトーデス（systemic lupus erythematosus：SLE）2 例，Sjögren 症候群 2 例，関節リウマチ 1 例であった。右心カテーテル検査による肺高血圧確定診断時の血行動態の平均値は，平均肺動脈圧 49±13 mmHg，肺血管抵抗 1507±809 dyn・s・cm^{-5}，心係数 2.1±0.9 L/min m^2であった。肺動脈楔入圧は全例正常範囲

Keiko Ohta-Ogo, et al.：Coexisting pulmonary venous occlusive lesions in pulmonary arterial hypertension associated with connective tissue disease：a histopathologic study of autopsy lungs

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表 1 CTD-PAH 10例の臨床的背景と肺血管病変の組織学的所見

症例	年齢(歳)/性	結合組織病	PH診断時の血行動態			%DLCO (%)	PaO_2 (mmHg)	PAH-特異的治療	経口ステロイド	ワルファリン	肺動脈病変		肺静脈閉塞性病変			
			平均肺動脈圧 (mmHg)	心係数 ($L/min/m^2$)	肺血管抵抗 (dynes・sec・cm^{-5})						Heath-Edwards Grade	新旧血栓	隔壁内静脈	隔壁前細静脈	再疎通像	静脈炎
1	67/女	SSc	50	2.7	1305	ND	41	2剤 (経口 PGI2＋ERA)	−	−	3	+	+	+	+	
2	58/女	SSc/MCTD	44	1.6	1600	62	75	1剤 (Epo)	−	+	3	+	+	+	−	+
3	35/女	MCTD	30	4.3	309	46	83	−	+	−	3	+	+	+	+	−
4	33/女	MCTD	57	2.8	907	41	71	1剤 (経口 PGI2)	+	+	3	+	+	+	−	+
5	36/女	MCTD	50	1.9	1200	64	81	1剤 (経口 PGI2)	−	+	5	+	−	+	+	−
6	41/女	SLE	52	0.9	3072	ND	52	1剤 (Epo)	+	+	5	+	+	+	+	+
7	40/女	SLE	34	2.3	510	79	78	3剤 (Epo＋ERA＋PDE5I)	+	+	5	−	−	−	−	−
8	60/女	Sjögren	50	1.2	2089	71	51	3剤 (Epo＋ERA＋PDE5I)	+	−	5	+	+	+	+	+
9	66/女	Sjögren	45	1.6	1680	39	55	1剤 (経口 PGI2)	+	+	3	+	+	+	+	+
10	41/女	RA	79	1.8	2400	ND	53	3剤 (Epo＋ERA＋PDE5I)	+	−	5	+	+	+	−	+

DLCO；diffusing lung capacity to carbon monooxide, Epo；epoprostenol, ERA；endothelin receptor antagonist, ND；not done, PDE5I；phosphodiestrase type V inhibitor

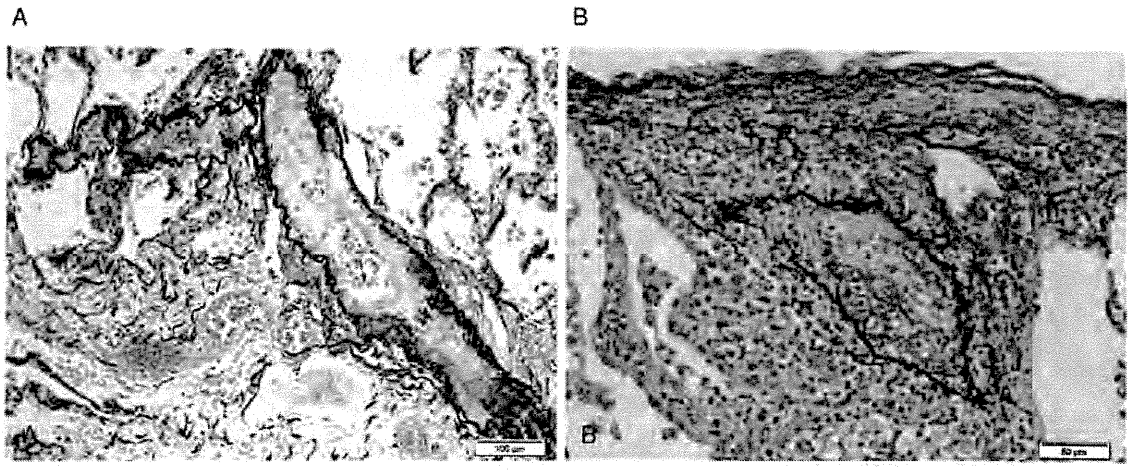

図 1　A：隔壁内静脈へと続く細静脈。線維性内膜肥厚による内腔の狭窄～閉塞がみられる。周囲には，慢性のうっ血・出血を示唆するヘモジデリン貪食マクロファージもみられる（SSc 症例（No. 1），EVG 染色）。
B：隔壁前細静脈にみられた静脈炎。細静脈壁内および周囲に炎症細胞浸潤があり，内腔はほぼ閉塞している（MCTD 症例（No. 4），EVG 染色）。

内（3～10 mmHg）であった。また肺機能（% 肺活量，一秒率）は，限局的な間質性肺疾患を認めた 1 例を含め全例で正常範囲であったが，肺拡散能（% DLCO，7 例で施行）は平均 57± 14%で，症例により軽度から高度の低下がみられた。治療に関しては，9 例で何らかの PAH 特異的治療薬が使用され，うち 5 例でエポプロステノール持続静注療法が行われていた。また 7 例に経口ステロイドが投与されていたがその他の免疫抑制剤の使用はなかった。なおワルファリンによる抗凝固療法は 6 例に行われていた。

肺動脈の組織学的検討では，半数は内膜線維化および中膜肥厚からなる狭窄性病変（Heath-Edwards Grading 3 度までに相当）であったが，残りの 5 例は叢状病変と拡張病変（同 4～5 度に相当）を含む高度の肺動脈リモデリングを呈していた。フィブリノイド壊死を伴う血管炎（同 6 度相当）は認めなかったものの，しばしば血管周囲の炎症細胞浸潤がみられた。また新旧の血栓も 9 例にみられた。静脈系の検索では SLE の 1 例を除く全例（9/10 例；90%）に隔壁内静脈や小葉内細静脈に線維性内膜肥厚を主とする閉塞性病変を認めた（**図 1A**）。血栓を示唆する再疎通像は 6 例にみられ，局所的な静脈炎の所見は 6 例にみられた（**図 1B**）。

3　考　　察

今回 CTD-PAH で PVOD 様病態を併発している可能性を考え 10 剖検肺を評価した結果，ほとんどの症例（90%）に肺静脈閉塞性病変があり，従来知られる血栓再疎通像のほか，半数以上に静脈炎の所見を認めるという結果を得た。文献的に CTD に合併する PVOD の症例報告も散見されるが，まとまった組織学的検討である 2007 年のフランスからの報告[3]を中心に考察を進める。

それによれば CTD-PAH で肺静脈閉塞性病変がみられたのは 8 例（うち 4 例が SSc）中 6 例（75%）と，特発性 PAH（5/29 例：17%）に比し高率で，さらに CTD-PAH のうち 6 例に血管周囲性炎症細胞浸潤を認めたという。われわれの所見はこの結果を支持しており，CTD-PAH ではより静脈が侵されやすいことを示唆している。剖検例は一般的に予後不良群と考えられるが，今後肺静脈病変を定量化し，PH 特異的治療の期間や反応，臨床・画像所見などとの関連を検討していきたい。また SSc と異なり，SLE や MCTD など炎症の関与の大きい CTD では免

疫抑制剤により肺高血圧が劇的に改善する場合があることが知られ，原疾患のコントロールが肺静脈を含む血管病変の抑制に重要である可能性を示唆している。今回肺静脈病変はステロイド使用の有無にかかわらずみられたが，今後，病変や炎症の程度と CTD の罹患期間やステロイド投与の量・期間との関係も検討していきたい。また血栓を示唆する再疎通像の所見からやはり抗凝固療法も重要であろう。

フランスの報告との相違点として肺動脈リモデリングの程度が挙げられる。彼らは CTD-PAH 例に叢状病変や拡張病変は認めなかったとしているが，われわれの症例の約半数には特発性 PAH 同様の高度の肺動脈病変がみられた。われわれの症例には，叢状病変はまれとされる SSc 例が少ない一方，高頻度とされる MCTD，SLE などの症例が多いこと，遺伝性 PAH の疑われる 2 例が含まれることなどが影響している可能性がある。いずれにせよ肺動脈病変のみの場合に比べ，より重篤で治療抵抗性を示すと推側される。

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ORIGINAL ARTICLE
Pulmonary Circulation

Safety and Efficacy of Epoprostenol Therapy in Pulmonary Veno-Occlusive Disease and Pulmonary Capillary Hemangiomatosis

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Background: Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension. There is no proven medical therapy to treat these diseases, and lung transplantation is thought to be the only cure. Administration of vasodilators including epoprostenol sometimes causes massive pulmonary edema and could be fatal in these patients.

Methods and Results: Eight patients were treated with epoprostenol for 387.3±116.3 days (range, 102–1,063 days), who were finally diagnosed with PVOD or PCH by pathological examination. The maximum dose of epoprostenol given was 55.3±10.7 ng·kg^{-1}·min^{-1} (range, 21.0–110.5 ng·kg^{-1}·min^{-1}). With careful management, epoprostenol therapy significantly improved the 6-min walk distance (97.5±39.2 to 329.4±34.6 m, P<0.001) and plasma brain natriuretic peptide levels (381.3±136.8 to 55.2±14.4 pg/ml, P<0.05). The cardiac index significantly increased from 2.1±0.1 to 2.9±0.3 L·min^{-1}·m^{-2} (P<0.05). However, pulmonary artery pressure and pulmonary vascular resistance were not significantly reduced. For 4 patients, epoprostenol therapy acted as a bridge to lung transplantation. For the other patients who had no chance to undergo lung transplantation, epoprostenol therapy was applied for 528.0±216.6 days and the maximum dose was 63.9±19.0 ng·kg^{-1}·min^{-1}.

Conclusions: This study data suggest that cautious application of epoprostenol can be considered as a therapeutic option in patients with PVOD and PCH. (*Circ J* 2012; **76:** 1729–1736)

Key Words: Epoprostenol; Pulmonary capillary hemangiomatosis; Pulmonary hypertension; Pulmonary veno-occlusive disease

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension, and their categories have been changed at every World Symposium on Pulmonary Hypertension.[1,2] The latest clinical classification of pulmonary hypertension categorized these diseases as Group 1' considering the similarity of risk factors and the genetic mutations in idiopathic pulmonary arterial hypertension (IPAH).[3,4] Continuous intravenous infusion of epoprostenol decreases pulmonary vascular resistance and improves the prognosis of IPAH,[5,6] and it has become a standard therapy for IPAH. However, the indication of epoprostenol for other subgroups of pulmonary hypertension including PVOD and PCH is controversial. A few patients with PVOD have been reported to show amelioration by application of epoprostenol.[7,8] In contrast, other reports have warned that epoprostenol precipitates severe pulmonary edema in patients with PVOD or PCH,[9,10] which never occurs in patients with IPAH. This is why epoprostenol is not widely accepted as a standard therapy for PVOD and PCH.

Montani et al reported the possible efficacy of epoprostenol for PVOD as a bridge to lung transplantation.[11] They successfully treated 12 patients (10 patients with PVOD proven by pathological studies and 2 patients with a clinical diagnosis of PVOD) for 210 days with a maximal dose of 13 ng·kg^{-1}·min^{-1} of epoprostenol. This was the first report to show the clinical application of epoprostenol therapy in a series of patients with PVOD. However, no reports have described the successful

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Table 1. Baseline Data, Histological Diagnosis and Outcome

Patient no.	Age (years)	Sex	WHO FC	Mean PAP (mmHg)	%DLco (%)	Histological diagnosis	Outcome
1	42	M	III	39	24	PVOD	Death
2	26	M	IV	60	31	PVOD	Death
3	29	M	IV	114	NA	PVOD	Death
4	11	M	IV	52	64	PCH	Death
5	25	F	IV	55	36	PCH	LDLLT
6	28	F	III	65	81	PVOD	LDLLT
7	16	F	III	63	61	PVOD	LDLLT
8	32	F	III	44	23	PVOD	LDLLT

Age, age at diagnosis; WHO FC, World Health Organization classification of functional status of patients with pulmonary hypertension; PAP, pulmonary artery pressure; %DLco, diffusion capacity of the lung for carbon monoxide expressed as % predicted; M, male; F, female; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; LDLLT, living-donor lobar lung transplantation.

application of epoprostenol for PCH. We report on 8 patients (6 patients with PVOD and 2 with PCH) whose diagnoses were confirmed by pathological examination, and who were treated with a higher dose of epoprostenol and for a longer period than previously reported. With great caution, epoprostenol was safely applied and improved the clinical status in all patients. Careful application of long-term epoprostenol therapy appears to be a safe option and results in a favorable therapeutic outcome in patients with PVOD and PCH.

Methods

We treated patients with pulmonary hypertension with epoprostenol at 2 institutions (Okayama University Hospital and National Hospital Organization Okayama Medical Center, Okayama, Japan) between April 1999 and April 2010. Diagnosis of pulmonary hypertension was made according to a standard diagnostic algorithm including physical examination, chest radiograph, blood tests including screening for the cause of secondary pulmonary hypertension, pulmonary function testing, transthoracic Doppler echocardiography, and right heart catheterization.[12]

Eight patients had the clinical diagnosis of pulmonary hypertension, which was finally determined to be PVOD or PCH, in this study period. We performed a standardized chart review from the medical records to extract clinical data from them retrospectively. We compared clinical, hemodynamic, and radiographic data before and after application of epoprostenol. Data after epoprostenol treatment were obtained at the time when patients achieved the best values for the cardiac index by right heart catheterization.

Seven patients underwent pulmonary function tests when first admitted to our hospital. Vital capacity and forced expiratory volume at 1 s were calculated by using standard formulas. Diffusion capacity of the lung for carbon monoxide (DLco) was measured by the single-breath method and expressed as %DLco (% predicted). Cardiac catheterization was routinely performed at baseline before starting epoprostenol therapy and then repeatedly after starting epoprostenol therapy according to the patients' condition. Chest radiographs were obtained from all patients at the initial visit and were repeatedly taken according to their status. All patients underwent high-resolution computed tomography (CT) of the chest to define coexisting conditions, including pulmonary venous congestion, pulmonary arterial enlargement, atelectasis, or pleural effusion.

Titration of Epoprostenol Therapy

Epoprostenol therapy was initiated at a dose of 0.25–0.5 $ng \cdot kg^{-1} \cdot min^{-1}$, and the dose was gradually titrated upward in increments of 0.5–1.0 $ng \cdot kg^{-1} \cdot min^{-1}$, based on adverse effects and tolerance. When the cardiac index was below 2.0 $L \cdot min^{-1} \cdot m^{-2}$, continuous intravenous catecholamines were added to epoprostenol therapy. On adjusting the dose of epoprostenol, we paid careful attention to hypotension and signs of deterioration of heart failure and pulmonary edema. When the patients' chest radiographs showed deterioration, we stopped increasing the dose of epoprostenol and added diuretics or intravenous infusion of catecholamines, depending on the severity of pulmonary edema. After improvement, titration of the dose of epoprostenol was resumed.

Pathological Examination

No open or thoracoscopic lung biopsy was performed in any of the patients, because all patients were severely ill and they were considered intolerable to a lung biopsy. Lung specimens were obtained by living-donor lobar lung transplantation (LDLLT) or autopsy. Lung tissue was fixed in 10% formalin. Histological sections were stained with hematoxylin and eosin stain and elastica-Masson's trichrome stain.

Statistical Analysis

Results are reported as mean±standard error of the mean. Differences between groups in variables measured at baseline and after epoprostenol therapy were tested by the paired t-test. Differences were considered statistically significant at a P value of <0.05.

Results

Baseline Data, Pathological Findings and Outcome

Eight patients undergoing epoprostenol therapy had the histological diagnosis of PVOD or PCH (Table 1). The patients included 4 males and 4 females with a mean age of 26.0±3.4 years at the time of diagnosis of pulmonary hypertension. At baseline, 4 patients with PVOD were in the World Health Organization (WHO) functional class III and the other 4 patients (PVOD, n=2; PCH, n=2) were in the functional class IV. All patients showed a high mean pulmonary artery pressure (PAP) and 4 patients showed a marked decrease in %DLco as low as below 40%.

Two patients (patients 4 and 5) were finally diagnosed with PCH and the other cases were diagnosed with PVOD. Representative histology is shown in Figure 1. In all cases, foci of

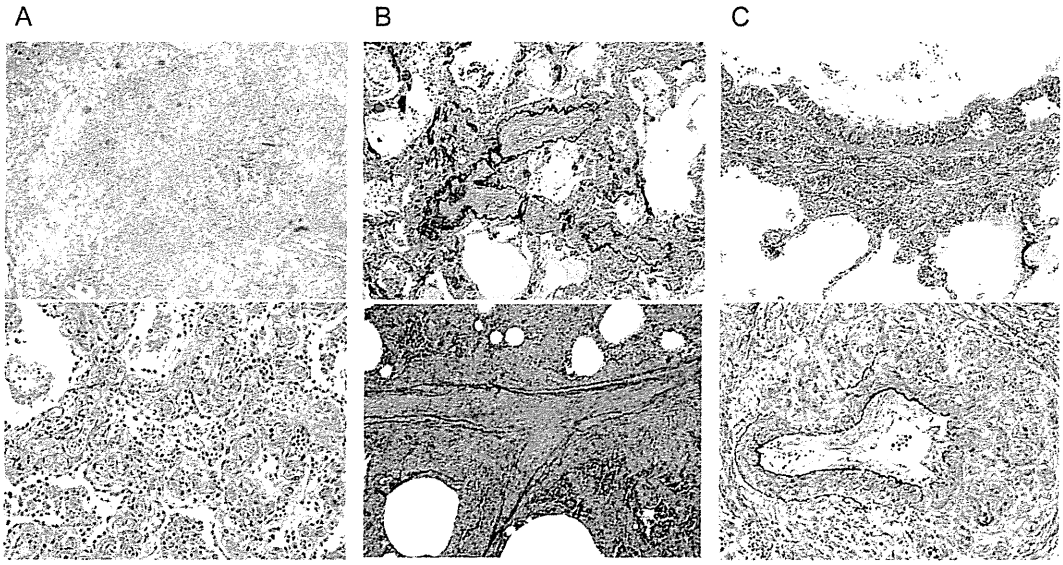

Figure 1. Pathological findings of lung specimens. (A) Specimens of pulmonary veno-occlusive disease (PVOD) show centrilobular congestion at low magnification (**Upper panel**) and characteristic alveolar capillaries at a higher magnification (**Lower panel**). These foci are seen in both PVOD and pulmonary capillary hemangiomatosis (PCH) (hematoxylin and eosin stain). (B) Venous vessel walls are thickened by intimal fibrous proliferation. Markedly stenosed (**Upper panel**) and completely obliterated (**Lower panel**) veins can be seen in PVOD (elastica-Masson's trichrome stain). (C) Proliferating capillaries are shown in the walls of bronchi (**Upper panel**) and arteries (**Lower panel**) in PCH (elastica-Masson's trichrome stain).

Table 2. Clinical and Hemodynamic Data Before and After Epoprostenol Therapy

	Baseline	After epoprostenol therapy	P value
WHO FC (n)			
II	0	5	
III	4	3	
IV	4	0	
6MWD (m)	97.5±39.2	329.4±34.6	<0.001
BNP (pg/ml)	381.3±136.8	55.2±14.4	<0.05
Hemodynamics			
Systolic PAP (mmHg)	89.4±11.0	90.9±4.9	NS
Diastolic PAP (mmHg)	44.1±7.2	43.4±4.0	NS
Mean PAP (mmHg)	61.5±8.1	61.5±3.9	NS
PCWP (mmHg)	7.0±1.3	11.8±3.6	NS
RAP (mmHg)	6.9±2.2	7.6±1.5	NS
SvO_2 (%)	59.6±5.3	64.9±4.8	NS
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.1±0.1	2.9±0.3	<0.05
PVR ($dyne \cdot s \cdot cm^{-5}$)	1,449.3±194.9	1,096.3±199.5	NS
Epoprostenol therapy			
Duration (days)		164.1±79.7	
Dose ($ng \cdot kg^{-1} \cdot min^{-1}$)		24.4±5.6	
Associated therapy (n)			
Anticoagulation	8	6	
Digitalis	4	3	
Bosentan	2	2	
Sildenafil	2	2	

After epoprostenol therapy, at the time when patients achieved the best values for cardiac index; 6MWD, 6-min walk distance; BNP, plasma concentrations of brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; CI, cardiac index; PVR, pulmonary vascular resistance; duration, time from initiation of epoprostenol; NS, not significant; dose, dose of epoprostenol. All other abbreviations are as per Table 1.

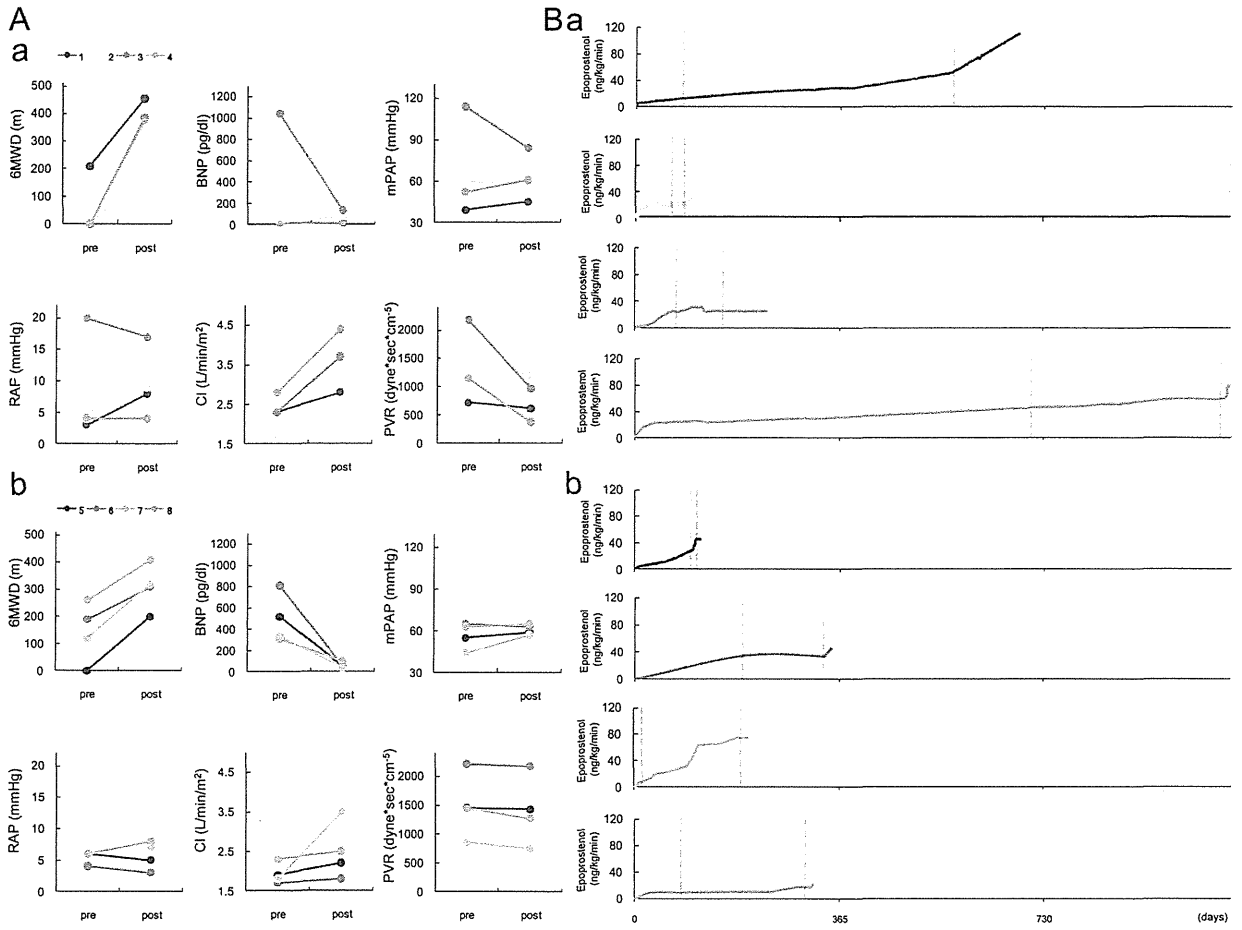

Figure 2. Changes in parameters and dose titration of epoprostenol. (A) Parameters before and after epoprostenol therapy were compared in patients without lung transplantation (a) and patients who underwent living-donor lobar lung transplantation (LDLLT) (b). Data after epoprostenol treatment were obtained at the time when patients achieved the best values for the cardiac index (CI) by right heart catheterization. The 6-min walk distance (6MWD), plasma concentrations of brain natriuretic peptide (BNP), and CI were significantly improved by epoprostenol therapy. mPAP, mean pulmonary artery pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance. (B) Dose titration of epoprostenol of each patient is shown (patients without lung transplantation (a) and patients who underwent LDLLT (b)). Red dotted lines indicate the time when patients achieved the best values for CI. Gray dotted lines indicate the time when patients showed deterioration.

Table 3. Epoprostenol Therapy and Associated Therapy

Patient no.	After epoprostenol therapy				Final	
	Time from initiation (days)	Dose ($ng \cdot kg^{-1} \cdot min^{-1}$)	Bosentan (mg/day)	Sildenafil (mg/day)	Time from initiation (days)	Dose ($ng \cdot kg^{-1} \cdot min^{-1}$)
1	82	12.5	–	–	685	110.5
2	66	15.0	–	–	102	33.7
3	70	24.9	–	60	234	32.0
4	708	46.3	–	–	1,063	79.2
Mean of patients 1–4	231.5±158.9	24.7±7.7			528.0±216.6	63.9±19.0
5	98	45.0	–	–	115	46.0
6	193	34.9	–	–	351	45.4
7	14	7.5	125	40	202	75.2
8	82	9.0	250	–	318	21.0
Mean of patients 5–8	96.8±36.9	24.1±9.4			246.5±54.2	46.7±11.1

After epoprostenol therapy, at the time when patients achieved the best values for cardiac index; final, at the time of lung transplantation or death; time from initiation, time from initiation of epoprostenol therapy; dose, dose of epoprostenol.

centrilobular congestion were observed at low magnification, and characteristic dilatation of alveolar capillaries was observed at a higher magnification (Figure 1A). Hemosiderin-laden macrophages were often observed in the alveolar space. PVOD was characterized by marked stenosis and occlusion of small intrapulmonary veins (Figure 1B). Vessel walls were thickened by intimal fibrous proliferation. In patients 4 and 5, invasive proliferation of capillaries were also observed in the walls of bronchi and arteries, leading to the diagnosis of PCH (Figure 1C). These capillaries were engorged and tortuous.

Four patients successfully underwent LDLLT and the remaining 4 patients had no suitable living donors of the lung and finally died while awaiting cadaveric lung transplantation. The causes of death were respiratory failure or concomitant respiratory infection. No patient died from adverse effects of epoprostenol itself.

Patient Characteristics Before Epoprostenol Therapy

Patient characteristics before epoprostenol therapy are shown in Table 2. All patients were in WHO functional class III and IV. The 4 patients who were in WHO functional class IV could not walk because of severe oxygen desaturation at baseline. The other 4 patients in WHO functional class III could only walk approximately 200 m (Figure 2A). Plasma BNP levels were not always elevated. Three patients showed low BNP levels in spite of the severity of their general condition and inability to walk. For the pulmonary function test, 2 patients showed mild restrictive defects (62% and 72%), and another patient showed a mild obstructive defect (65%). Overall, lung function was within normal limits (%vital capacity: 86.4±6.3%; forced expiratory volume at 1 s: 77.4±3.1%) except for low %DLco (45.8±8.6%). All patients manifested pulmonary hypertension with a mean PAP of 61.5±8.1 mmHg on right heart catheterization. Pulmonary capillary wedge pressure and right atrial pressure were within the normal range in all patients. In 4 patients, the cardiac index was lower than 2.0 $L \cdot min^{-1} \cdot m^{-2}$.

Table 4. Radiographic Findings at Baseline and After Epoprostenol Therapy

Radiographic findings	PVOD and PCH (n=8)
Baseline	
Dilated pulmonary arteries	8
Kerley B lines	2
Interstitial infiltrates	8
Ground-glass opacities	7
Pleural effusion	2
Interlobular thickening	8
Lymphadenopathy	3
After epoprostenol therapy	
Increase in pleural effusion	3
Thickened interlobular septae	8
Deterioration of ground-glass opacities	8

Data indicates the number of patients.
PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis.

Efficacy of Epoprostenol Therapy

Patients were cautiously treated with epoprostenol for 387.3±116.3 days (range, 102–1,063 days) (Table 3; Figure 2B). The maximum dose of epoprostenol given was 55.3±10.7 $ng \cdot kg^{-1} \cdot min^{-1}$ (range, 21.0–110.5 $ng \cdot kg^{-1} \cdot min^{-1}$). Patients who had no chance to undergo a lung transplantation had epoprostenol therapy applied for 528.0±216.6 days and the maximum dose was 63.9±19.0 $ng \cdot kg^{-1} \cdot min^{-1}$. The best value for cardiac

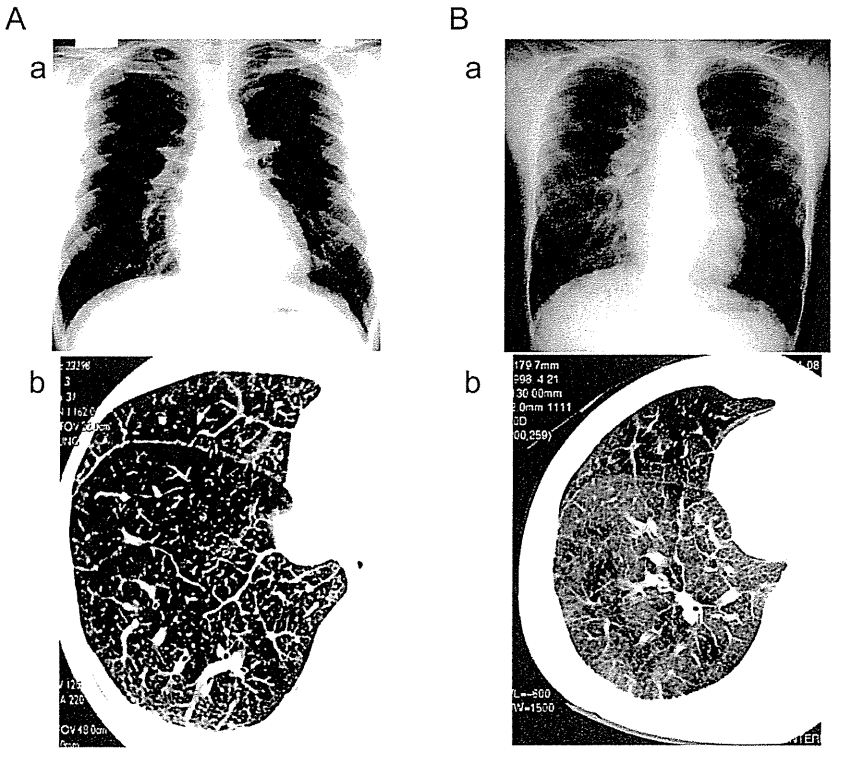

Figure 3. Representative radiographic findings. (A) Radiographic findings of pulmonary veno-occlusive disease (patient 1). (a) A chest radiograph shows a prominent main pulmonary artery and interstitial infiltrates. (b) A chest computed tomography (CT) scan of the right lobe shows multiple thickened interlobular septal lines, ground-glass opacities, and pleural effusion. (B) Radiographic findings of pulmonary capillary hemangiomatosis (patient 4). (a) A chest radiograph shows a prominent main pulmonary artery and main truncus of the right pulmonary artery. Faint nodular opacities and numerous Kerley B lines are also shown. (b) A chest CT scan shows diffuse, ill-defined, ground-glass opacities, and interlobular septal thickening is less prominent.

Table 5. Flow of Supplemental Oxygen Required Before and After Starting Epoprostenol Therapy

Patient no.	Baseline	Best	Later
1	3	2	9
2	2	5	8
3	3	2	15
4	4	4	10
5	2	3	12
6	NA	3	10
7	3	3	12
8	3	4	10
P value		NS	<0.01

Data indicate the flow of supplemental oxygen (L/min).
Repeated-measures analysis of variance with Bonferroni correction was performed. P values indicate "best" and "later" values compared with the "baseline" value.
Baseline, before starting epoprostenol therapy; best, at the time when patients achieved the best values for cardiac index; later, maximum oxygen flow required while the dose of epoprostenol was increased later.

index was obtained at 164.1±79.7 days after initiation of epoprostenol with a dose of 24.4±5.6 $ng \cdot kg^{-1} \cdot min^{-1}$.

After the application of epoprostenol, the WHO functional class improved at least temporarily to class II or III in all patients. The mean 6-min walk distance significantly increased from 97.5±39.2 to 329.4±34.6 m (P<0.001) (Table 2; Figure 2A). As mentioned above, plasma levels of BNP were not always elevated at baseline. In patients who had high BNP levels prior to epoprostenol therapy, BNP levels were significantly reduced after therapy. In total, the mean BNP levels were significantly reduced from 381.3±136.8 to 55.2±14.4 pg/ml (P<0.05). The mean cardiac index significantly improved from 2.1±0.1 to 2.9±0.3 $L \cdot min^{-1} \cdot m^{-2}$ (P<0.05). However, the mean PAP and right atrial pressure did not change between before and after epoprostenol therapy. Although mixed venous oxygen saturation was increased and pulmonary vascular resistance was decreased after epoprostenol therapy, these differences were not statistically significant.

Associated Therapy

Associated therapy before and after epoprostenol therapy is shown in Tables 2 and 3. At baseline, anticoagulation and diuretics were used in all patients, digitalis was given in 4 patients (patients 2, 5, 6, and 7), and no calcium channel blockers were used in any of these patients. An endothelin receptor antagonist, bosentan, was used in 2 patients (patient 7: 125 mg/day; patient 8: 250 mg/day) and a phosphodiesterase 5 inhibitor, sildenafil, was used in 2 patients (patient 3: 60 mg/day; patient 7: 40 mg/day). The doses of bosentan and sildenafil were unchanged during epoprostenol therapy. Catecholamines were not used at the time when patients achieved the best values for the cardiac index. Anticoagulation was discontinued in 2 patients (patients 3 and 4) based on our previous report regarding the risk of alveolar hemorrhage induced by concomitant use with epoprostenol.[13] Digitalis was stopped in patient 5 who manifested bradycardia. All other medications were unchanged after epoprostenol therapy.

Radiographic Changes and Oxygen Supplementation During Epoprostenol Therapy

All 8 patients manifested atypical radiographic features as IPAH at baseline (Table 4; Figure 3). Their chest radiographs revealed not only dilated pulmonary arteries and enlargement of the heart, but also peripheral interstitial infiltrates in both lung fields, and sometimes prominent septal lines. High-resolution CT scans showed pleural effusion, thickened interlobular septa, bilateral ground-glass opacities, and a mosaic pattern of lung attenuation. Lymphadenopathy in the mediastinum, which is sometimes observed as a reactive adenopathy in PVOD, was detected in 1 patient with PVOD and 2 patients with PCH. After initiation of epoprostenol therapy, all patients' chest X-rays or CTs showed thickened interlobular and intralobular septae and an increased density of interstitial opacities. Three of them also showed an increase in pleural effusion. At that time, we temporarily stopped increasing the dose of epoprostenol and added diuretics and/or intravenous infusion of catecholamines. After congestion improved, we started to titrate the dosage of epoprostenol again.

Before epoprostenol therapy, patients required oxygen supplementation with 2.9±0.3 L/min (Table 5). At the time when patients achieved the best values for cardiac index, patients needed 3.3±0.4 L/min of supplemental oxygen. As the dose of epoprostenol was increased, patients showed deterioration of oxygen desaturation and an increase in interstitial infiltrates on chest X-rays. They finally needed an oxygen supplement at a significantly higher flow (10.8±0.8 L/min) than they did before epoprostenol therapy (P<0.01).

Discussion

Among a variety of diseases that can lead to pulmonary hypertension, PVOD and PCH are especially rare, and their classification has been changed at all the World Symposiums on Pulmonary Hypertension. In the previous classification of pulmonary hypertension, they were categorized in a subgroup of pulmonary arterial hypertension, termed "pulmonary arterial hypertension associated with significant venous or capillary involvement".[2] In the most recent Dana Point classification, these diseases are classified as Group 1', similar to but with some differences from Group 1, because of their similarities in histological changes, clinical presentations, risk factors and having shared mutations in the BMPR2 gene, similar to that for IPAH.[3]

The prognosis of PVOD and PCH is still unknown because of the rareness of the disease. It is believed to be poor, with most patients with PVOD dying within 2 years from the initial presentation.[7] Most PCH patients rapidly progress to death over several months of the clinical disease.[14] In the last decade, PAH-targeted drugs have improved the survival of patients with PAH.[6,15,16] However, no medical treatment has been proven to improve the survival of patients with PVOD and PCH. Therefore, patients with PVOD and PCH have a higher mortality and a lower chance of survival compared with patients with IPAH.

Currently, lung transplantation is the only method to cure these diseases and patients who desire it are placed on the list for lung transplantation as soon as possible.[4] However, there are few organ donors available to undergo cadaveric lung transplantation. In Japan, where organ transplantation has been recently introduced, chances of transplantation are very limited and the mean waiting time for lung transplantation is reported to be approximately 3 years. In most cases, it is difficult for patients to survive for this long period of time considering their poor prognosis. Although LDLLT is expected to be an alternative for cadaveric lung transplantation, there are more strict criteria for donors of LDLLT.[17,18] Not all patients and their families who desire to receive lung transplantation can

undergo LDLLT. A therapeutic option is required for patients waiting for a suitable donor or for those who are not candidates for lung transplantation.

Continuous intravenous infusion of epoprostenol has been reported to improve the prognosis of IPAH.[6,19] However, its indication for PVOD and PCH is still controversial. Some reports have cautioned against the possibility of causing massive pulmonary edema by application of epoprostenol for patients with PVOD or PCH.[9,10] Application of epoprostenol for PVOD or PCH might be unsuccessful because when the pulmonary arterioles dilate and resistance of the pulmonary veins remains fixed, transcapillary hydrostatic pressure might increase and pulmonary edema might occur.[20] In contrast, some patients with PVOD have been reported to show temporary amelioration by application of epoprostenol.[7,8] There is 1 case report that showed that long-term epoprostenol therapy improved exercise capacity and pulmonary hemodynamics in PVOD.[8] The authors concluded that in this case, the administration of epoprostenol played a role in the regulation of vascular tone in pulmonary venules rather than in the pulmonary arteries. Detailed hemodynamic measurements showed that microvascular pressures initially increased during an infusion of no more than $6\,ng \cdot kg^{-1} \cdot min^{-1}$ of epoprostenol, but at higher doses, cardiac output increased and the calculated pulmonary vascular resistance decreased.[21] To the best of our knowledge, there are no reports that have described patients with PCH being successfully treated with epoprostenol.

We administered epoprostenol to 8 patients with PVOD or PCH because they had no other therapeutic option besides lung transplantation. In our cases, we cautiously administered epoprostenol, starting with a low dose. When we increased the dose of epoprostenol too quickly, an imbalance of dilatation between pulmonary arterioles and veins occurred. However, if we slowly increased the dose in a step-wise manner and used diuretics or inotropes as necessary, the transcapillary hydrostatic pressure decreased and we could avoid severe pulmonary congestion.

For the successful treatment of PVOD and PCH with epoprostenol, early recognition and diagnosis of PVOD/PCH are essential in addition to the careful application of epoprostenol. A lung biopsy is the only method of definitively diagnosing PVOD and PCH. However, in most cases, it is difficult to perform a lung biopsy because of the severity of the patients' condition. This is why it is important to clinically diagnose PVOD/PCH with available data and results of examinations. It is vital to be aware of poor oxygenation, low DLco, and distinct radiographic findings to diagnose or suspect PVOD and PCH.[20,22] In the present study, all patients presented with marked oxygen desaturation on exertion and a severe decrease in DLco. Their chest radiographs and high-resolution CT scans revealed radiographic findings that were characteristic for PVOD and PCH, but not IPAH (Table 4; Figure 3).[14,23] Early recognition of PVOD/PCH in patients with pulmonary hypertension is possible based on these clinical and radiographic characteristics. This might lead to careful introduction and dose adjustment of epoprostenol and to successful treatment of these complicated diseases.

The present study showed that as a result of epoprostenol therapy, clinical and hemodynamic data were improved (Table 2; Figure 2), at least temporarily. All patients were critically ill before starting epoprostenol therapy. The mean 6-min walk distance, which is reported to correlate well with the prognosis in IPAH, was significantly increased after therapy. Our data showed that epoprostenol significantly improved exercise capacity and increased cardiac output of patients with PVOD or PCH, but did not decrease PAP and right atrial pressure, which are known to determine the survival of IPAH.[24] This might be one of the reasons why patients eventually showed deterioration. Most patients showed maximal improvement within half a year after starting epoprostenol therapy. In some cases, with cautious control of epoprostenol therapy, there is a possibility of longer survival than previously reported. The dose of epoprostenol given at the time when patients showed maximal improvement in clinical status was $24\,ng \cdot kg^{-1} \cdot min^{-1}$, regardless of whether they could undergo LDLLT. Although they could walk further in the 6-min walk test because of increased cardiac output with epoprostenol therapy, patients showed deterioration of interstitial infiltration in chest X-rays and CT scans and needed a higher flow of supplemental oxygen. Considering severe oxygen desaturation and limited prognosis with epoprostenol therapy, further studies are required to determine better therapeutic strategies to treat PVOD and PCH.

Conclusions

We applied epoprostenol treatment to 8 patients with atypical clinical and radiographic findings such as IPAH. Histological findings revealed that 6 patients had PVOD and the other 2 patients had PCH. Epoprostenol was applied at a higher dose and for a longer period than previously reported cases, and worked as a bridge to lung transplantation for 4 patients. It was also applied in 4 patients who had no chance to undergo lung transplantation. All patients showed temporary amelioration in WHO functional class, exercise capacity, and cardiac index with long-term epoprostenol therapy. When patients are suspected of having PVOD or PCH by characteristic clinical and radiographic findings, careful application of epoprostenol can be considered as a bridge to lung transplantation or as the only method to improve their clinical condition because they have no other therapeutic options.

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Novel Insights from Clinical Experience

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Sorafenib Is Effective in the Treatment of Pulmonary Veno-Occlusive Disease

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Established Facts

- The efficacy of sorafenib, a multikinase inhibitor, in the treatment of pulmonary arterial hypertension (PAH) has been explored and, indeed, studies have demonstrated that it improves experimental PAH in animals.
- Pulmonary veno-occlusive disease (PVOD) is a disease in which the lesions affect the pulmonary capillary veins and not the pulmonary arteries. The efficacy of sorafenib in the treatment of pulmonary hypertension other than PAH, such as PVOD, is still unclear.
- Combination therapy of epoprostenol plus imatinib, a tyrosine kinase inhibitor, was reported to be effective in treating a patient with PVOD.

Novel Insights

- In our case report, imatinib proved ineffective, but sorafenib improved the hemodynamics and symptoms of PVOD. Sorafenib alone is effective in the treatment of PVOD without the need for combination therapy with epoprostenol. Sorafenib may be a potential therapeutic strategy for the treatment of PVOD.

Key Words
Hypertension · Imatinib · Pulmonary veno-occlusive disease · Side effect · Sorafenib

Abstract
The present study is the first report of the effectiveness of sorafenib in the treatment of pulmonary veno-occlusive disease (PVOD). A 66-year-old woman with PVOD was started on sorafenib. After 3 months of treatment with a maximum dosage of 400 mg/day sorafenib, there was an improvement in the patient's New York Heart Association (NYHA) functional class from IV to III. However, because of severe painful eruptions as a side effect of sorafenib, the patient stopped sorafenib and was started on imatinib instead. This treatment resulted in a worsening of the patient's NYHA class from III to IV, so sorafenib was restarted at a reduced dosage of 300 mg/day. The resumption of sorafenib was associated with clinical improvement, specifically NYHA class from IV to II and hemodynamic amelioration, and tolerable eruptions. In conclusion, sorafenib may be a potential therapeutic strategy for the treatment of PVOD.

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Introduction

Sorafenib, a multikinase inhibitor, is a recently developed molecular targeting agent that has been used in the treatment of cancer [1]. The possibility of using sorafenib in the treatment of pulmonary arterial hypertension (PAH) has also been explored and, indeed, studies have demonstrated that it improves experimental PAH in animals [2, 3]. Furthermore, a previous report presented the results of a phase Ib study of sorafenib in PAH patients [4]. However, the efficacy of sorafenib in the treatment of pulmonary hypertension other than PAH is not known.

Patients with pulmonary veno-occlusive disease (PVOD), in which the lesions affect the pulmonary capillary veins and not the pulmonary arteries, develop pulmonary hypertension, leading to right heart failure and a grave prognosis. In the present study, we report on the efficacy of sorafenib in the treatment of a patient with PVOD.

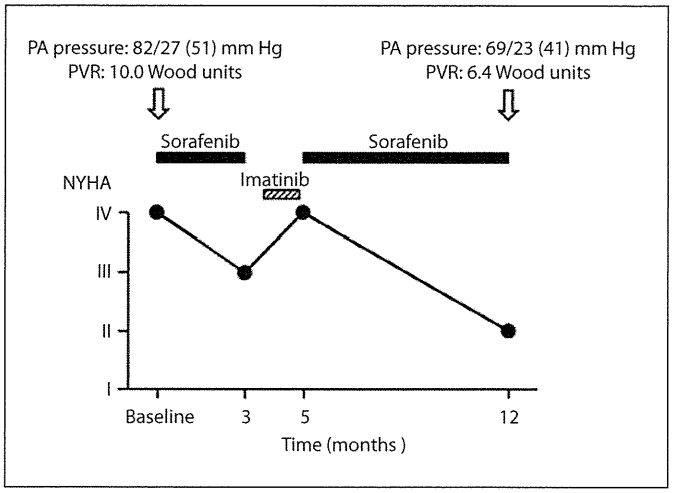

Fig. 1. Time course of changes in the patient's NYHA functional classification, pulmonary arterial (PA) pressure, and pulmonary vascular resistance (PVR) in relation to the administration of sorafenib and imatinib. A right-sided heart catheterization was performed at baseline and then again after 12 months.

Case Description

A 66-year-old woman was diagnosed with PVOD after collagen vascular disease, pulmonary disease, pulmonary thromboembolism, left heart abnormality, and other systemic diseases had been ruled out. The diagnosis was confirmed by lung computed tomography findings compatible with PVOD. The patient was started on sorafenib at a dose of 100 mg/day, which was increased to 200 mg/day after 3 weeks, then to 300 mg/day after another 2 weeks, and finally to 400 mg/day after 2 weeks, dose at which it was maintained.

The study protocol was approved by the Ethics Committee at Kyorin University Hospital. The purpose of the study was explained to the patient, who provided written informed consent before sorafenib treatment was started.

Figure 1 shows the time course of changes in the patient's New York Heart Association (NYHA) functional classification. Three months after starting sorafenib, the patient's NYHA functional classification had improved from class IV to class III. However, as a side effect of sorafenib, the patient developed mildly swollen eruptions that were itchy and painful. Thus, sorafenib treatment was stopped.

As an alternative to sorafenib, the patient was started on 200 mg/day imatinib, a tyrosine kinase inhibitor. After cessation of sorafenib treatment, the eruptions improved. However, after 1 month of treatment with imatinib, the patient's NYHA functional classification had deteriorated to nearly class IV, her symptoms and dyspnea were exacerbated, and leg edema developed due to right-sided heart overload. Thus, imatinib treatment was deemed ineffective for this patient and was stopped.

The patient was restarted on sorafenib at a dose of 300 mg/day. After 7 months with 300 mg/day sorafenib, the patient's NYHA classification had improved to class II. Although the eruptions also redeveloped as a side effect of sorafenib, they were minor and tolerable.

The right-sided heart catheterization and 6-min walk distance (6MWD) tests were performed at baseline and then again after 12 months. Catheterization demonstrated improvements in pulmonary vascular resistance (from 10.0 to 6.4 Wood units), systolic pulmonary arterial pressure (from 82 to 69 mm Hg), mean pulmonary arterial pressure (from 51 to 41 mm Hg), and mean right atrial pressure (from 6 to 2 mm Hg), as well as an increase in cardiac output (from 4.4 to 6.1 liter/min). The 6MWD increased from 200 to 245 m.

Discussion

In our patient, sorafenib improved the hemodynamics and symptoms of PVOD, whereas imatinib proved ineffective. In a previous case report, a combination of epoprostenol plus imatinib was reported to be effective in treating a patient with PVOD [5]; however, on the basis of the findings of the present study, it is possible that imatinib alone, without epoprostenol, would not have been sufficient to treat PVOD in the previous study. We did not use epoprostenol in our patient. Our findings suggest that sorafenib alone is effective in the treatment of PVOD without the need for combination therapy with epoprostenol. Thus, sorafenib may be a potential therapeutic strategy for the treatment of PVOD.

Conflict of Interest

None.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Survival of Japanese Patients with Pulmonary Arterial Hypertension after the Introduction of Endothelin Receptor Antagonists and/or Phosphodiesterase Type-5 Inhibitors

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Abstract

Objective Although endothelin receptor antagonists (ERAs) and phosphodiesterase type 5 (PDE5) inhibitors have become the most commonly used treatments for pulmonary arterial hypertension (PAH) since their introduction in 2005, it remains unknown whether these medications play a significant role in the survival of Japanese patients with PAH.

Methods The cardiac catheterization and survival data of 103 PAH patients were retrospectively reviewed. A comparison of survival benefits with regard to the type of PAH was completed in PAH patients diagnosed between 2005 and 2012 and those diagnosed between 1983 and 2004 and in patients undergoing treatment with ERAs and/or PDE5 inhibitors and those being treated with conventional therapy and/or oral beraprost. Although pulmonary vascular resistance (PVR) at baseline differed, the more recent group showed better survival rates compared with those observed in the early group (5-year survival: 70.1% vs. 44.8) ($p<0.05$). In addition, the survival of PAH patients treated with ERAs and/or PDE5 inhibitors was superior to that of the patients treated without these medications (5- and 8-year survival: 77.8% and 66.7% vs. 39.0% and 37.0%, respectively) ($p<0.05$), especially in patient with idiopathic and heritable PAH.

Conclusion Superior survival rates are observed in patients with idiopathic and heritable PAH after introduction of ERAs and PDE5 inhibitors, and the use of these drugs provides benefits for survival.

Key words: pulmonary arterial hypertension (PAH), endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors

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Introduction

An important pathological feature of pulmonary arterial hypertension (PAH) is pulmonary vascular remodeling associated with marked proliferation of pulmonary artery endothelial cells (ECs) and/or smooth muscle cells (SMCs) as well as components of the extracellular matrix that results in the obstruction of blood flow in resistant pulmonary arteries (1, 2). Moreover, it appears that all of these conditions ultimately lead to signaling imbalances between vasoconstrictive (e.g., endothelin) and vasodilatory (e.g., prostacyclin and nitric oxide) compounds (3).

There are three classes of drugs approved for the evidence-based treatment of PAH (4): prostacyclin analogues (e.g., epoprostenol, beraprost, treprostinil and iloprost [treprostinil and iloprost are approved outside Japan]), endothelin receptor antagonists (ERAs) (5, 6) (e.g., ambrisentan and bosentan) and phosphodiesterase type 5 (PDE5) inhibitors (7) (e.g., sildenafil and tadalafil). These drugs, which are currently used for the treatment of PAH, act not only by opposing any abnormal vasoconstriction, but also by inhibiting the growth of normal SMC (2). Because the drugs currently approved to treat PAH are not curative, patients require long-term therapy. In addition, long-term use of these drugs may provide sustained benefits in terms of exercise capacity and pulmonary hemodynamics in comparison to placebos or historical controls in patients with PAH (3).

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Because of their availability and convenience, oral drugs (e.g., ambrisentan, bosentan, sildenafil and tadalafil) have recently become common treatments for PAH in Japan after being introduced in 2005. However, it remains to be elucidated whether these oral medications significantly improve survival in Japanese patients with PAH in comparison to conventional therapy.

Historically, the management of patients with PAH has been limited to conventional therapies such as anticoagulants, calcium channel blockers, diuretics, digoxin and supplemental oxygen. Beraprost was the first orally active and chemically stable prostacyclin analog to be developed and has been available for the treatment of PAH in Japan since 1992. Patients treated with beraprost demonstrate improvements in exercise capacity and symptoms within short-term durations (8). However, no beneficial effects of oral beraprost are observed on exercise capacity at nine or 12 months (9). This indicates that oral beraprost may not have sustained long-term effects. Therefore, this drug has a weak recommendation in the PAH evidence-based treatment algorithm (4) and has been approved only in Japan and Korea (10). In fact, because of its cost and availability, oral beraprost was the first-line therapy for PAH in Japan before the approval of ERAs and PDE5 inhibitors for the treatment of PAH. Therefore, in this study, the beneficial effects of ERAs and PDE5 inhibitors on survival were evaluated without regard to oral beraprost therapy.

The aim of this study was to investigate cumulative survival benefits with regard to types of PAH in patients with PAH after the introduction of ERAs and PDE5 inhibitors in comparison to those observed in patients treated with conventional therapy and/or oral beraprost.

Materials and Methods

Study subjects

From June 1983 to February 2012, 103 patients older than 15 years with PAH were treated at Chiba University Hospital. In all patients, the diagnosis of PAH was established using cardiac catheterization and based on a documented mean pulmonary arterial pressure ≥25 mmHg and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤15 mmHg. All patients were classified as Group 1.1 to 1.4 on the current Dana Point classification (11). The study exclusion criteria were: 1) distal chronic thromboembolic pulmonary hypertension; 2) pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH); 3) left heart disease; and 4) chronic pulmonary disease (11). Although six of the 103 patients were classified as being in WHO function class IV, only four patients were treated with intravenous infusion of epoprostenol. Three of these patients were treated with ERAs and/or PDE5 inhibitors before the introduction of epoprostenol. According to Japanese legislation, informed consent is not required for retrospective collection of data corresponding to current practice. However, the database was anonymized and complied with the restrictive requirements of the Ministry of Health, Labor and Welfare dedicated to privacy, information technology and civil rights in Japan. The Ethics Committees of Chiba University Hospital approved the study protocol.

Efficacy measurements

The subjects were retrospectively divided into two groups: those diagnosed between 1983 and 2004 (n=66) and those diagnosed between 2005 and 2012 (n=37), since the introduction of ERAs and PDE5 inhibitors in Japan occurred in 2005. The subjects were further separated into two groups: those treated with ERAs and/or PDE5 inhibitors (n=36) and those treated with conventional therapy, including anticoagulants, calcium channel blockers, diuretics, digoxin, supplemental oxygen and/or oral beraprost and epoprostenol (n=67). In this analysis, the most recent hemodynamic data obtained before treatment were investigated. For more detailed analyses, the subjects were divided into subgroups according to types of PAH. The survival status of all patients was followed on a yearly basis and at the end of the study. Five of the 103 patients were lost to follow-up. The date of initiation of ERAs and PDE5 inhibitors was selected as the starting point to determine the survival period for assessing the effects of the drugs. The survival rates were calculated for all patients and by subgroups using Kaplan-Meier estimates. The baseline demographic and hemodynamic data were investigated in all patients and by subgroups.

Statistical analysis

The data were analyzed using JMP 9.0.0 (Japanese version, SAS Institute Inc., Tokyo, Japan) and the Excel-Toukei 2010 software program (Social Survey Research Information Co., Ltd., Tokyo, Japan). All results are expressed as the mean ± the SD for continuous variables and as the number or percentage for categorical variables. The baseline demographic and hemodynamic data were compared using unpaired Student's *t*-tests. The survival from all-cause death was estimated using the Kaplan-Meier method, and differences between groups were examined for significance using the log-rank test. Univariate and multivariate cox proportional hazards models were used to investigate the independent effects of the factors on survival. A p value of 0.05 was considered to be statistically significant.

Results

Baseline characteristics

One hundred and three patients with PAH were initially enrolled in this study (Table 1). The mean patient age was 46.9±15.0 years (range: 15 to 75) with a 4:1 female to male ratio. Forty-four patients (42.7%) were identified as having idiopathic and heritable PAH. The patients were followed for a mean period of 58.3±61.3 months and a median of

Table 1. **Baseline Clinical Characteristics and Hemodynamics in the Patients with PAH**

	1983-2012, n=103	1983-2004, n=66	2005-2012, n=37
Female/male	86/17	53/13	33/4
Age(yrs)	46.9±15.0	46.0±15.4	48.3±14.4
Survivor, n (%)	50 (47.6%)	21 (31.8%)	29 (78.4%)
Type of PAH			
Idiopathic and heritable PAH, n (%)	44 (42.7%)	31 (47.0%)	13 (35.1%)
PAH associated with connective tissue disease, n (%)	39 (37.9%)	25 (37.9%)	14 (37.8%)
PAH associated with congenital heart disease, n (%)	8 (7.8%)	3 (4.5%)	5 (13.5%)
PAH associated with portal hypertension, n (%)	12 (11.7%)	7 (10.6%)	5 (13.5%)
Hemodynamics			
mRAP, mmHg	5.2±6.1	4.3±4.7	6.9±7.8
mPAP, mmHg	47.9 ±13.2	48.8 ±13.9	46.2 ±11.7
mPCWP, mmHg	6.4±3.0	5.7±2.9	7.6±2.7*
CO, L/min	4.2±1.4	3.9±1.2	4.7±1.5*
CI, L/min per m^2	2.7±0.9	2.5±0.8	3.1±1.0*
PVR, dyne sec cm^{-5}	898.7±504.6	984.6±521.2	754.8±446.1*
mSAP, mmHg	89.3±14.9	90.5±13.4	87.2±17.2
Heart rate, beats/min	78.2±13.8	79.3±13.9	76.4±13.8
SvO_2, %	68.4±8.6	68.3±9.0	68.5±8.0
WHO functional class			
I, n (%)	1 (1.2%)	0 (0%)	1 (2.7%)
II, n (%)	32 (37.2%)	17 (32.7%)	15 (40.5%)
III, n (%)	47 (54.7%)	30 (57.7%)	17 (46.0%)
IV, n (%)	6 (7.0%)	5 (9.6%)	1 (2.7%)
Treatment			
Bosentan, n (%)	22 (21.4%)	8 (12.1%)	14 (37.8%)
Ambrisentan, n (%)	1 (1.0%)	0 (0.0%)	1 (2.7%)
Sildenafil, n (%)	20 (19.4%)	3 (4.5%)	17 (45.9%)
Tadalafil, n (%)	2 (1.9%)	0 (0.0%)	2 (5.4%)
Epoprostenol, n (%)	4 (3.9%)	3 (4.5%)	1 (2.7%)
Oral beraprost, n (%)	36 (35.0%)	20 (30.3%)	16 (43.2%)

*p<0.05; vs 1983-2004

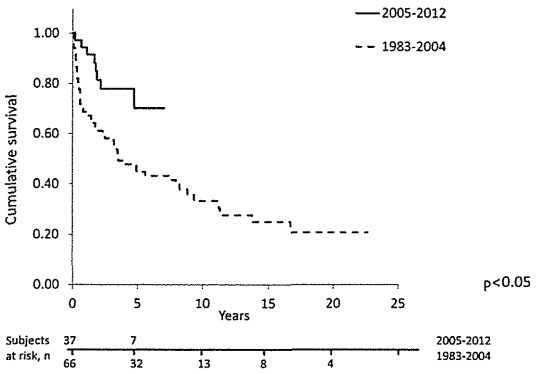

Figure 1. **The Kaplan-Meier survival estimates for the PAH patients. The survival rate for patients treated between 2005 and 2012 (solid line) was 70.1% at 5-years compared with 44.8% for patients treated between 1983 and 2004 (dashed line; p<0.05 by the Cox-Mantel log-rank test).**

41.5±61.3 months (range: 1 to 276). The mean pulmonary arterial pressure (PAP) and mean pulmonary vascular resistance (PVR) were 47.9 ±13.2 mmHg and 898.7±504.6 dyne. sec. cm^{-5}, respectively.

Survival

Patients diagnosed between 1983 and 2004 (n=66) vs. those diagnosed between 2005 and 2012 (n=37)

We divided the patients into two groups based on the timing of diagnosis (Table 1). We found that the patients diagnosed between 2005 and 2012 had a better survival rate than the patients diagnosed between 1983 and 2004 (5-year survival: 70.1% vs. 44.8%) (p<0.05) (Fig. 1). However, cardiac output (CO) and pulmonary vascular resistance (PVR) at baseline significantly differed between the two groups (Table 1), and these differences make it difficult to attribute the superior outcome to the introduction of ERAs and PDE5 inhibitors.

Outcomes of patients treated with ERAs and/or PDE5 inhibitors (n=36) and those treated with conventional therapy and/or oral beraprost (n=67)

To elucidate the absolute benefits of ERAs and/or PDE5 inhibitors on the survival of Japanese patients with PAH, an analysis was completed comparing the results of patients treated with ERAs and/or PDE5 inhibitors (n=36) and the

Table 2. **Baseline Clinical Characteristics and Hemodynamics in the Patients with PAH**

	The PAH patients, n=106		The idiopathic and heritable PAH patients, n=44		The associated PAH patients, n=59	
	ERA and/or PDE5 Inhibitors therapy, n=36	PAH therapies without ERA and PDE5 inhibitor, n=67	ERA and/or PDE5 Inhibitors therapy, n=16	PAH therapies without ERA and PDE5 inhibitor, n=28	ERA and/or PDE5 Inhibitors therapy, n=20	PAH therapies without ERA and PDE5 inhibitor, n=39
Female/male	33/3	53/14	13/3	19/9	20/0	34/5
Age(yrs)	47.3±14.4	46.7±15.5	44.8±14.0	41.7±15.2	49.2±14.7	50.2±14.9
Survivor, n (%)	28 (69.4%)	21 (29.9%)	14 (87.5%)	5 (17.9%)	14 (70.0%)	16 (41.0%)
Hemodynamics						
mRAP, mmHg	5.5±7.9	5.1±4.9	3.9±2.7	5.3±6.6	6.8±410.2	5.0±3.4
mPAP, mmHg	44.9 ±11.8	49.5 ±13.7	44.4 ±11.1	54.5±16.7*	45.3 ±12.6	46.2±10.1
mPCWP, mmHg	6.7±2.4	6.2±3.2	6.6±2.5	6.0±3.4	6.8±2.4	6.4±3.2
CO, L/min	4.4±1.1	4.1±1.5	4.4±0.9	3.7±1.4	4.4±1.3	4.4±1.6
CI, L/min per m^2	2.9±0.7	2.7±1.0	2.7±0.5	2.4±0.8	3.0±0.9	2.8±1.1
PVR, dyne $sec\ cm^{-5}$	771.4±440.3	971.4±527.6*	736.7±338.9	1166.7±609.7*	799.2±514.4	842.9±427.2
mSAP, mmHg	88.8±14.2	89.6±15.3	84.4±14.9	89.2±14.1	92.3±12.9	89.9±16.3
Heart rate, beats/min	75.9±12.7	79.6±14.3	73.1±13.3	83.0±14.3	78.1±12.1	77.2±14.0
SvO_2, %	68.1±7.7	68.5±9.1	67.5±6.1	66.1±9.5	68.7±8.9	70.1±8.7
WHO functional class						
I, n (%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
II, n (%)	15 (41.7%)	16 (23.9%)	6 (37.5%)	5 (17.9%)	9 (45.0%)	11 (28.2%)
III, n (%)	12(33.3%)	32(47.8%)	8 (50.0%)	14 (50.0%)	7 (35.0%)	18(46.2%)
IV, n (%)	1 (2.8%)	5 (7.5%)	0 (0.0%)	3 (10.7%)	1 (5.0%)	2 (5.1%)
Treatment						
Bosentan, n (%)	22 (61.1%)	0 (0.0%)	11 (68.8%)	0 (0.0%)	11 (55.0%)	0 (0.0%)
Ambrisentan, n (%)	1 (2.8%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sildenafil, n (%)	18 (50.0%)	0 (0.0%)	7 (43.8%)	0 (0.0%)	11 (55.0%)	0 (0.0%)
Tadalafil, n (%)	2 (5.6%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
Epoprostenol, n (%)	3 (8.3%)	1 (1.5%)	3 (18.8%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
Oral beraprost, n (%)	14 (38.9%)	22 (32.8%)	7 (43.8%)	8 (28.6%)	7 (35.0%)	14 (35.9%)

*p<0.05; vs ERA and/or PDE5 Inhibitors therapy

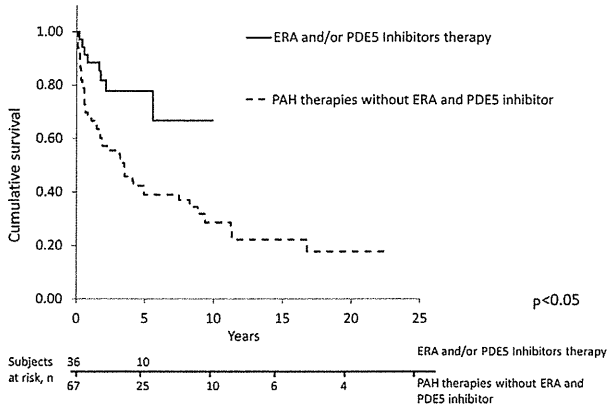

Figure 2. The Kaplan-Meier survival estimates for the PAH patients. The survival rates for patients treated with ERA and/or PDE5 inhibitor therapy (solid line) were 77.8% and 66.7% at five and eight years compared with 39.0% and 37.0% for patients treated with PAH therapies without ERA or PDE5 inhibitors (dashed line; p<0.05 by the Cox-Mantel log-rank test).

results of patients treated without ERAs and/or PDE5 inhibitors (n=67) (Table 2). A significant difference was observed between the two groups in the Kaplan-Meier survival curve (77.8% and 66.7% vs. 39.0% and 37.0%, respectively) (p< 0.05) (Fig. 2) and in PVR (Table 2). In particular, the patients with idiopathic and heritable PAH treated with ERAs and/or PDE5 inhibitors (n=16) showed significantly better survival outcomes than those not treated with these drugs (n=28) (Table 2) (5- and 8-year survival: 92.9% and 69.6% vs. 26.0% and 20.8%, respectively) (p<0.05) (Fig. 3). However, in the associated PAH patients (Table 2), no significant differences were observed between the groups (Fig. 4).

A univariate Cox proportional hazard analysis showed that cardiac index (CI), mean pulmonary arterial pressure (mPAP) and the use of ERA and/or PDE5 inhibitor therapy were associated with cumulative survival. Moreover, CI and ERA and/or PDE5 therapy were the significant predictors of survival in the multivariate analysis. The use of ERA and/or PDE5 inhibitor therapy was an independent predictor for superior outcomes (Table 3).

Discussion

The data presented here show that the patients treated be-