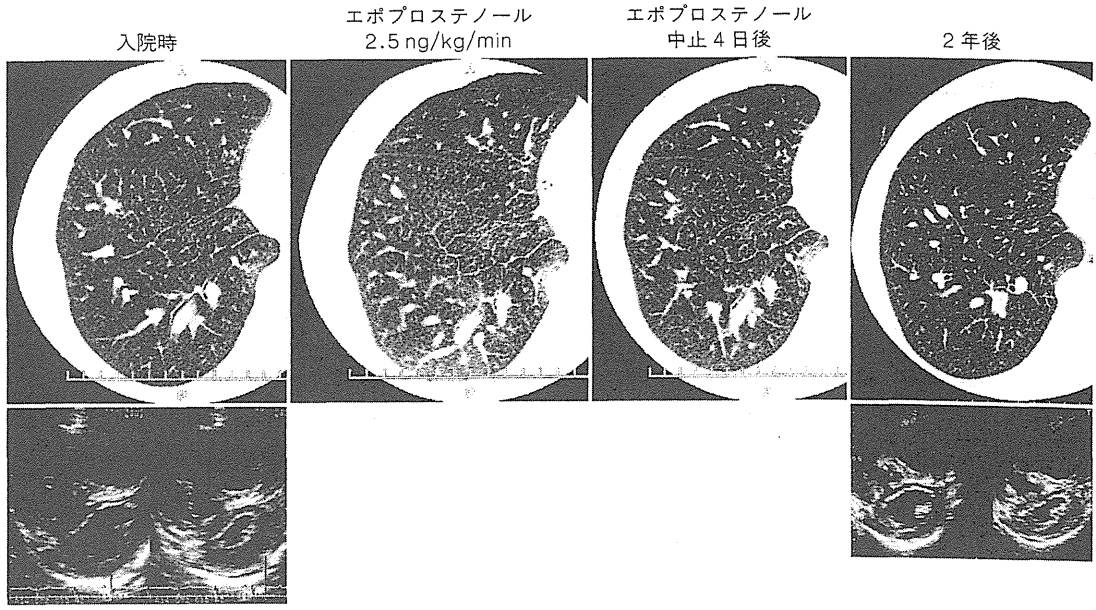

図 4　イマチニブを投与した PVOD の 1 例
上段：HRCT 画像，下段：心エコー図．入院時 HRCT で粒状影と小葉間隔壁の肥厚を認めた．エポプロステノール投与開始後悪化したが中止した後は改善した．イマチニブ投与を開始した後，2 年経過しても画像上悪化は認めなかった．治療により，心エコー図における左室圧排の程度はやや軽減した．

困難であるが，上述した多くの特徴的な症状や検査所見をもとに，PVOD の診断が除外可能か検討することが重要である．少数でも該当する所見がある症例は疑診例とし，早期に治療経験の豊富な施設との連携を図ることが望ましい．

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ORIGINAL ARTICLE
Pulmonary Circulation

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

Aiko Ogawa, MD, PhD; Katsumasa Miyaji, MD, PhD; Ichiro Yamadori, MD, PhD; Yoko Shinno, MD; Aya Miura, BSc; Kengo F. Kusano, MD, PhD; Hiroshi Ito, MD, PhD; Hiroshi Date, MD, PhD; Hiromi Matsubara, MD, PhD

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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Department of Clinical Science (A.O., H.M.), Department of Clinical Pathology (I.Y., Y.S.), Division of Cardiology (K.M., H.M.), National Hospital Organization Okayama Medical Center, Okayama; Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama (A.M., K.F.K., H.I.); and Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto (H.D.), Japan

Mailing address: Aiko Ogawa, MD, PhD, Department of Clinical Science, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan. E-mail: aiko-oky@umin.ac.jp

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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

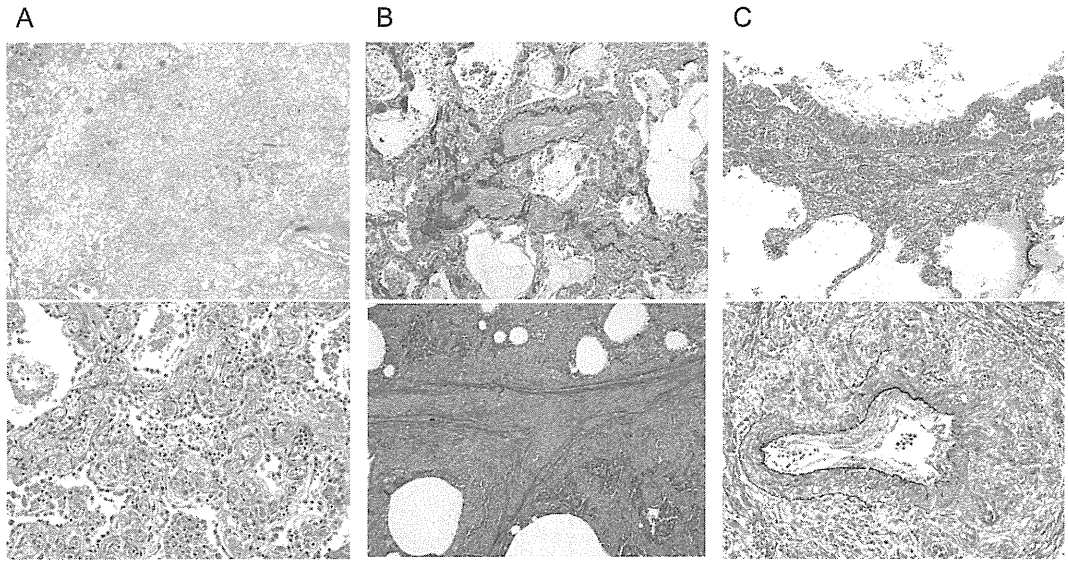

Figure 1. Pathological findings of lung specimens. (**A**) Specimens of pulmonary veno-occlusive disease (PVOD) show centrilobular congestion at low magnification (**Upper panel**) and characteristic alveolar capillaries at a higher magnification (**Lower panel**). These foci are seen in both PVOD and 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.

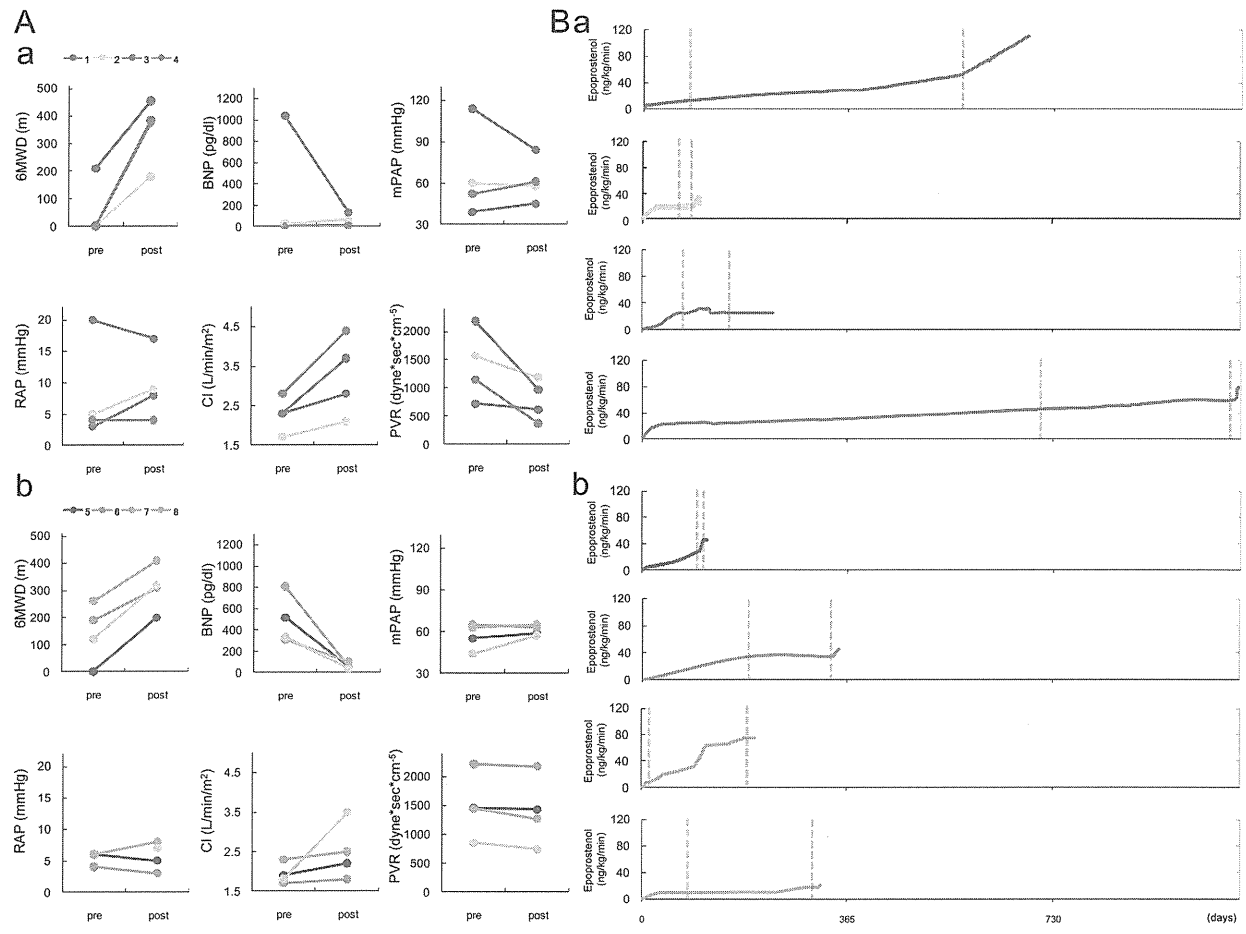

Figure 2. Changes in parameters and dose titration of epoprostenol. (**A**) Parameters before and after epoprostenol therapy were compared in patients without lung transplantation (**a**) and patients who underwent living-donor lobar lung transplantation (LDLLT) (**b**). Data after epoprostenol treatment 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

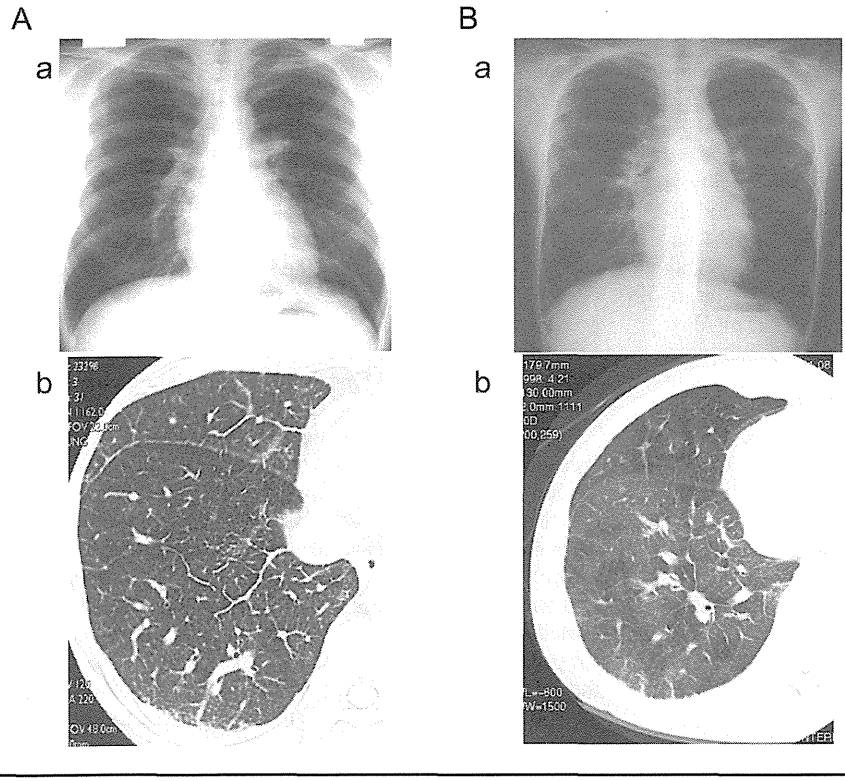

Figure 3. Representative radiographic findings. (**A**) Radiographic findings of pulmonary veno-occlusive disease (patient 1). (**a**) A chest radiograph shows a prominent main pulmonary artery and interstitial infiltrates. (**b**) A chest computed tomography (CT) scan of the right lobe shows multiple 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·kg^{-1}·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·min^{-1}·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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Original contribution

Stromal plasma cells expressing immunoglobulin G4 subclass in non–small cell lung cancer

Masakazu Fujimoto MD[a], Akihiko Yoshizawa MD[a,b], Shinji Sumiyoshi MD[a], Makoto Sonobe MD[c], Masashi Kobayashi MD[c], Itsuko Koyanagi[a], Wulamujiang Aini PhD[a], Tatsuaki Tsuruyama MD[a], Hiroshi Date MD[c], Hironori Haga MD[a,*]

[a]*Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto 606-8507, Japan*
[b]*Department of Laboratory Medicine, Shinshu University Hospital, Matsumoto 390-8621, Japan*
[c]*Department of Thoracic Surgery, Kyoto University Hospital, Kyoto 606-8507, Japan*

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Summary Inflammatory cell infiltration in tumor stroma may represent the interaction between the tumor and the immune system. The significance of immunoglobulin (Ig) G4+ plasmacytic infiltration, however, is poorly understood. Here, we analyzed the number of stromal IgG4+ plasma cells and the IgG4/IgG ratio of plasma cells in 294 primary non–small cell lung cancers (NSCLCs) using tissue microarray (TMA) and conventional surgical specimens. In TMA, 35 (12%) cases of NSCLC revealed more than 20 IgG4+ plasma cells per high-power field. In surgical specimens, most (97%) of those IgG4+ plasma cell–enriched cases showed obliterative phlebitis or arteritis, one of the key morphologic features of IgG4-related disease, within or at the periphery of the tumor. Clinically, none of the patients showed symptoms associated with IgG4-related systemic diseases. In patients with stage I squamous cell carcinoma, IgG4-enriched stroma was significantly associated with a favorable prognosis ($P = .04$). In conclusion, considerable IgG4+ plasma cell infiltration can be seen in a minority of cases of NSCLC and might contribute to prognostic modulation of NSCLC.

1. Introduction

Despite a number of recent studies focused on the tumor microenvironment, the role of plasma cells in cancer is not well understood [1]. The class and subclass of immunoglobulin (Ig) produced by plasma cells are defined primarily by their heavy-chain constant domain sequences, which affect the function of the antibody [2]. IgG4, the least abundant subclass in the IgG class, shows weak or negligible binding ability to both C1q and Fcγ receptors compared with the other IgG subclasses, which leads to a limited capacity to activate the classical complement pathway [2,3]. Thus, until recently, it was believed that IgG4 plays only a limited role in immune activation [3]. As a consequence of the current familiarity of IgG4-related diseases (IgG4-RD) to pathologists and the widespread use of anti-IgG4 antibody for immunohistochemical staining, cases of carcinoma accompanied by severe IgG4+ plasma cell infiltration in patients with or without a medical history of IgG4-RD have been identified [4-9], although the prevalence and significance of this phenomenon remain unclear.

* Corresponding author. Department of Diagnostic Pathology, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: haga@kuhp.kyoto-u.ac.jp (H. Haga).

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Table 1 Comparison of lung cancers with and without greater than 20 IgG4+ plasma cells/HPF in the TMA core (n = 294)

	No. of IgG4+ plasma cells/TMA core		*P*
	>20/HPF	≤20/HPF	
No. of cases	35 (11.9%)	259 (88.1%)	
IgG4/IgG ratio in TMA core, median (range)	0.13 (0.021-0.47)	0 (0-0.75)	<.0001 *
Male	30 (85.7%)	144 (55.6%)	.0005 *
Age (y), median (range)	72 (41-88)	67 (23-94)	.1783
Never smokers	4 (11.4%)	107 (41.3%)	.0004 *
Preoperative history of cancer	7 (20.0%)	48 (18.5%)	.8189
Preoperative history of asthma	4 (11.4%)	8 (3.1%)	.0417 *
Preoperative history of collagen vascular disease	1 (2.8%)	9 (3.5%)	1
Preoperative history of interstitial pneumonia	1 (2.9%)	15 (5.8%)	.7032
Squamous cell carcinomas (G1/G2/G3)	17 (3/12/2) (48.6%)	35 (6/18/11) (13.5%)	<.0001 *
G3 squamous cell carcinomas	2 (5.7%)	11 (4.2%)	.6583
Adenocarcinomas (G1/G2/G3)	17 (0/2/15) (48.6%)	216 (60/88/68) (83.4%)	.0001 *
G3 adenocarcinomas	15 (42.9%)	68 (26.3%)	.0468 *
Gene mutation in adenocarcinomas			
EGFR	3/14 (21.4%)	99/199 (49.0%)	.0524
KRAS	1/14 (7.1%)	22/199 (11.1%)	1
TP53	5/7 (71.4%)	26/122 (21.3%)	.0088 *
Stage I cancers	19 (54.3%)	196 (75.7%)	.0134 *
Recurrence rate [a]	34.3% (10.5%)	32.8% (20.9%)	.8502 (.3773)
Death rate [a]	20.0% (0%)	22.8% (12.2%)	.8111 (.1395)

[a] Of stage I cancers.
* Statistically significant.

Differential diagnosis of IgG4-RD and cancers can be problematic because IgG4-RD often forms tumefactive lesions and peritumoral desmoplastic tissue can mimic IgG4-RD when there is an abundance of IgG4+ plasma cells in a biopsy specimen. Some morphologic findings such as obliterative phlebitis are considered to be rather more specific to IgG4-RD than to cancer, but existing evidence supporting this idea seems weak [10]. Serum IgG4 concentration is a helpful laboratory finding to differentiate IgG4-RD and cancer, but it is not always elevated in patients with IgG4-RD, whereas it can be elevated in patients with cancer without IgG4-RD [4,8]. In addition, clinicians must keep in mind the possibility of synchronous cancer and IgG4-RD [11].

Table 2 Logistic regression analysis for estimation of significant factors related to greater than 20/HPF intratumoral IgG4+ plasma cell infiltration

Variable	Odds ratio	95% CI	*P*
Sex (male/female)	1.8285	0.5631-6.9714	.3392
Smoking history (never/current or former)	0.6118	0.1400-2.2837	.4829
Preoperative history of asthma (present/absent)	2.7665	0.6253-11.2757	.1581
Squamous cell carcinoma	15.4307	4.5863-71.6024	<.0001 *
G3 adenocarcinoma	8.5662	2.5946-38.8643	.0013 *
Cancer stage (stage I/stage II-IV)	0.6655	0.2968-1.4987	.3215

* Statistically significant.

In this study, we identified cases of lung cancer with stromal IgG4+ plasma cell infiltration using tissue microarray (TMA). We analyzed the clinicopathologic characteristics of these cases to investigate the relevance of lung cancer and IgG4+ plasma cells.

2. Materials and methods

2.1. Tissue microarray

Paraffin-embedded tumor blocks from 363 cases of lung cancer surgically resected from different patients in Kyoto University Hospital between 2001 and 2007 were selected from the electronic pathology files of Kyoto University Hospital for construction of TMA, with the patients' consent. TMAs were constructed by 2 of the authors (A.Y. and S.S.) basically using the approach described by Kononen et al [12]. Briefly, the most morphologically representative region of the tumor was selected on a hematoxylin and eosin–stained slide. Then, a tissue core 2 mm in diameter was punched out from each donor tumor block using a thin-walled stainless steel needle for TMA construction (Azumaya, Tokyo, Japan) and was arrayed in a recipient paraffin block. Small cell carcinomas, recurrent carcinomas, carcinomas with neoadjuvant chemotherapy, and cases with multiple carcinomas (both synchronous and metachronous), which were in the TMA for other research, were excluded from this study (n = 45).

2.2. Immunohistochemistry

Immunostains against IgG4 and IgG using mouse antihuman IgG4/HRP (MCA2098P, dilution 1:200; AbD Serotec, Oxford, UK) and IgG (polyclonal, dilution 1:2 of prediluted product; Ventana, Tucson, AZ) were performed on an autoimmunostainer (Ventana XT System Benchmark; Ventana Medical Systems).

2.3. Evaluation of immunohistochemistry

In TMA sections, we regarded tumors infiltrated by more than 20 IgG4+ plasma cells per high-power field (HPF) (×40 objective lens with field number 22) as IgG4+ cell–enriched cases because this criterion is used for diagnosing IgG4-RD in lung biopsy specimens [10]. To calculate the IgG4/IgG ratio in each TMA section, the total numbers of IgG4+ and IgG+ plasma cells per core were counted manually under a light microscope by M.F. and A.Y. For those IgG4+ cell–enriched cases with greater than 25% IgG4/IgG ratio, immunohistochemistry for IgG4 and IgG was performed on the original surgical specimens to extract the cases fulfilling the quantitative criteria for IgG4-RD (>50/HPF of plasma cells with IgG4/IgG ratio >40%) [10]. In each case, IgG4 and IgG were counted in the region most highly stained for IgG4 in 3 HPFs to calculate the IgG4/IgG ratio.

2.4. Histologic evaluation

Histologic types of lung cancers were determined according to the 2004 World Health Organization classification [13]. In adenocarcinomas, the predominant histologic subtype or variant in each case was identified according to the new lung adenocarcinoma classification proposed by the International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society [14]. Non–small cell carcinomas were graded as well differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3) based on the 2004 World Health Organization classification by 3 of the authors (M.F., A.Y., and S.S.) [13]. IgG4+ cell–enriched cases were evaluated by 2 of the authors (M.F. and A.Y.) for the presence of obliterative phlebitis/arteritis and increased number of eosinophils, which we defined as more than 50 eosinophils per 10 HPFs [6].

2.5. Clinical information

The electronic chart of Kyoto University Hospital, the electronic database of the Department of Thoracic

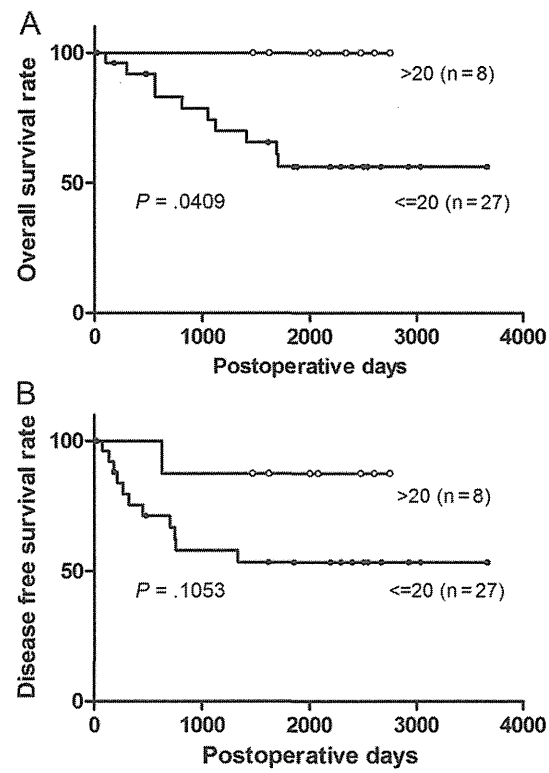


Fig. 1 Kaplan-Meier survival curves of 35 patients with stage I squamous cell carcinomas separated by the number of IgG4+ plasma cells/HPF in the TMA core (>20/HPF versus ≤20/HPF). A, OS curves (log-rank test, $P = .0409$). B, DFS curves (log-rank test, $P = .1053$).

Table 3 Clinicopathologic characteristics of 6 lung cancers that fulfilled the histologic criteria of lung IgG4-RD [a]

	Case no.					
	1	2	3	4	5	6
Sex	Male	Male	Male	Male	Male	Male
Age at surgery (y)	59	61	61	65	72	75
Smoking status	Current	Former	Former	Former	Never	Current
Medical history	None	Hypopharyngeal squamous cell carcinoma	None	Asthma, hepatitis C	Diabetes mellitus, arrhythmia	Colon carcinoma, renal carcinoma (histology not available)
Site	Right upper lobe	Left upper lobe	Right lower lobe	Right upper lobe	Left upper lobe	Left lower lobe
Stage	1B (T2aN0M0)	1A (T1aN0M0)	1A (T1bN0M0)	1B (T2aN0M0)	2A (T1bN1M0)	1A (T1aN0M0)
Histology	Adenosquamous carcinoma, G3	Adenocarcinoma, solid predominant, G3	Squamous cell carcinoma, G1	Squamous cell carcinoma, G2	Adenocarcinoma, micropapillary predominant, G3	Squamous cell carcinoma, G2
Obliterative phlebitis/ arteritis	Present	Present	Absent	Present	Present	Present
Eosinophilic infiltration >50/10 HPF	Absent	Absent	Absent	Present	Absent	Absent
IgG4/IgG ratio in TMA core (%)	206/820 (25.1)	570/1204 (47.3)	172/625 (27.5)	258/1012 (25.5)	216/648 (33.3)	348/1211 (28.7)
IgG4/IgG ratio in surgical specimen (%)	51.7/103.7 (49.9)	80.0/137.0 (58.4)	67.7/146.7 (46.1)	53.3/125.3 (42.5)	69.7/170.7 (40.8)	50.6/105.3 (48.1)
EGFR	Not done	Wild	Wild	Wild	Mutated	Wild
KRAS	Not done	Mutated	Wild	Wild	Wild	Wild
TP53	Not done	Not done	Mutated	Wild	Not done	Wild
Recurrence of lung carcinoma	Absent	Absent	Absent	Absent	Present	Absent
Outcome	Alive	Alive	Alive	Alive	Died of disease	Alive
Follow-up period (days)	3480	1666	2747	2002	376	1468

[a] IgG4/IgG ratio >40% and >50/HPF IgG4+ plasma cells in surgical specimen.

Surgery of Kyoto University Hospital, and the electronic pathology database of Kyoto University Hospital were used to search for patients' prognosis and medical history.

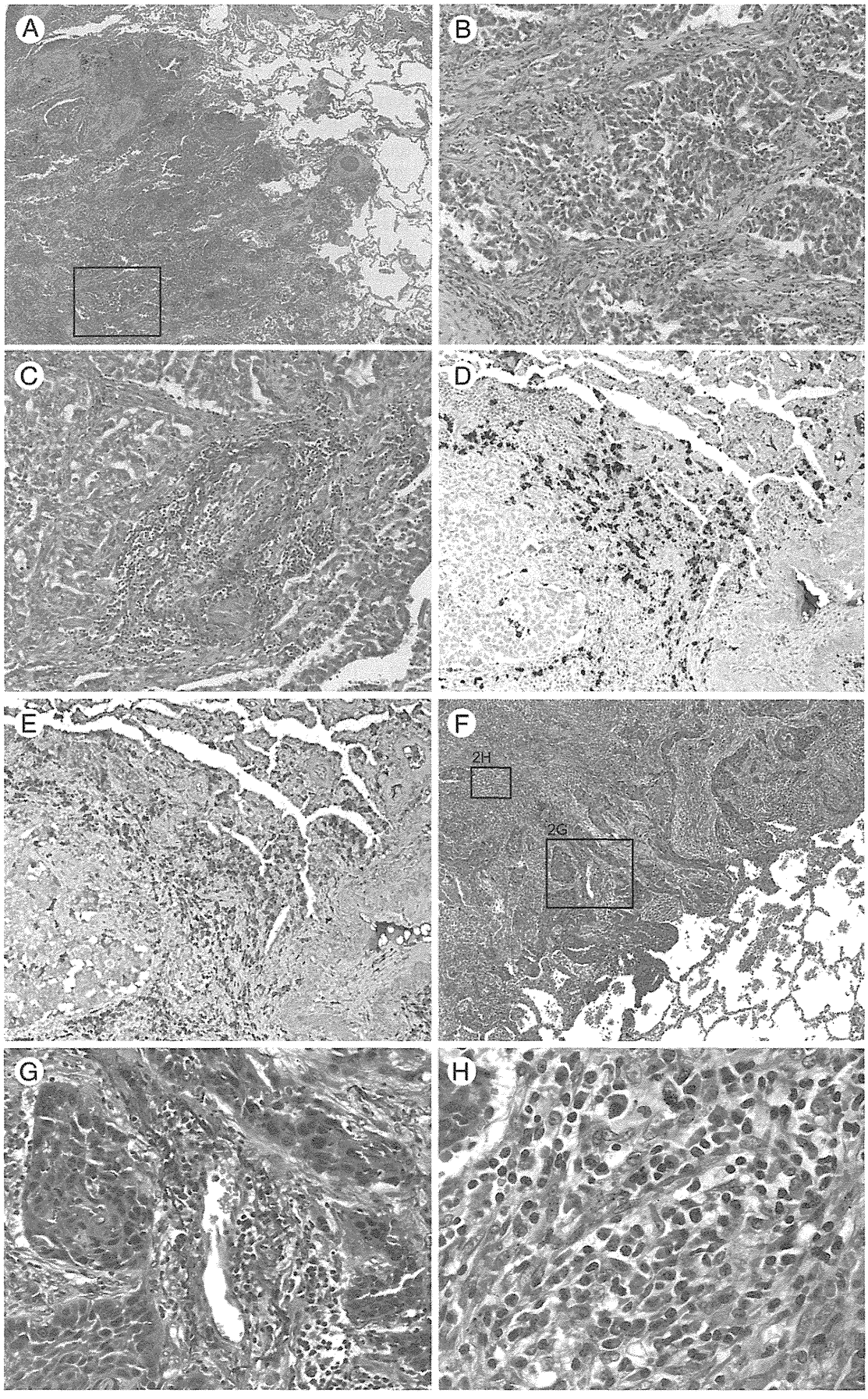
2.6. Somatic *EGFR*, *KRAS*, and *TP53* mutations

EGFR, *KRAS*, and *TP53* mutation analyses were performed in selected cases by methods described previously [15,16].

2.7. Statistical analysis

GraphPad Prism (GraphPad Software, San Diego, CA) and JMP Start Statistics (Statistical Discovery Software SAS Institute, Cary, NC) were used for statistical analyses. Comparisons between 2 groups were performed using the Fisher exact test or Mann-Whitney test to analyze categorical variables and continuous variables, respectively. The Kaplan-Meier method was used to evaluate patients' prognosis,

Fig. 2 Histology of lung cancers fulfilling the histologic criteria for lung IgG4-RD, A-E, Case 2. F-H, Case 4. A, Case 2, solid predominant G3 adenocarcinoma (×20). B, Higher-magnification image of boxed area in panel A (×100). C, Intratumoral obliterative phlebitis (×100). D, IgG4+ plasma cells of greater than 50/HPF in the cancer stroma (×200). E, IgG immunostain at the same area as in panel D, with IgG4/IgG ratio greater than 40% (×200). F, Case 4, squamous cell carcinoma, G2 (×40). G and H, Higher magnification of the areas demarcated by boxes in panel F; obliterative vasculitis and eosinophilic infiltration are shown, respectively (×200 and ×400).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and log-rank tests were used to compare the survival rates among groups. Logistic regression analysis was performed to examine the interaction of the multiple clinicopathologic variables. Significance was defined as $P < .05$.

3. Results

TMA cores that were not completely enclosed on the sections or did not include viable tumor on the sections were excluded from this study (n = 24). As a result, 294 primary non–small cell lung carcinomas (NSCLCs) were extracted. The median follow-up period of patients was 1748 days (range, 7-3805).

The 294 lung cancers consisted of 233 adenocarcinomas (79.3%), 52 squamous cell carcinomas (17.7%), and 9 other NSCLC (3.1%) (6 large cell carcinomas, 2 sarcomatoid carcinomas, and 1 adenosquamous carcinoma). According to the 7th Union for International Cancer Control (UICC) TNM classification [17], 215 cases (73.1%) were stage I, 37 cases (12.6%) were stage II, 31 cases (10.5%) were stage III, and 11 cases (3.7%) were stage IV. Among the 233 adenocarcinomas, 60 cases (25.8%) were G1, 90 cases (38.6%) were G2, and 83 cases (35.6%) were G3. Among the 52 squamous cell carcinomas, 9 cases (17.3%) were G1, 30 cases (57.7%) were G2, and 13 cases (25.0%) were G3. The median numbers of IgG4+ and IgG+ plasma cells in the TMA core were 0 (range, 0-570) and 134 (range, 0-2178), respectively. None of the 294 patients had IgG4-RD in their medical history, and serum IgG4 concentration was not measured in any of the patients.

In adenocarcinomas, mutation analysis of *EGFR*, *KRAS*, and *TP53* was performed in 213, 213, and 129 cases, respectively, and the mutation was confirmed in 102 (47.9%), 23 (10.8%), and 31 cases (24.0%), respectively.

3.1. Lung cancers with IgG4+ cell enrichment (n = 35)

Of 294 cases, 35 cases (11.9%) were IgG4+ cell–enriched, including 17 adenocarcinomas (7.3% of all adenocarcinomas), 17 squamous cell carcinomas (32.7% of all squamous cell carcinomas), and 1 adenosquamous carcinoma. Among the 17 adenocarcinomas, 15 cases (88.2%) were G3 and 2 cases (11.8%) were G2. G1 adenocarcinoma was not observed. Among the 17 squamous cell carcinomas, 3 cases (17.6%) were G1, 12 cases (70.6%) were G2, and 2 cases (11.8%) were G3.

The median number of original tumor slides observed per case was 3 (range, 1-9), and Victoria blue hematoxylin and eosin stain and/or Elastica van Gieson stain was performed in all but 1 case. Fibrosis was evident in cancer stroma of all 35 cases, but none of them showed storiform pattern fibrosis. Obliterative phlebitis/arteritis was found in 34 cases (97.1%) associated with desmoplasia. An increased number of eosinophils were seen in 3 cases (8.6%). In all 35 cases, pathological change for which IgG4-RD was suspected was absent in nonneoplastic lung tissue surrounding the cancers.

The result of comparison between IgG4+ cell–enriched cases and the cases with at least 20 IgG4+/HPF in the TMA core is shown in Table 1. We also performed multivariate logistic regression analysis to determine which factors, among those showing statistical significance in univariate analysis, were more significantly associated with greater than 20/HPF IgG4+ plasma cell infiltration (Table 2). This analysis revealed that squamous cell carcinoma and G3 adenocarcinoma were associated with greater than 20/HPF IgG4+ plasma cell infiltration with high statistical significance ($P < .0001$ and $P = .0013$, respectively).

No statistical difference in recurrence rate or death rate was observed between the 2 groups (Table 1). In stage I carcinoma, however, none of the 19 IgG4+ cell–enriched cases (10 adenocarcinomas, 8 squamous cell carcinomas, and 1 adenosquamous carcinoma) were associated with patient death, and only 1 squamous cell carcinoma and 1 adenocarcinoma recurred. In contrast, among 27 stage I squamous cell carcinomas with at least 20 IgG4+ plasma cells/HPF, 10 patients (37.0%) died of disease and 11 cases (40.7%) recurred. Among 110 stage I G2-3 adenocarcinomas with at least 20 IgG4+ plasma cells/HPF, 13 patients (11.8%) died of disease and 29 cases (26.4%) recurred. A significant difference of overall survival (OS) rate was observed in stage I squamous cell carcinoma ($P = .0409$), but this was not the case for disease-free survival (DFS) rate ($P = .1053$; Fig. 1). No significant difference in OS or DFS was observed in stage I G2-3 adenocarcinoma ($P = .3280$ and $P = .4407$, respectively).

3.2. Lung cancers with greater than 50 IgG4+ plasma cells/HPF and greater than 40% IgG4/IgG plasma cells in surgical specimens (n = 6)

Among 35 IgG4+ cell–enriched cases in the TMA cores, 12 cases were associated with greater than 25% IgG4/IgG ratio, and 6 of them showed greater than 50 IgG4+ plasma cells/HPF and greater than 40% IgG4/IgG ratio in the surgical specimens. The clinicopathologic features of these 6 cases are summarized in Table 3. Histologic figures of selected cases are shown in Fig. 2.

In comparison of these 6 cases and the other 29 IgG4+ cell–enriched cases, no statistically significant difference was obtained in any parameters shown in Table 1, except the IgG4/IgG ratio in the TMA core (median, 0.28 versus 0.12; $P = .0062$). In addition, the numbers of cases with obliterative phlebitis/arteritis and increased number of eosinophils in these 2 groups did not differ significantly (83.3% versus 100% [$P = .1714$] and 16.7% versus 6.9% [$P = .4417$], respectively).

4. Discussion

IgG4+ plasma cell infiltration in cancer and its relevance to IgG4-RD have been a matter of debate in practical

medicine [4-9]. Because chronic inflammation is associated with a risk of cancer development, it could be hypothesized that IgG4-RD is a source of carcinoma [11,18]. In our series, however, the idea that the patients with IgG4+ cell–enriched tumor had lung IgG4-RD seems unlikely for 2 main reasons. Firstly, none of the IgG4+ cell–enriched cases showed histology of IgG4-RD in the nonneoplastic lung tissue, suggesting that the cancer is the factor causing the inflammation and not the other way round. Second, although IgG4-RD is a systemic disease and the affected patients commonly develop multivisceral lesions or multiple lesions in the same organ at the time of diagnosis or during the follow-up [6,19], none of the patients in our series were clinically complicated by IgG4-RD at the time of diagnosis or during the follow-up of cancer.

Considering the favorable prognosis observed in IgG4-enriched stage I squamous cell carcinomas, IgG4 infiltration might cause prognostic modulation of NSCLC. At first, this result seemed inconsistent with the notable antiimmune function of IgG4, as seen in the transition of serum IgG4 level in immunotherapy [20]. Other previous reports, however, show that the functional role of IgG4 varies in different pathophysiologic circumstances and that IgG4 can be a pathogenic antibody in certain immunologic disorders [21-25]. Our data may suggest that IgG4 reacts against certain lung cancer antigens and damages tumor cells despite its poor complement- and leucocyte-activating properties. By multivariate analysis, we found that squamous cell carcinomas and high-grade adenocarcinomas are more likely to be accompanied by intratumoral IgG4+ plasma cells; however, the reason for this tendency is unclear at present.

In stage I squamous cell carcinoma, intratumoral IgG4+ plasma cell infiltration may be a better prognostic factor than conventional histologic grade because the histologic grade of lung squamous cell carcinoma is not clearly related to its prognosis [13]. IgG4+ plasma cells might have a cancer-inhibiting role in adenocarcinomas as well, but our data did not show statistical significance. In adenocarcinomas, high-grade histology or non-*EGFR* gene mutation may be a more powerful prognostic factor than IgG4+ cell infiltration [15,16,26].

A common histologic finding of IgG4-RD is sclerosing fibrosis arranged at least focally in a storiform pattern accompanied by marked IgG4+ plasma cell infiltration, usually associated with obliterative phlebitis; however, there is variability in the findings in certain organs [10]. In lung IgG4-RD, stroriform-type fibrosis is uncommon; thus, histologic findings tend to overlap with other pulmonary fibroinflammatory conditions. In the pericancerous fibrous stroma of our IgG4+ cell–enriched cancers, even obliterative phlebitis/arteritis, the histologic finding of which is believed to be quite specific to lung IgG4-RD, was observed in most cases. Pathologists should be aware of this fact when diagnosing lung IgG4-RD on biopsy specimens.

In conclusion, a nonnegligible minority of cases of squamous cell carcinoma and high-grade adenocarcinoma of the lung showed IgG4+ plasma cell infiltration in the stroma. Obliterative vascular changes were commonly seen in those cases without clinical evidence of IgG4-RD. Because IgG4+ cell–enriched cases were associated with favorable prognosis in stage I squamous cell carcinomas, IgG4 infiltration may be part of the anticancer immune response.

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Novel Insights from Clinical Experience

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

Masaharu Kataoka[a, b] Ryoji Yanagisawa[a] Keiichi Fukuda[b] Hideaki Yoshino[a] Toru Satoh[a]

[a]Division of Cardiology, Department of Medicine, Kyorin University School of Medicine, and [b]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

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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Toru Satoh, MD
Division of Cardiology, Department of Medicine
Kyorin University School of Medicine
6-20-2 Shinkawa, Mitaka, Tokyo 181-8611 (Japan)
E-Mail tsatoh@ks.kyorin-u.ac.jp

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.

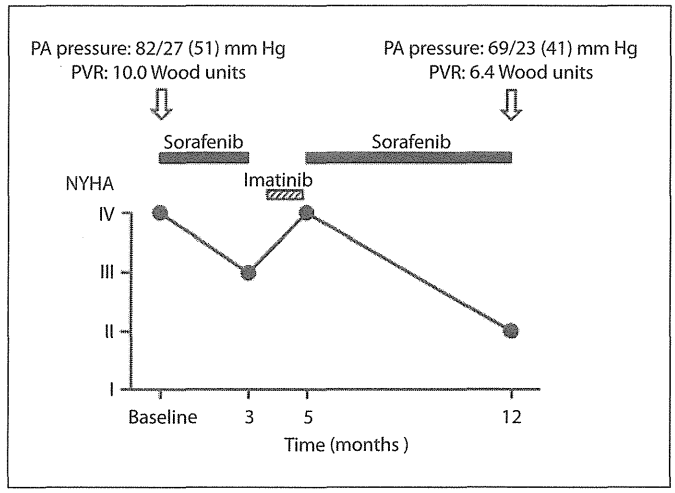

Fig. 1. Time course of changes in the patient's NYHA functional classification, pulmonary arterial (PA) pressure, and pulmonary vascular resistance (PVR) in relation to the administration of sorafenib and imatinib. A right-sided heart catheterization was performed at baseline and then again after 12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