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Intensive Immunosuppressive Therapy Improves Pulmonary Hemodynamics and Long-Term Prognosis in Patients With Pulmonary Arterial Hypertension Associated With Connective Tissue Disease

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Background: Pulmonary arterial hypertension (PAH) remains a serious disease characterized by elevated pulmonary artery pressure (PAP) and increased pulmonary vascular resistance (PVR). Among its subtypes, PAH associated with connective tissue disease (CPAH) has the worse prognosis, because of resistance to conventional vasodilator therapy. We hypothesized that intensive immunosuppressive therapy (IIT) could improve the pulmonary hemodynamics in CPAH.

Methods and Results: In our pulmonary hypertension (PH) cohort of 182 patients, we evaluated 13 consecutive patients with CPAH who received IIT combined with cyclophosphamide and glucocorticosteroids (IIT group, mean age 45±8 years, 12 females and 1 male). We compared them with 8 historical controls (control group: mean age 52±18 years, 8 females) for pulmonary hemodynamics and prognosis. Both groups were treated with conventional vasodilator therapy. Although the mean PAP (mPAP) remained unchanged in the control group, IIT significantly decreased mPAP (40±9 to 29±11 mmHg, P<0.01) and tended to decrease PVR (700±434 to 481±418 dyne·s·cm^{-5}, P=0.07). Importantly, in 6 of the 13 patients in the IIT group, mPAP was almost normalized (<25 mmHg) and remained stabilized for more than 1 year. Furthermore, the IIT group showed significantly better prognosis compared with the control group (P<0.01).

Conclusions: These results suggest that IIT as well as conventional vasodilator therapy improves the pulmonary hemodynamics and long-term prognosis of patients with CPAH. (*Circ J* 2011; **75:** 2668–2674)

Key Words: Connective tissue disease; Immunosuppressive therapy; Pulmonary arterial pressure; Pulmonary vascular resistance

Pulmonary arterial hypertension (PAH) is a serious condition caused by small pulmonary artery obstruction as a result of vascular proliferation and remodeling.[1–3] It is defined as a mean pulmonary arterial pressure (mPAP) greater than 25 mmHg at rest.[4,5] Among the subtypes of pulmonary hypertension (PH), connective tissue disease-associated PAH (CPAH) has the worst prognosis, because of its resistance to conventional vasodilator therapy, evidenced by the fact that patients with systemic sclerosis (SSc) had a 1-year survival rate of only 45% before the introduction of advanced vasodilator therapies.[6] Although several vasodilators, anticoagulant agents and lung transplantation are currently used for the treatment of CPAH, more effective treatment needs to be developed.[7–9]

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It is widely accepted that immunological and inflammatory mechanisms contribute to the progression of PAH in patients with connective tissue disease (CTD), such as SSc, systemic lupus erythematosus (SLE) and mixed CTD (MCTD).[10,11] Indeed, inflammatory cells (eg, macrophages and lymphocytes)

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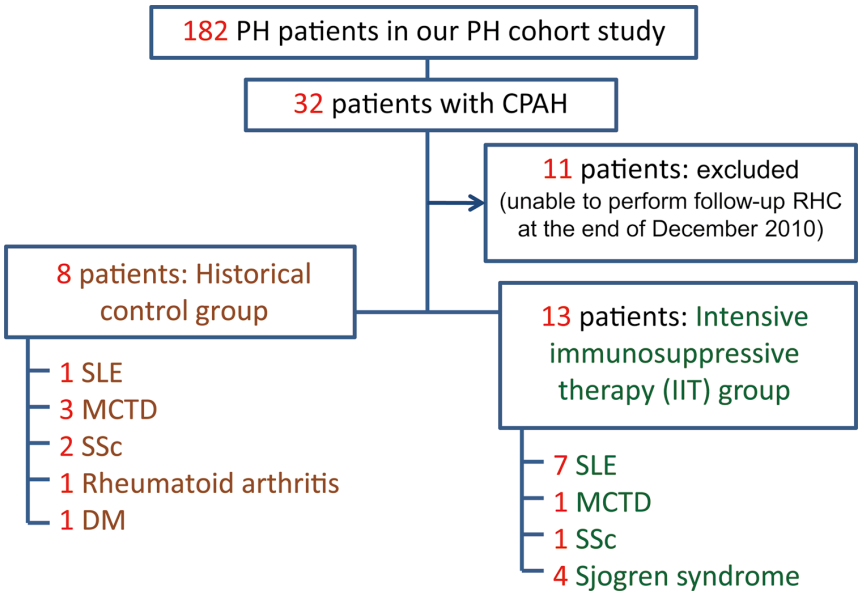

Figure 1. Enrolment algorithm. Of the 182 patients in our pulmonary hypertension cohort, 32 were diagnosed as having connective tissue disease-associated pulmonary arterial hypertension (CPAH) and 11 of them were excluded because we were unable to perform follow-up right-heart catheterization by the end of December 2010.

have been detected in the plexiform lesions in the lung from CPAH patients.[12,13] It has been recently reported that immunosuppressive therapy is effective in patients with SLE or MCTD, where half of the patients who responded to the first line of immunosuppressive therapy alone showed improvement in symptoms, exercise tolerance and pulmonary hemodynamics.[14,15] However, immunosuppressive therapy alone without vasodilators did not normalize mPAP in those patients.[14,15]

Therefore, in the present study we tested our hypothesis that intensive immunosuppressive therapy (IIT) combined with cyclophosphamide and glucocorticosteroids, as well as vasodilator therapy, can improve the pulmonary hemodynamics and long-term prognosis in patients with CPAH.

Methods

The study protocol was approved by the Ethical Committee of Tohoku University and all patients provided written informed consent.

Cohort of PH Patients

Our cohort consisted of 182 consecutive patients with PH who were admitted to Tohoku University Hospital between 1974 and 2010 (**Figure 1**).[16] We regularly follow them every 6–12 months by various examinations, including cardiac catheterization.[16] Besides this regular follow-up, we hospitalize them when their symptoms or right-heart failure worsen.[16]

Diagnosis of PH Subtypes

We performed right-heart catheterization in all 182 patients with PH, which was defined as mPAP >25 mmHg at rest.[4,5] The definition of PAH has the additional criterion that the pulmonary arterial wedge pressure (PCWP) must be ≤15 mmHg.[4,5,17] CTD and liver disease were diagnosed clinically and by blood tests, as defined by the respective criteria.[18–26] Congenital heart disease-associated PH (CHD-PH) was diagnosed by echocardiography and chronic thromboembolism-associated PH (CTEPH) by ventilation–perfusion RI scans and computed tomography (CT). Pulmonary function tests, arterial blood gases, chest X-ray and CT scan were used to diagnose lung disease and hypoxia. When the abovementioned abnormalities were ruled out, the patients were diagnosed as idiopathic PAH (IPAH).[5,17,27] Heritable PAH was diagnosed as IPAH with a family history or gene mutation of PAH.[5,17,27,28] Pulmonary veno-occlusive disease (PVOD) was diagnosed by pathological examination or suspected on high-resolution CT scan.[29]

Patients' Inclusion

Using the preceding criteria, we diagnosed the following subtypes of PH: IPAH (n=51), heritable PAH (n=3), CPAH (n=32), CHD-PAH (n=30), portal hypertension (porto-PH, n=11), PVOD (n=4), and CTEPH (n=51) (**Figure 1**).

Among the 32 patients with CPAH, we excluded 11 because we were unable to follow them with right-heart catheterization by the end of December 2010 (**Figure 1**). Among the remaining 21 patients with CPAH, 13 consecutive patients have been treated with IIT (IIT group) since 2007, and 8 patients with CPAH with conventional vasodilator therapy alone before 2007 (historical control group) (**Figure 1**). The follow-up period was 914±456 days for the historical control group and 565±431 days for the IIT group.

Data Collection

Baseline demographic information (age, sex, height and body weight), clinical diagnosis, comorbidities (CTDs, liver diseases, congenital heart diseases, and thyroid dysfunction), plasma levels of B-type natriuretic peptide, 6-min walking distance and hemodynamic data from catheterization were recorded for each patient. Hemodynamic parameters examined included PCWP, pulmonary artery pressure (PAP), right ventricular end-diastolic pressure, right atrial pressure, cardiac output, cardiac index (CI), systolic blood pressure, diastolic blood pressure, mean blood pressure, pulmonary vascular resistance (PVR), systemic vascular resistance and mixed venous oxygen saturation. Lung transplantation and cardiovascular death were defined as cardiopulmonary death.

IIT for CPAH

Our IIT was a combination therapy with cyclophosphamide (500 mg IV 10 times in a year, once a month for the first

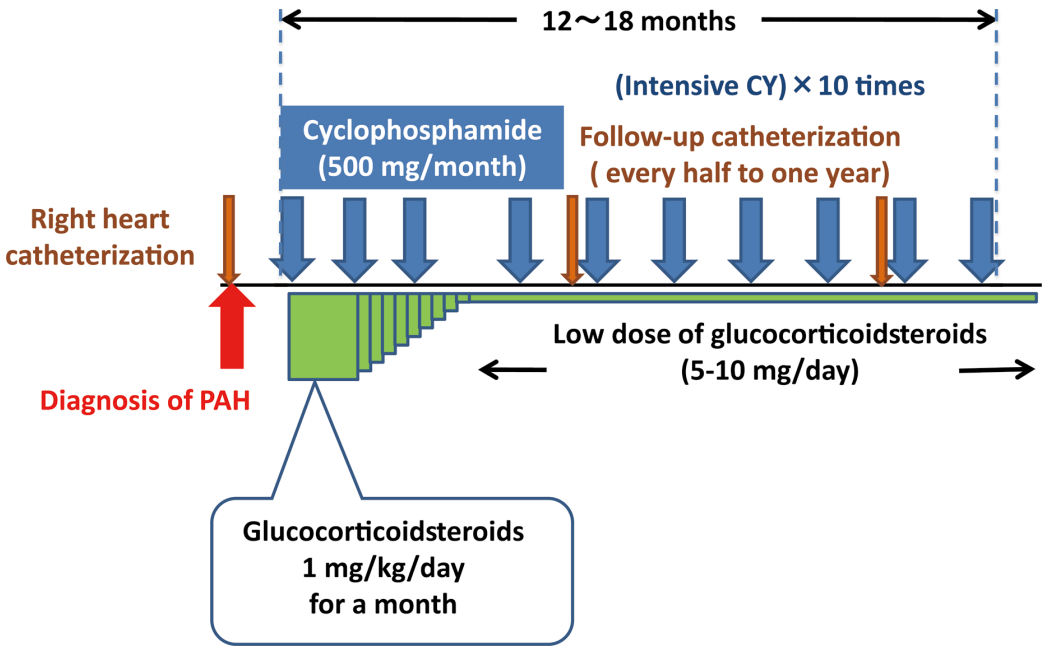

Figure 2. Protocol of the intensive immunosuppressive therapy, a combination therapy with cyclophosphamide (CY: 500 mg IV 10 times in a year, once a month for the first 3 months followed by once every 3 months) and glucocorticosteroids (1 mg·kg^{-1}·day^{-1} PO in the first month, followed by gradual tapering afterward by 5–10 mg/day every 2–4 weeks to a maintenance dose of 5–10 mg/day). Right-heart catheterization was performed in all patients at baseline and every 6–12 months in the follow-up period.

Table. Baseline Characteristics of the Patients With Pulmonary Hypertension

	Historical control group	IIT group	P value
n	8	13	
Age (years)	52±18	42±8	NS
M/F	0/8	1/12	NS
Vasodilator therapy			
Beraprost	3	9	NS
Epoprostenol	3	2	NS
Bosentan	2	5	NS
PDE-5 inhibitors	0	6	<0.05
Observation period (days)	914±456	565±431	NS
Hemodynamics			
Mean PAP	43.5±16.3	39.5±9.2	NS
PVR	1,131±898	700±434	NS
Blood test			
BNP (pg/ml)	303±290	201±398	NS
CRP (mg/dl)	0.65±0.74	0.20±0.22	NS
WHO functional class			NS
I	0	2	
II	4	6	
III	3	5	
IV	1	0	
6-min walking distance	358±27	442±54	<0.05

Values are mean±SD.
IIT, intensive immunosuppressive therapy; NS, not significant; PDE-5 inhibitors, phosphodiesterase type 5 inhibitors (sildenafil and tadalafil); PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; BNP, B-type natriuretic peptide; CRP, C-reactive protein; WHO, World Health Organization; IV, intravenous.

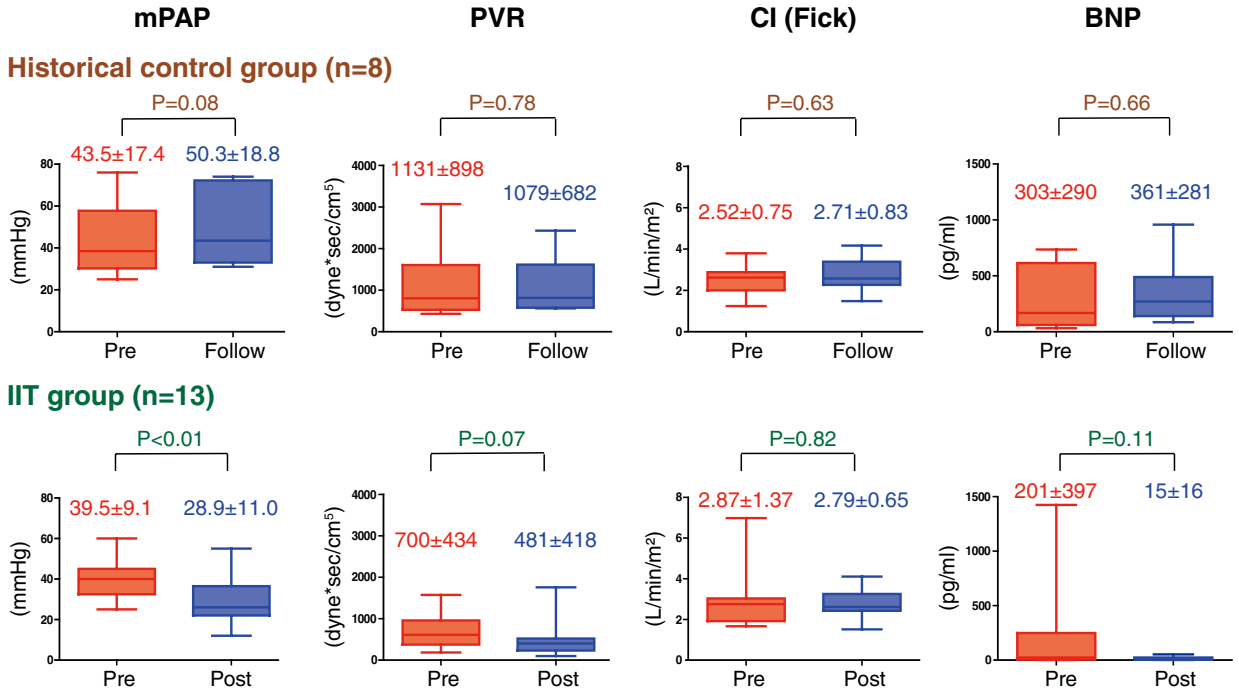

Figure 3. Effects of intensive immunosuppressive therapy (IIT) on pulmonary hemodynamics in patients with connective tissue disease-associated pulmonary arterial hypertension. In the historical control group, mPAP and PVR remained unchanged during the follow-up period. In contrast, the IIT therapy significantly reduced the mPAP and tended to decrease PVR. CI was well maintained in both groups. There were no statistically significant changes in plasma levels of B-type natriuretic peptide (BNP). CI, cardiac index; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

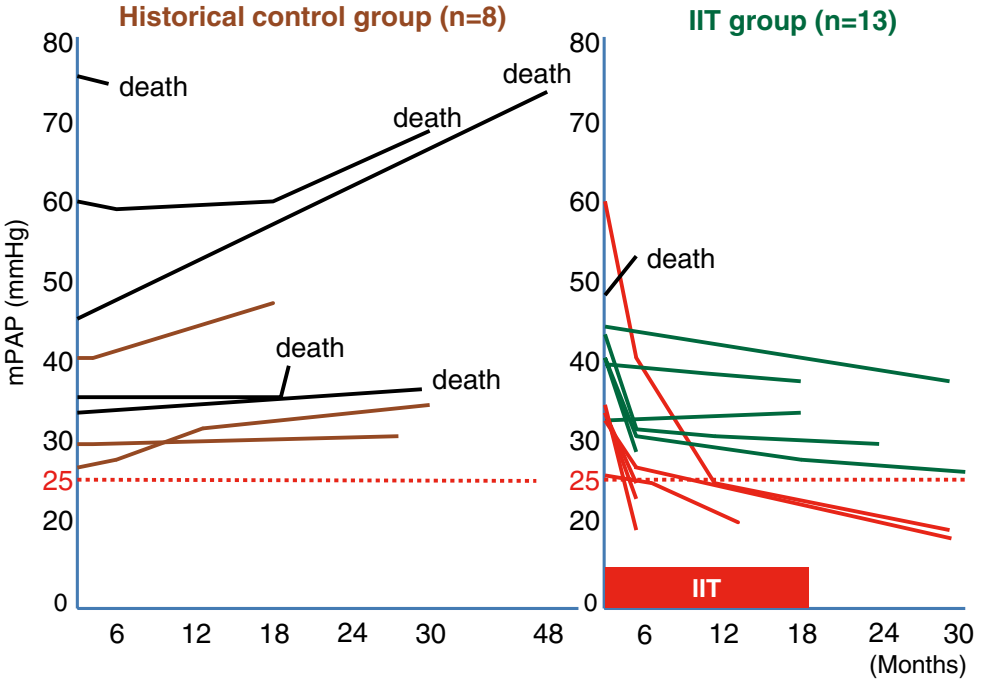

Figure 4. Effects of intensive immunosuppressive therapy (IIT) on serial change in the mean pulmonary artery pressure (mPAP) in patients with connective tissue disease-associated pulmonary arterial hypertension. mPAP remained unchanged or progressively deteriorated in the historical control group, whereas it progressively improved in the IIT group.

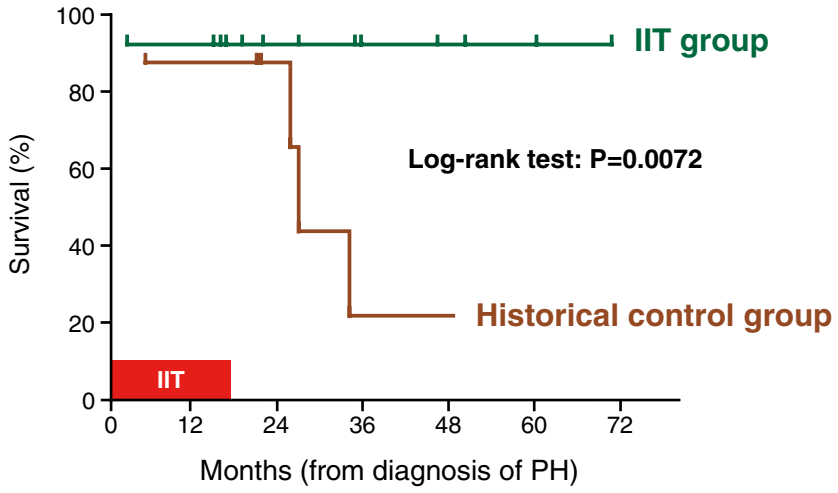

Figure 5. Kaplan-Meier curves of the immunosuppressive therapy (IIT) and control groups. The survival curve from the diagnosis of connective tissue disease-associated pulmonary arterial hypertension (CPAH) was significantly better in the IIT group than in the historical control group: 5 of 8 patients in the historical control group and 1 of 13 patients in the IIT group died of cardiovascular causes. No lung transplantation was performed in those CPAH patients.

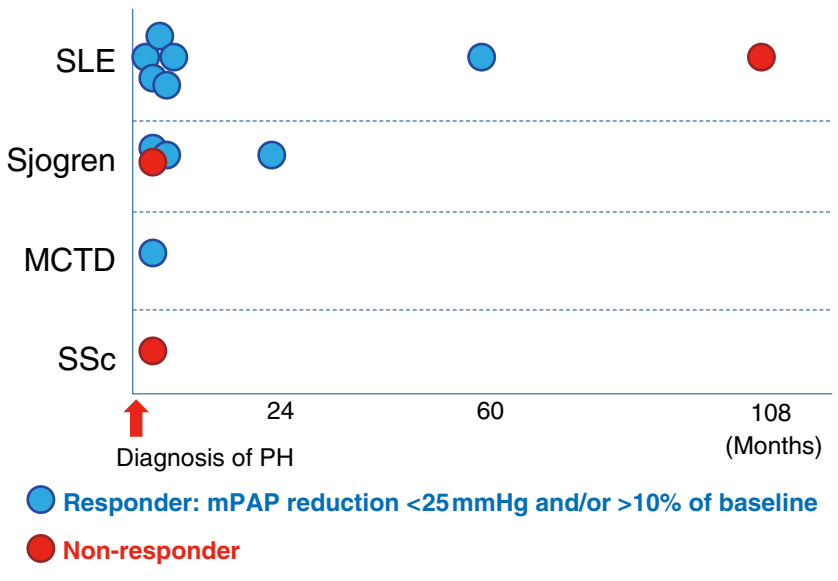

Figure 6. Time elapsed from diagnosis of CPAH to first intensive immunosuppressive therapy and response. The effects of treatment are most evident when it was started immediately after diagnosis of the disorder. CPAH, connective tissue disease-associated pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure.

3 months followed by once every 1–3 months) and glucocorticosteroids (1 mg·kg^{-1}·day^{-1} PO in the first month, followed by gradual tapering afterward by 5–10 mg/day every 2–4 weeks to a maintenance dose of 5–10 mg/day) (Figure 2). Right-heart catheterization was performed in all patients at baseline and every 6–12 months during the follow-up period (Figure 2). Hemodynamic responders were defined as mPAP reduction <25 mmHg or >10% reduction of baseline value.

Vasodilator Therapy for CPAH

We usually start oral prostacyclin (beraprost) at a starting dose of 60 μg/day and increase the dose in a stepwise manner up to 240 μg/day, if tolerated.[16] In daily practice, we usually start intravenous prostacyclin (epoprostenol) therapy during hospitalization at a starting dose of 0.5–1 ng·kg^{-1}·min^{-1}.[16] Thereafter, the dose of epoprostenol is carefully increased in a stepwise manner on the basis of symptoms and side-effects of the drug.[16] Similarly, we usually start bosentan at 31.25 mg/day combined with dobutamine and/or milrinone for PH patients with heart failure and 62.5 mg/day for those without heart failure, and then carefully increase the dose in a stepwise manner every week.[16] Regarding sildenafil, we usually start at 30 mg/day and increase the dose up to 60 mg/day if tolerated.[16] Also, we usually start at 20 mg/day of tadalafil and increase the dose up to 40 mg/day. In the present study, we treated the CPAH patients with prostacyclin, bosentan, sildenafil, and tadalafil as monotherapy or in combination (Table).[16]

Statistical Analysis

Results are expressed as the mean±SD. Paired t-test was used for comparison of continuous variables and Fisher's exact test for categorical variables. Survival from all-cause/cardiovascular death or lung transplantation was estimated by Kaplan–Meier method and differences between the curves were examined for significance using the log-rank test. Statistical analyses were performed using GraphPad Prism 5.0E (GraphPad Software Inc, La Jolla, CA, USA). P values <0.05 were considered to be statistically significant.

Results

Clinical Characteristics of Patients With CPAH

The clinical characteristics of the CPAH patients in the historical control and IIT groups are shown in Table. There were no significant differences in baseline characteristics between the 2 groups except for the use of phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil and tadalafil) and 6-min walking distance (Table).

Effects of IIT on Pulmonary Hemodynamics

Although mPAP and PVR remained unchanged in the historical control group, IIT significantly reduced mPAP and tended to decrease PVR by the end of follow-up period (Figure 3). The CI was well maintained in both groups by the end of the follow-up (Figure 3). In the historical control group, mPAP remained unchanged or progressively deteriorated with subsequent death of 5 of the 8 patients (Figure 4). In contrast, in the IIT group, mPAP progressively improved in 10 of the 13 patients and in 6 of them the mPAP normalized (Figure 4). One patient in the IIT group died shortly after the initiation of the therapy (Figure 4).

Effects of IIT on Long-Term Survival

The IIT group showed a markedly improved long-term survival as compared with the historical control group (Figure 5). There were no cases of PH-unrelated death or lung transplantation in the present study.

Elapsed Time From Diagnosis to First IIT and Response to IIT

In most of the CPAH patients, the first round of intensive cyclophosphamide therapy was started 2–4 months after the diagnosis. However, the initiation of IIT therapy was delayed in 1 patient with Sjögren syndrome (at 24 months) and 2 patients with SLE (at 60 and 108 months) after the diagnosis of CPAH (Figure 6). In the present study, 3 of the 13 patients with CPAH were diagnosed as non-responders: 1 SLE, 1 Sjögren, and 1 SSc patient (Figure 6). Only 2 of the 13 patients had mild liver dysfunction as a side-effect of cyclophosphamide.

Discussion

The novel findings of the present study are that IIT combined with cyclophosphamide and glucocorticosteroids, as well as conventional vasodilator therapy, markedly improved the pulmonary hemodynamics and long-term prognosis of patients with CPAH. The effects of the IIT were evident when it was started immediately after the diagnosis of CPAH. The results suggest that IIT with conventional vasodilator therapy in the early phase of CPAH is a promising therapeutic strategy for this fatal disorder.

Current Therapy for CPAH

The current treatment for CPAH follows the same algorithm as for IPAH.[17] The recommendation is based on the fact that most of the major trials for PAH therapy have included CPAH patients, in whom intravenous epoprostenol therapy, bosentan, sitaxsentan, sildenafil, and subcutaneous treprostinil exerted favorable effects.[17] Also, immunosuppressive therapy combined with cyclophosphamide and glucocorticosteroids showed clinical improvement in patients with SLE and MCTD-associated PAH.[14,15] However, none of the previous trials was able to normalize pulmonary hemodynamics in CPAH patients.

In the present study, we were able to normalize pulmonary hemodynamics in 6 of 13 patients and to improve the long-term prognosis of those patients. Further, it seems that the patients with a better response to the IIT in the initial right-heart catheterization had a better response in the chronic phase (Figure 4). The protocol of the present immunosuppressive therapy is original in 2 ways: we started the therapy combined with conventional vasodilator therapy in the early phase of the disorder, regardless of immunological activity, and we used cyclophosphamide more frequently than in previous studies (Figure 2).[14,15]

Pulmonary Hemodynamics in CPAH Patients

CPAH is one of the most malignant types of PH and there is only one case report in which pulmonary arterial pressure was normalized with conventional therapy.[30] Indeed, in the present study, mPAP remained unchanged or progressively deteriorated in the historical control group treated with only pulmonary vasodilators and glucocorticosteroids, and it improved only when IIT was added. Thus, we consider that the combination of the immunosuppressive therapy with cyclophosphamide and glucocorticosteroids and conventional pulmonary vasodilator therapy is crucial for dilating the pulmonary arteries and ameliorating the pulmonary arteriopathy in CPAH.

The present immunosuppressive therapy was ineffective in 1 patient with SSc-associated PAH, a consistent finding in previous studies.[6,31,32] However, it has been recently reported that combination therapy with imatinib and cyclophosphamide was well tolerated without major side-effects in patients with SSc-associated interstitial lung disease.[33] The effect of this combined immunosuppressive therapy for SSc-associated PAH remains to be examined in a future study.

Prognosis of CPAH Patients

It has been reported that patients with CPAH have a poorer prognosis than those with IPAH,[34,35] and that the presence of PAH is a significant prognostic factor in CTDs such as SLE, MCTD and SSc.[6,36,37] To the best of our knowledge, the present study is the first to demonstrate that IIT can improve not only the pulmonary hemodynamics but also long-term prognosis of patients with CPAH.

Study Limitations

Several limitations of the present study should be mentioned. First, this was an observational cohort study from a single center, so our finding regarding the effectiveness of the combination of IIT and conventional pulmonary vasodilator therapy remains to be confirmed in a large multicenter study. Second, the present CPAH patients were treated individually, not in a randomized manner, based on pulmonary hemodynamics and comorbidities. However, it is difficult to perform a randomized study for patients with a rare and fatal disorder. Third, the present study results suggest that SSc may be resistant even to the novel combination therapy. Effective therapy for SSc-associated PAH remains to be developed. Fourth, the historical control group tended to have less chance of receiving pulmonary vasodilators because of the availability of medicines, which may have affected their pulmonary hemodynamics and prognosis. Further, because there was a statistically significant difference in treatment with PDE-5 inhibitors (ie, sildenafil and tadalafil), it remains to be examined in future studies whether PDE-5 inhibitors with or without the immunosuppressive therapy can normalize pulmonary arterial pressure and improve the prognosis. Fifth, it is suggested that the prognosis of PAH differs among the underlying CTDs, such as SLE, SSc, and MCTD, which may have influenced the results

of long-term prognosis in this study. Further, we did not evaluate the activity of each CTD for 2 major reasons: a reliable activity scoring system is not available for some CTDs, and there is substantial variation in the activity of a given CTD. Therefore, we were unable to examine the correlation between CTD activity and the effects of the immunosuppressive therapy.

Conclusions

In the present study, we were able to demonstrate that the combination of the IIT with cyclophosphamide, glucocorticosteroids and conventional pulmonary vasodilator therapy markedly improved the pulmonary hemodynamics and long-term prognosis of patients with CPAH, especially in the early phase of CPAH.

Acknowledgments

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