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Clinical Outcomes and Treatment Options in Patients With Pulmonary Hypertension Who Received Pulmonary Hypertension-Specific Drugs

— Single-Center Case Series —

Chiaki Kamiya, MD; Keiichi Odagiri, MD, PhD; Akio Hakamata, MD, PhD; Naoki Inui, MD, PhD; Hiroshi Watanabe, MD, PhD

Background: Recent progress in the development of pulmonary hypertension (PH)-specific pharmaceutical agents has improved mortality and morbidity remarkably. Today, these PH-specific drugs have become a standard treatment for PH.

Methods and Results: We herein summarize the treatment options and longitudinal clinical outcomes of 21 patients with PH who received PH-specific drugs at the present institution. Sixteen patients began treatment with a single PH-specific drug; 9 of them needed additional PH-specific drugs, but the other 7 were still taking the same drug at the last follow-up. Five patients began treatment with a combination of 2 or 3 PH-specific drugs, and their drugs were not discontinued. Most patients (17/21) were taking a phosphodiesterase type 5 (PDE5) inhibitor at the last follow-up. During the 6.5±4.4 years' follow-up, 5 patients died, but only 1 death was related to PH. At 5 and 10 years, the estimated PH-related death-free and lung transplantation-free survival rate was 100% (95% CI: 100–100%) and 87.5% (95% CI: 38.7–98.1%), respectively. The estimated 5- and 10-year estimated overall survival rates were 77.9% (95% CI: 50.8–91.3%) and 68.2% (95% CI: 37.4–86.2%), respectively.

Conclusions: PDE5 inhibitors played a central role in the treatment options. The long-term prognosis of PH was favorable at the present institution.

Key Words: Drug therapy; Efficacy; Mortality; Pulmonary hypertension; Safety

Pulmonary hypertension (PH) is a progressive lethal disease, and effective treatment has long been sought. In the 1980s, limited pharmaceutical agents were available for treatment of PH, and the 5-year survival rate was ≤40%.[1,2] In 1995, epoprostenol, the first PH-specific agent, was approved in the USA, and the prognosis of PH was improved; the effectiveness, however, was not entirely satisfactory because the 3-year mortality rate was approximately 35%.[3] Recent improvements in the understanding of the molecular biology underlying the onset and disease progression of PH have led to more detailed knowledge of pathways involving pharmacological targets, such as the prostacyclin pathway, endothelin pathway, and nitric oxide–cyclic guanosine monophosphate pathway;[4,5] as a result, several PH-specific pharmaceutical agents have been developed. With the development of these PH-specific drugs in the 21st century, the management of PH was established and the disease mortality rate was reduced.[6]

We have used phosphodiesterase type 5 (PDE5) inhibitors, especially sildenafil, for patients with PH since 2002. This represents 1 of the longest histories of sildenafil use for PH in Japan. Sufficient knowledge and medical experience regarding the safety and efficacy of PDE5 inhibitors were not available before we began using sildenafil. The clinical evidence of PH-specific drugs, however, has since become established, and these drugs are now the standard first-line treatment for PH, especially pulmonary arterial hypertension (PAH).[7–10] In the present retrospective observational case series, we describe the treatment options in 21 patients with PH who received PH-specific drugs, and the longitudinal clinical outcomes at the present institution.

Methods

Study Design

We conducted a single-center, retrospective observational study to summarize the treatment options for patients with PH who received PH-specific drugs and to analyze their long-term prognosis at Hamamatsu University Hospital. We enrolled patients with PH who had received PH-specific drugs in this study. The diagnosis of PH was based on a detailed medical history, physical examination, and

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Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan
Mailing address: Keiichi Odagiri, MD, PhD, Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan. E-mail: kodagiri@hama-med.ac.jp

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Table 1. Baseline Subject Demographic and Clinical Characteristics

Patient ID no.	Age (years)	Year of PH diagnosis	Gender	Classification of PH	Right heart catheterization				
					mPAP (mmHg)	mRAP (mmHg)	PCWP (mmHg)	CO (L/min)	PVR (dyn·s·cm^{-5})
1	54.6	2002	F	CTD-PAH (SLE)	NA	NA	NA	NA	NA
2	45.8	2002	F	CTD-PAH (SLE)	54	NA	12	2.53	1,326.7
3	48.4	2003	M	IPAH	NA	NA	NA	NA	NA
4	33.1	2005	F	CTD-PAH (SLE)	48	5	5	3.36	1,022.8
5	52.3	2005	F	IPAH	39	NA	NA	NA	NA
6	33.2	2006	F	CTD-PAH (SLE)	42	5	8	4.73	574.5
7	68.7	2007	F	CTD-PAH (SLE)	NA	NA	NA	NA	NA
8	50.5	2007	F	PAH-CHD (ASD)	29	4	13	4.18	305.9
9	56.1	2007	M	CTD-PAH (DM)	36	6	17	3.61	420.6
10	13.8	2008	F	CTD-PAH (SSc)	53	NA	7	2.41	1,525.4
11	43.7	2009	M	IPAH	39	3	6	3.48	757.9
12	65.9	2009	F	IPAH	50	NA	6	3	1,044
13	43.2	2010	F	PAH-CHD (PDA)	NA	NA	NA	NA	NA
14	55.3	2010	F	CTEPH	NA	NA	NA	NA	NA
15	16.2	2013	F	IPAH	84	10	13	7.75	732.2
16	70.6	2013	F	CTEPH	38	7	18	3.57	447.7
17	32.2	2014	F	CTD-PAH (SLE)	43	10	8	3.1	902.3
18	34.4	2014	F	CTD-PAH (SLE)	54	7	4	3.81	1,048.8
19	74.9	2014	F	PH due to lung diseases	35	5	9	3.68	564.7
20	77.1	2015	M	CTEPH	40	3	5	3.5	799.2
21	71.3	2015	F	CTEPH	49	NA	13	2.5	1,150.8

ASD, atrial septal defect; CTD-PAH, PAH associated with connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; CO, cardiac output; DM, dermatomyositis; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; mRAP, mean right arterial pressure; NA, not applicable; PAH, pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart disease; PCWP, pulmonary capillary wedge pressure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SSc, systemic sclerosis; SLE, systemic lupus erythematosus.

standardized diagnostic approach for PH.[11] We retrospectively reviewed the medical records to obtain demographic and clinical data, such as the classification of PH, right heart catheterization (RHC) data, clinical course, and additional PH-specific drugs.

Follow-up and Endpoints

The patients were followed from the time of diagnosis until 31 August 2016. The primary endpoint of this analysis was the incidence of the composite of PH-related death (sudden cardiac death and death caused by heart failure) and lung transplantation; the secondary endpoint was all-cause mortality. In addition, information regarding first-line and additional PH-specific drugs was summarized to characterize the treatment options. Study participation was considered to be complete for any individual patient at the time of occurrence of the endpoints, loss to follow-up, or completion of follow-up until 31 August 2016. The exposure time was calculated as the time from the treatment starting point to either the incidence of an endpoint or the date of the last study visit, whichever came first.

Statistical Analysis

Data are expressed as mean±SD unless otherwise specified. The probabilities of PH-related death, survival after lung transplantation, and all-cause mortality were estimated using the Kaplan–Meier method. We divided the study patients into 2 groups according to treatment strategy: monotherapy and combination therapy. Differences in survival between the 2 groups were assessed using the log-rank test and a Cox proportional hazard model. $P<0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, USA).

Ethics Statement

The study protocol complied with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects and was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval no. E16-222). The committee waived the requirement to obtain informed consent because the study was a retrospective observational analysis. Use of the "opt-out" approach to consent was approved. A written explanation of the use of data from clinical investigations was provided on the university websites. Patients did not provide written informed consent but were allowed to decline participation.

Results

Baseline Patient Characteristics

In total, 21 patients with PH (4 men and 17 women; mean age, 49.6±18.2 years; age range, 53–77 years) were enrolled in this study. Patients who received no PH-specific drugs (i.e., PDE5 inhibitors, endothelin receptor antagonists, prostanoids, or soluble guanylate cyclase stimulators) were not included. The 21 patients consisted of 16 with PAH (5 with idiopathic PAH, 9 with connective tissue disease-associated PAH [CTD-PAH], and 2 with congenital heart

Table 2. Follow-up Data

Patient ID no.	Status	Follow-up period (years)	Year of starting initial drugs	Initial PH-specific drugs	Last visit PH-specific drugs	Cause of death
1	Alive	13.9	2002	Oral PG	PDE5i, oral PG	
2	Alive	14.5	2001	Oral PG	PDE5i, oral PG	
3	Alive	13.5	2003	Oral PG	PDE5i, oral PG	
4	Alive	10.7	2005	PDE5i	PDE5i, ERA	
5	Dead	7.8	2005	PDE5i	PDE5i, oral PG	Right heart failure
6	Alive	10.3	2006	PDE5i, oral PG	PDE5i, ERA, oral PG	
7	Dead	4.7	2011	Oral PG	Oral PG	Septic shock
8	Alive	9.2	2007	PDE5i	PDE5i, ERA	
9	Dead	2.8	2007	ERA, oral PG	PDE5i, ERA, oral PG	Lung cancer
10	Alive	8	2008	PDE5i	PDE5i, ERA	
11	Alive	7.1	2010	PDE5i	PDE5i	
12	Alive	7.1	2009	PDE5i	PDE5i, ERA	
13	Alive	6.3	2009	PDE5i, oral PG	PDE5i, oral PG	
14	Alive	5.7	2011	Oral PG	Oral PG	
15	Alive	3.1	2013	ERA, PDE5i, oral PG	PDE5i, ERA, i.v. PG	
16	Alive	2.7	2014	PDE5i	PDE5i	
17	Alive	2.1	2014	PDE5i	PDE5i, ERA, oral PG	
18	Alive	2.5	2014	PDE5i, ERA	PDE5i, ERA	
19	Dead	0.63	2014	PDE5i	PDE5i	Idiopathic interstitial pneumonia
20	Alive	1.6	2015	sGCs	sGCs	
21	Dead	0.12	2015	sGCs	sGCs	Septic shock

ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase type 5 inhibitors; PG, prostaglandin; sGCs, soluble guanylate cyclase stimulator.

disease-associated PAH [CHD-PAH]), 1 with lung disease-associated PH and 4 with chronic thromboembolic PH (CTEPH). Detailed demographic and clinical subject characteristics are listed in **Table 1**.

Treatment Options

As shown in **Table 2**, 16 patients were started on monotherapy. During the study period, 9 of these patients needed additional PH-specific drugs (i.e., sequential combination therapy), but the other 7 patients were on the same monotherapy at the last follow-up. Five patients were started on dual or triple initial combination therapy, and their PH-specific drugs were not discontinued. Most patients (13/21; 61.9%) were started on a PDE5 inhibitor as first-line therapy. Nine patients were started on an oral prostanoid as the first-line therapy, and the oral prostanoid was transitioned to an i.v. prostanoid in 1 patient (patient 15). Two patients who were started on an endothelin receptor antagonist as first-line therapy received dual or triple initial combination therapy (patients 9,15). Two patients who were started on soluble guanylate cyclase stimulators had CTEPH. At the last registered visit, no patients had discontinued their PH-specific pharmacotherapy, and most of the patients (17/21; 81.0%) were receiving a PDE5 inhibitor.

Hemodynamic Parameters

The medical records lacked information on RHC data in 5 patients; thus, we analyzed the hemodynamic parameters in 16 patients. **Table 1** lists the detailed RHC data. According to the hemodynamic data, mean pulmonary arterial pressure (mPAP) was 45.8±12.6 mmHg (7/16 patients, i.e., 43.8% had mPAP >45 mmHg), mean right atrial pressure (mRAP) was 5.9±2.4 mmHg, mean pulmonary capillary wedge pressure (mPCWP) was 9.6±4.5 mmHg, and mean cardiac output (CO) was 3.7±1.3 L/min. The mean calculated pulmonary vascular resistance (PVR) was 841.6±349.2 dyn·s·cm^{-5}.

The mPAP and PVR were lower in the monotherapy group than in the combination therapy group (mPAP: 40.2±5.3 vs. 48.4±14.3 mmHg, P=0.242; PVR: 744.1±268.7 vs. 890.3±386.9 dyn·s·cm^{-5}, P=0.465, respectively), but these differences did not reach statistical significance. mRAP, mPCWP, and CO were similar between the monotherapy group and combination therapy group (mRAP: 4.5±1.9 vs. 6.7±2.4 mmHg, P=0.154; mPCWP: 10.2±5.3 vs. 9.3±4.2 mmHg, P=0.727; and CO: 3.34±0.5 vs. 3.8±1.5 L/min, P=0.497, respectively).

Mortality

We followed the patients for 6.5±4.4 years (range, 0.12–14.6 years, 135.5 person-years). During the follow-up period, 5 patients died, but only 1 death was related to PH (right heart failure due to PH, patient 10). No patients underwent lung transplantation, but 1 patient had been placed on the lung transplant waiting list (patient 15). As shown in **Table 2**, the other 4 deaths were related to comorbidities: respiratory failure caused by rapid deterioration in a patient with idiopathic interstitial pneumonia (patient 19), septic shock in 2 patients (patients 7,21), and lung cancer in 1 patient (patient 9).

The overall incidence of the composite primary endpoint was 7.3 per 1,000 person-years. At 5 and 10 years, the estimated PH-related death-free and lung transplantation-free survival rate was 100% (95% CI: 100–100%) and 87.5% (95% CI: 38.7–98.1%), respectively (**Figure 1**). When the patients were divided into 2 groups according to treatment strategy, the estimated 5-year PH-related death-free and

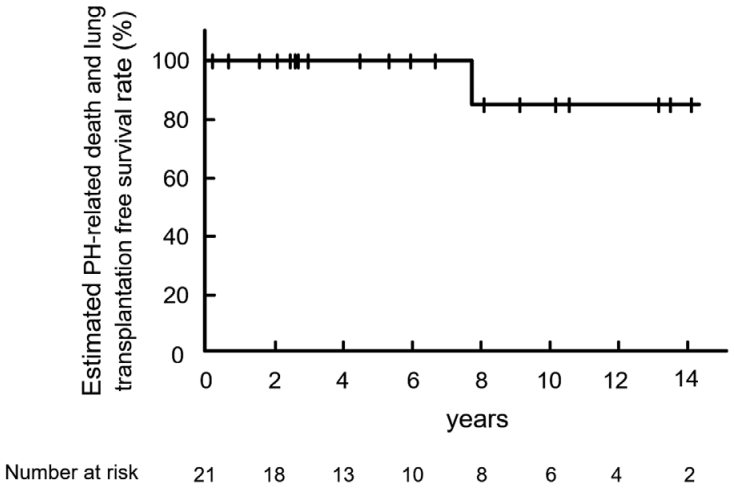

Figure 1. Kaplan–Meier curve for the composite primary endpoint of pulmonary hypertension-related death-free and lung transplantation-free survival.

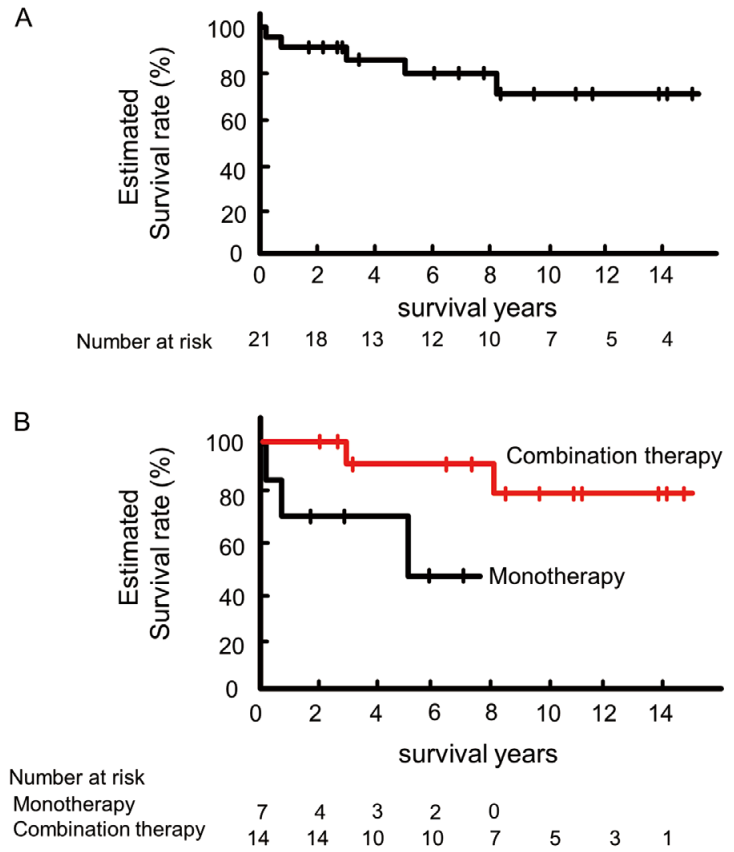

Figure 2. Kaplan–Meier curves for the secondary endpoint of all-cause death in (**A**) the overall study patients; and (**B**) according to treatment strategy.

lung transplantation-free survival rate was also 100% (95% CI: 100–100%) in both the combination therapy group and the monotherapy group. The estimated 10-year PH-related death-free and lung transplantation-free survival rate in the combination therapy group was 87.5% (95% CI: 38.7–98.1%), while that in the monotherapy group was not calculated. The unadjusted hazard ratio for the primary endpoint with combination therapy vs. monotherapy was not calculated because the number of events was too small.

The overall incidence of the secondary endpoint was 36.9 per 1,000 person-years. At 5 and 10 years, the estimated survival rate was 77.9% (95% CI: 50.8–91.3%) and 68.2% (95% CI: 37.4–86.2%), respectively (**Figure 2A**). The estimated 5-year survival rate was higher in the combination therapy group than in the monotherapy group (91.7%, 95% CI: 53.9–98.8% vs. 47.6%, 95% CI: 7.5–80.8%, respec-

tively; P=0.03; **Figure 2B**). Comparison of the estimated 10-year survival rate was not applicable because the rate in the monotherapy group was not calculated. The unadjusted hazard ratio for the secondary endpoint with combination therapy vs. monotherapy was 0.12 (95% CI: 0.012–1.14; P=0.064).

Because treatment options differed between the PH etiologies, we also evaluated the efficacy of the PH-specific drugs in PAH patients and CTEPH patients. In IPAH and CTD-PAH, the estimated PH-related death-free and lung transplantation-free survival rate was 100% (95% CI: 100–100%) and 66.7% (95% CI: 5.4–94.6%), respectively, at 5 and 10 years, and the estimated survival rate was 100% (95% CI: 100–100%) and 66.7% (95% CI: 5.4–94.6%), respectively, at 5 and 10 years. In CHD-PAH patients, the estimated PH-related death-free and lung transplantation-free survival rate was 100% (95% CI: 100–100%) and 100% (95% CI: 100–100%), respectively, at 5 and 10 years, and the estimated survival rate was 100% (95% CI: 100–100%) and 100% (95% CI: 100–100%), respectively, at 5 and 10 years. In CTEPH patients, the estimated PH-related death-free and lung transplantation-free survival rate was 100% (95% CI: 100–100%) at 5 years, and the estimated survival rates was 75% (95% CI: 12.8–96.1%) at 5 years. The 10-year mortality rate could not be calculated in CTEPH patients. These results indicate that the prognosis of PAH patients and CTEPH patients was generally good.

Discussion

We have herein reported the treatment options and outcomes in 21 patients with PH who received PH-specific pharmacotherapy. The 3 main findings of the current investigation are as follows. First, PDE5 inhibitors played a central role in the treatment options. In total, 66.7% (14 of 21) of the study patients received dual or triple combination therapy (5 received initial combination therapy and 9 received sequential combination therapy), and all of them were receiving a PDE5 inhibitor at the last registered visit. Second, the PH-related mortality rate was low, and the estimated 5- and 10-year PH-related death-free and lung transplantation-free survival rate was 100% (95% CI: 100–100%) and 87.5% (95% CI: 38.7–98.1%), respectively. And third, no advantage of combination therapy over monotherapy was observed.

Japanese physicians often prescribed the oral prostanoid beraprost as a first-line drug through the first half of the 2000s. Beraprost was developed as the first oral prostanoid and has been used in Japan since 1999. Although small retrospective observational studies have suggested that beraprost improves hemodynamic parameters, symptoms, and mortality,[12,13] the efficacy of beraprost is unsatisfactory.[14,15] At the same time, the i.v. prostanoid epoprostenol was also approved in Japan. Epoprostenol was shown to improve survival, symptoms, and hemodynamics in patients with moderate–severe PAH,[16,17] but it also had serious adverse effects, including catheter-related infection, and its handling is uncomfortable and difficult for patients. Thus, beraprost was often used in patients with mild PH in Japan despite its lower efficacy.

Approximately two-thirds of patients received a PDE5 inhibitor as another first-line drug. In 2001, Japanese physicians had no options for treatment of PH except for oral or i.v. prostanoids and calcium blockers. Therefore, we performed a clinical trial to evaluate the efficacy and safety of sildenafil in patients with PH, and we first reported that oral sildenafil improved hemodynamic parameters without serious adverse effects.[18] Since the second half of the 2000s, the efficacy and safety of treatment have improved as sildenafil monotherapy began to be provided.[19,20] Based on our experience and such evidence, we often use a PDE5 inhibitor as a first-line drug in patients with PAH.

Although the prognosis of PH was improved by PH-specific drugs, patients often had an unsatisfactory clinical response to monotherapy. Accordingly, Japanese physicians often selected combination therapy based on their experience, and we also chose combination therapy in the early days of our clinical experience. All 14 patients who received combination therapy in the present study (all of them had PAH) were taking a PDE5 inhibitor. Notably, combination therapy with a focus on PDE5 inhibitors was the main treatment option. Although 2 patients died during the follow-up period (1 died of lung cancer [patient 9] and the other died of right heart failure [patient 5]), the long-term efficacy and safety of the combination therapy with a focus on PDE5 inhibitors was generally satisfactory.

The remaining 7 patients received monotherapy, and 4 of them had CTEPH. Two patients with CTEPH began riociguat monotherapy (patients 20,21) in accordance with the Japanese health insurance system. The other 2 patients with CTEPH received an off-label oral prostaglandin or a PDE5 inhibitor (patients 14,16), and they were still on the same monotherapy at the last follow-up, suggesting that these drugs had good efficacy, tolerability, and safety. Before the soluble guanylate cyclase stimulator riociguat was approved to treat CTEPH in Japan in 2015, no pharmaceutical treatment options were available for CTEPH except for anticoagulation; however, vasodilators including prostaglandins, PDE-5 inhibitors, and endothelin receptor antagonists were often used in an off-label manner because some clinical trials suggested that these drugs had beneficial effects in patients with CTEPH.[17,19–21] One patient with lung disease-associated PH also received the off-label PDE5 inhibitor sildenafil (patient 19). In spite of this patient's good tolerability of a PDE5 inhibitor, she died of acute exacerbation of interstitial lung disease. Although no evidence from large-scale randomized clinical trials has indicated the efficacy of PH-specific pharmacotherapy, some reports have suggested that sildenafil could be useful for treatment of PH in patients with interstitial lung disease.[22,23] The remaining 2 patients with PAH had good clinical response to monotherapy and did not require the addition of another PH-specific drug (patients 7,11). One of them was still alive at the end of follow-up (patient 11). The other survived for 4.7 years but eventually died of non-cardiac disease (patient 7).

Hemodynamic parameters have diagnostic value and can support treatment decisions for patients with PH. The recent European Society of Cardiology/European Respiratory Society guideline proposed that RAP and CO, which are associated with right ventricular function, are prognostic factors in patients with PAH.[7] Despite the lack of evidence supporting RHC-guided treatment decision making, physicians often performed RHC and decided on treatment strategy according to mPAP and PVR. In the current study, no statistically significant differences in the hemodynamic parameters were observed between monotherapy and combination therapy. This reflects the fact that we decided on treatment options based not only on hemodynamic parameters but also on other factors, such as the World

Health Organization (WHO) clinical classification of PH, WHO functional class, clinical evidence of pharmaceutical agents, and clinical response.

In the present decade, combination therapy has become mainstream in the treatment of PH. Although recent PH management guidelines have given combination therapy a "high-grade" recommendation,[7] whether combination therapy is superior to monotherapy remains unresolved. Recent meta-analyses have shown that combination therapy has limited superiority over monotherapy: that is, although combination therapy does not improve mortality, it increases exercise capacity, reduces symptoms, and slows clinical worsening.[24–26] In addition, recent clinical trials have shown that even initial combination therapy had no survival benefit.[27,28] The current study showed no PH-related death-free or lung transplantation-free survival benefit with combination therapy vs. monotherapy. In contrast, the all-cause mortality rate was lower in combination therapy than monotherapy. We assumed several reasons for this result. First, as shown in **Table 2** and as described in the earlier section, 4 of 5 deaths were related to comorbidities, and 75% of the patients had received monotherapy. Second, 2 patients who had received monotherapy died after just a short treatment period (patients 19,21), suggesting that they were already in poor condition at the start of treatment. Taking these factors into consideration, we could not definitively conclude that combination therapy had a mortality benefit over monotherapy.

Study Limitations

The present study had several important limitations. First, we did not evaluate the relationship of exercise tolerability with treatment options and mortality. The 6-min walk test, which is the most commonly performed exercise tolerance test, was frequently used as an endpoint in several previous clinical trials,[19,29,30] but this test is not a reliable predictor of mortality in patients with PH.[31] Furthermore, cardiopulmonary exercise tests were not performed in most of the present patients at baseline. Thus, we did not assess the relationship of exercise tolerability with treatment options and mortality. Second, the present study lacked hemodynamic parameters at baseline. Because this study was designed retrospectively, missing data was a possibility. Most of these patients were diagnosed with PH on RHC at local city hospitals, and then they consulted the present university hospital for treatment. We usually did not re-perform RHC in such patients, but we clinically classified PH according to other findings, such as lung perfusion scintigraphy, echo cardiograph and laboratory data. Third, although the endpoint in recent studies of PH was mortality–morbidity composite outcomes,[28,32] we selected mortality and lung transplantation as endpoints because the present study was retrospective and medical records-based, and we could not accurately survey the morbidities. Finally, the present sample size was too small. PH, especially PAH and CTEPH, is a rare disease, thus, multicenter clinical trials or registries are necessary to evaluate disease prognosis and treatment efficacy. In the current study, we focused on the treatment options in 21 patients. Although we evaluated prognosis, the small number of patients could lead to a type II error.

Conclusions

We have herein described our historical treatment options for patients with PH. Most of the patients received a PDE5 inhibitor as monotherapy or in combination with other PH-specific drugs. No patients discontinued taking their PH-specific drugs throughout the follow-up period. In addition, the long-term prognosis of PH was favorable at the present institution. This suggests that treatment options centering on PDE5 inhibitors are safe and effective in patients with PH.

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Disclosures

The authors declare no conflict of interest.

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