Survival of Japanese Patients With Idiopathic/Heritable Pulmonary Arterial Hypertension

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Idiopathic/heritable pulmonary arterial hypertension has a poor prognosis despite the available therapeutic options. Survival of Japanese patients with this disease entity has not been reported in the multicenter setting. A retrospective study of 141 patients with idiopathic/heritable pulmonary arterial hypertension treated at 3 pulmonary hypertension centers in Japan from 1992 to 2012 investigated survival and determinants of survival. Mean survival time from treatment initiation was 14.7 ± 0.8 years (95% confidence interval, 13.1 to 16.3 years) and the 1-, 3-, 5-, and 10-year survival rates were 97.9%, 92.1%, 85.8%, and 69.5%, respectively. Patients showed significant improvement in exercise capacity and hemodynamics after treatment. Patients with 6-minute walk distance >372 m, mean pulmonary arterial pressure ≤46 mm Hg, and cardiac index >2.5 L/min/m^2 at follow-up had a significantly better prognosis. Most patients (99.2%) were receiving pulmonary hypertension-targeted drugs at follow-up. Use of endothelin receptor antagonists and intravenous epoprostenol were related to survival in the univariate analysis. Among the patients who were on intravenous epoprostenol therapy, those with endothelin receptor antagonists had a significantly better prognosis, whereas patients on warfarin had a significantly worse prognosis. In conclusion, survival of Japanese patients with idiopathic/heritable pulmonary arterial hypertension in this study was good, showing improvement in hemodynamic parameters supported by pulmonary hypertension-targeted drugs. **(Am J Cardiol 2017;119:1479−1484)**

Pulmonary arterial hypertension (PAH) is a progressive disease with increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure. The median survival of patients with idiopathic PAH was 2.8 years before PAH-targeted drugs became available.[1] Despite the progression in therapeutic options over the last 2 decades, overall survival continues to be unsatisfactory.[2−5] We previously conducted a retrospective study at a single center in Japan and reported improved survival of Japanese patients with idiopathic/heritable pulmonary arterial hypertension (I/HPAH),[6] whereby patients showed a significant improvement in hemodynamic parameters after treatment. To elucidate the survival of Japanese patients with I/HPAH on a larger scale, we conducted the first multicenter study on survival of Japanese patients with I/HPAH treated at 3 referral centers. This study also aimed to identify determinant factors for the survival of Japanese patients with I/HPAH, including hemodynamic changes and treatment regimen, and to confirm the improvement of hemodynamic parameters after treatment.

Methods

We conducted a retrospective chart review of patients with I/HPAH. Patients were treated at 3 pulmonary hypertension centers in Japan (National Hospital Organization Okayama Medical Center, Kyorin University Hospital, and Keio University Hospital) between November 1992 and August 2012. Diagnosis was performed using a standard approach for the diagnosis of PAH including physical examination and right heart catheterization.[7,8] The study protocol was approved by the institutional review board of each hospital. The follow-up period for analyses of survival data ended in December 2014. Patients who underwent lung transplantation were censored at the time of operation.

World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), plasma levels of brain natriuretic peptide (BNP), heart rate (HR), oxygen saturation (SpO_2), and hemodynamic parameters (mean pulmonary arterial pressure [mPAP], cardiac index [CI], mixed venous oxygen saturation [SvO_2], and PVR) were evaluated at baseline. Follow-up data were collected when patients achieved the best values for mPAP with preserved CI. Data regarding the treatment received by patients at follow-up were also collected.

Results are expressed as the mean ± standard deviation or median (minimum−maximum value), unless otherwise specified. The chi-square test was used to assess the

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Table 1
Clinical characteristics of patients

Variable	Baseline (n=141)	Follow-up (n=130)	*P* Value
Male	37 (26.2%)		
Age at diagnosis (years)	33.3±14.4		
Heritable pulmonary arterial hypertension	12 (8.5%)		
Time between baseline and follow-up, (years) median (min−max)		3.3 (0.2−14.4)	
WHO functional class (I/II/III/IV), n	1/18/91/31	10/83/34/3	<.001
6-minute walk distance (meters)	267.1±154.4	407.9±106.6	<.001
Brain natriuretic peptide (pg/mL)	326.2±348.1	74.1±172.2	<.001
Heart rate (bpm)	78.9±15.7	79.0±15.6	.385
Oxygen saturation (%)	95.2±4.2	96.1±3.5	.037
Mean pulmonary artery pressure (mm Hg)	60.3±14.7	37.6±11.4	<.001
Cardiac index (L/min/m^2)	2.1±0.9	3.2±1.1	<.001
Mixed venous oxygen saturation (%)	63.2±9.9	74.0±7.0	<.001
Pulmonary vascular resistance (dyn•s/cm^5)	1522.7±799.5	591.6±426.3	<.001

Values are expressed as mean ± SD unless otherwise specified. Follow-up data were evaluated in patients who underwent follow-up right heart catheterization.

significance of differences between categorical variables. Continuous variables at baseline and follow-up were compared using U tests.

Survival analyses were conducted using the Kaplan-Meier method. Survival time is expressed as mean ± standard error (95% confidence interval). Differences between survival curves were assessed using the log-rank test. A Cox proportional hazards model was used to determine the variables associated with increased mortality. Multivariate stepwise models were applied to candidate explanatory variables that remained significant ($p < 0.1$) in univariate analyses. The hazard ratio and 95% confidence interval were defined. Receiver operating characteristic curves were constructed to determine an optimal cutoff value for 6MWD, mPAP, CI, and HR. All analyses were undertaken with SAS Release 9.4 (SAS Institute, Cary, NC) and IBM SPSS 20 (IBM, Armonk, NY). Statistical significance was defined as $p < 0.05$.

Results

We conducted a retrospective chart review of 141 consecutive patients with I/HPAH. Patients' characteristics are listed in Table 1. Patients were predominantly women and in their 30s at diagnosis. At baseline, 86.5% of patients were in WHO functional class III or IV. Hemodynamic parameters were severely impaired, with mPAP >60 mm Hg and PVR >1,500 dyn•s/cm^5.

Data of 130 patients who underwent follow-up right heart catheterization were collected. At follow-up, WHO functional class, 6MWD, and BNP were significantly improved. HR was unchanged. SpO_2 and hemodynamic parameters (mPAP, CI, SvO_2, and PVR) were significantly improved over those at baseline ($p < 0.001$).

During the study period, 40 patients died and 7 underwent lung transplantation. Thirty-one patients (22.0%) died from right heart failure, 1 from alveolar hemorrhage, 1 from sudden death, 1 from acute renal failure, and 2 from adverse effects of drugs. In 4 patients, causes of death were unrelated to PAH (malignant lymphoma, esophageal carcinoma, gastrointestinal bleeding, and a traffic accident). The mortality rate related to PAH was 25.5% (Figure 1). Mean survival time from treatment initiation was 14.7 ± 0.8 years (95% confidence interval, 13.1 to

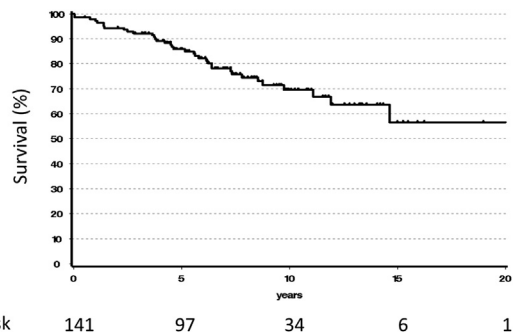

Figure 1. Overall survival. Survival representing mortality with disease-related death. Mean survival time from treatment initiation was 14.7 ± 0.8 years (95% confidence interval, 13.1 to 16.3 years), with 1-, 3-, 5-, and 10-year survival rates of 97.9%, 92.1%, 85.8%, and 69.5%, respectively.

Table 2
Cox proportional hazards analysis

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
Baseline			
Heat rate (bpm)	1.036	1.007−1.065	.014
At follow-up			
6-minute walk distance (meters)	0.994	0.988−0.9997	.040
Heart rate (bpm)	1.081	1.018−1.149	.012
Mean pulmonary artery pressure (mm Hg)	1.058	1.003−1.117	.038
Cardiac index (L/min/m^2)	0.102	0.028−0.382	<.001

p Values for each analysis are shown. Since cardiac index (CI) is related to mixed venous oxygen saturation and pulmonary vascular resistance, CI was chosen as a representative variable in multivariate analysis.