Life Sciences xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan

Aiko Ogawa [a], Kentaro Ejiri [b], Hiromi Matsubara [a,b,*]

[a] Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan
[b] Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

ARTICLE INFO

Article history:
Received 1 November 2013
Accepted 28 January 2014
Available online xxxx

Keywords:
Pulmonary hypertension
Peripheral vascular disease
Survival

ABSTRACT

Aims: Idiopathic/heritable pulmonary arterial hypertension (I/HPAH) carries a poor prognosis despite the therapeutic options available. Patient survival from Western countries has been reported, but data from Asia are scarce.

Main methods: We retrospectively reviewed 56 patients with I/HPAH treated at a single referral center in Japan. Survival analyses were conducted using the Kaplan–Meier method with the log-rank test. Variables associated with survival were determined using a Cox proportional hazard model.

Key findings: There were 41 women (73%) and the mean age at the diagnosis was 32 ± 17 years. Mean survival time from the diagnosis was 14.9 ± 0.8 years (95% CI, 13.4–16.4 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 98, 96, 96, 96 and 78%, respectively. In patients who underwent follow-up right-heart catheterization >3 months after initial catheterization, mean pulmonary arterial pressure (mPAP) was decreased significantly from 63 ± 15 to 35 ± 10 mm Hg with an improved cardiac index. Patients with high levels of brain natriuretic peptide (BNP) or low oxygen saturation at baseline showed worse survival. At follow-up, 98% of patients were on PAH-targeted drugs. WHO functional classes I and II, mPAP <42.5 mm Hg, cardiac index >2.5 L/min/m^2, BNP <52 pg/mL, and 6-min walk distance >347 m at follow-up were predictors of good prognosis in the univariate analysis.

Significance: The study revealed a long-term survival of Japanese patients with I/HPAH. Hemodynamic parameters improved significantly after treatment, which might be related to high prescription rates of PAH-targeted drugs. Multicenter studies are needed to reveal the prognostic factors for I/HPAH.

Introduction

Pulmonary arterial hypertension (PAH) has been reported to carry a poor prognosis despite the therapeutic options available. In the past two decades, several PAH-targeted drugs have become available. Each PAH-targeted drug has been reported to improve the prognosis or progression of PAH (Sitbon et al., 2002; McLaughlin et al., 2005; Rubin et al., 2011). A treatment algorithm that includes all of these treatment options is now shown in the guidelines for treatment of pulmonary hypertension (Galie et al., 2009). However, despite all the improvements in treatment, overall survival has been reported to be unsatisfactory (Humbert et al., 2010; Lee et al., 2012; Benza et al., 2012).

Although survival analyses of patients with PAH have been reported from Western countries, there is a shortage of data from Asia. A report from China demonstrated better survival of patients compared with previous reports despite the limited treatment options (Zhang et al., 2011). There is no report from Japan on the survival of patients treated with PAH-targeted drugs. To elucidate the survival of Japanese patients with idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension (I/HPAH), we conducted a retrospective study at a single center in Japan that deals with referrals for subjects with pulmonary hypertension.

Materials and methods

Patient selection

We undertook a retrospective review of medical charts on 56 consecutive patients with I/HPAH who received treatment at the National Hospital Organization Okayama Medical Center (Okayama, Japan) between October 1998 and December 2012. The study protocol was approved by the Institutional Review Board of our hospital. The diagnosis was based on detailed medical history, physical examination,

* Corresponding author at: Department of Clinical Science, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan. Tel.: +81 86 294 9911; fax: +81 86 294 9255.
E-mail address: matsubara.hiromi@gmail.com (H. Matsubara).

http://dx.doi.org/10.1016/j.lfs.2014.01.077

and standardized diagnostic approach for PAH (Galie et al., 2009). An "incident case" was defined as a patient who was referred to our hospital in <30 days after diagnostic catheterization, or the initial diagnostic catheterization was conducted at our hospital. All other cases were considered as "prevalent cases".

Study protocol

Physical examination, laboratory measurements, 6-min walk test, and right-heart catheterization were undertaken before treatment was initiated. Examinations were conducted repeatedly according to physical status. The follow-up period for analyses of survival data ended in March 2013. The end-point for survival analyses was disease-related death.

Clinical outcomes

Follow-up data were collected when patients achieved the best values for the mean pulmonary arterial pressure (mPAP) with preserved cardiac index. WHO functional class, 6-min walk distance (6MWD), plasma levels of brain natriuretic peptide (BNP) and uric acid, hemodynamic parameters [mPAP, right atrial pressure (RAP), pulmonary capillary wedge pressure, mixed venous oxygen saturation, cardiac index, and pulmonary vascular resistance (PVR)], heart rate, and oxygen saturation (SpO_2) were compared between baseline and follow-up. In patients who did not undergo follow-up catheterization, the last available data (other than hemodynamic data) was evaluated.

Treatments

We also evaluated the treatment received by patients. For survivors, treatment data were collected when the follow-up data were collected as described above. For non-survivors, treatment data were collected at the time when patients received maximum treatment. With regard to intravenous prostacyclin, all patients received epoprostenol except for one patient who received treprostinil. We evaluated the maximum doses of epoprostenol.

Statistical analyses

Results are expressed as the mean ± standard deviation, unless otherwise specified. Continuous variables were compared using *t*-tests. The χ^2 test was used to assess the significance of differences between categorical variables. WHO functional class is expressed as the median and number of patients in each class, and changes in WHO functional class were evaluated using the Wilcoxon signed rank test. Survival analyses were conducted using the Kaplan–Meier method. Differences between survival curves were assessed using the log-rank test. A Cox proportional hazard model was conducted to determine the variables associated with increased mortality. The hazard ratio (HR) and 95% confidence interval (CI) were defined. To confirm their predictive value, variables with $P < 0.1$ were tested in a multivariate model. Receiver operating characteristic (ROC) curves were constructed to determine an optimal cutoff value for 6MWD, BNP, mPAP, RAP, cardiac index, and SpO_2. All analyses were undertaken with IBM SPSS Statistics 20 (IBM, Armonk, NY, USA). Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics

There were 41 women (73%) and 15 men (27%) in the study. The mean age was 32 ± 17 years, with a range of 5–69 years at the diagnosis. There were 24 incident cases and 32 prevalent cases. Patients had been treated for 1.4 ± 2.3 years (0.0–8.1 years) at the beginning of the study. Time between the diagnosis and initiation of treatment was 0.4 ± 2.5 years (−0.1 to 18.9 years). Ninety-six percent of patients were initiated treatment <1 year after the diagnosis. At the time of diagnosis, 11 patients were in WHO functional class II, 39 in class III, and 6 in class IV. In 32 prevalent cases, one patient was in WHO functional class II, 20 in class III, and 11 in class IV at the time of diagnosis. By the time of referral, one patient improved from class IV to III, 16 patients remained in the same functional class, and 15 patients' conditions were deteriorated. Upon referral to our hospital, one patient was in WHO functional class II, 38 in class III, and 17 in class IV. Hemodynamic parameters measured at baseline were also evaluated: mPAP was 61 ± 15 mm Hg, cardiac index was 2.4 ± 0.9 L/min/m^2, and PVR was 1375 ± 611 dyn·s/cm^5.

HPAH and genetic testing

Eight families with 10 patients (18%) with a family history of pulmonary hypertension were included. Genetic analyses were conducted in 35 patients (including nine cases with HPAH). One patient with HPAH had not undergone genetic analyses. Four patients from two families (two patients from each pedigree included in this study) and two other patients with HPAH from two different families had a BMPR2 mutation. Of the remaining three patients with HPAH and 26 patients who seemed to be sporadic, no BMPR2 or ALK1 mutation was detected.

Treatment

All patients, except for one who responded to a calcium channel blocker, were receiving PAH-targeted drugs: prostacyclin analogs ($n = 52$, 93%), endothelin receptor antagonists ($n = 38$, 68%), and phosphodiesterase type 5 (PDE5) inhibitors ($n = 29$, 52%). Intravenous prostacyclin was highly prescribed ($n = 43$, 77%). Forty-two patients (75%) were treated with combination therapy. Thirteen patients (23%) were on warfarin and 53 patients (95%) were on oxygen therapy.

Overall survival

Seven patients died during the study period: one from alveolar hemorrhage and six from heart failure. Other than these patients, two patients were censored: one underwent lung transplantation and another died in a traffic accident, despite pulmonary hypertension being well controlled. Fig. 1A shows overall survival. Mean survival time from the diagnosis was 14.9 ± 0.8 years (95% CI, 13.4–16.4 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 98, 96, 96, 96 and 78%, respectively.

Baseline data of survivors and non-survivors

Baseline characteristics of survivors and non-survivors are shown in Table 1. WHO functional class, 6MWD, BNP, and RAP were significantly worse in non-survivors than in survivors. There was no significant difference in remaining baseline hemodynamic parameters between survivors and non-survivors. Treatment was also evaluated. There was no significant difference in prescription rate, except for PDE5 inhibitors and triple PAH-targeted therapy. Non-survivors received PDE5 inhibitors less frequently than survivors (14% vs. 57%, $P < 0.05$) and none of the non-survivors received triple therapy.

Follow-up data

At follow-up, WHO functional class, 6MWD, and BNP were significantly improved (Table 2). Forty-three patients underwent follow-up right-heart catheterization >3 months after initial catheterization at our hospital. An average of the time by the follow-up catheterization evaluated in this study was 3.7 ± 2.8 years (0.1–11.7 years).

Please cite this article as: Ogawa A, et al, Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan, Life Sci (2014), http://dx.doi.org/10.1016/j.lfs.2014.01.077

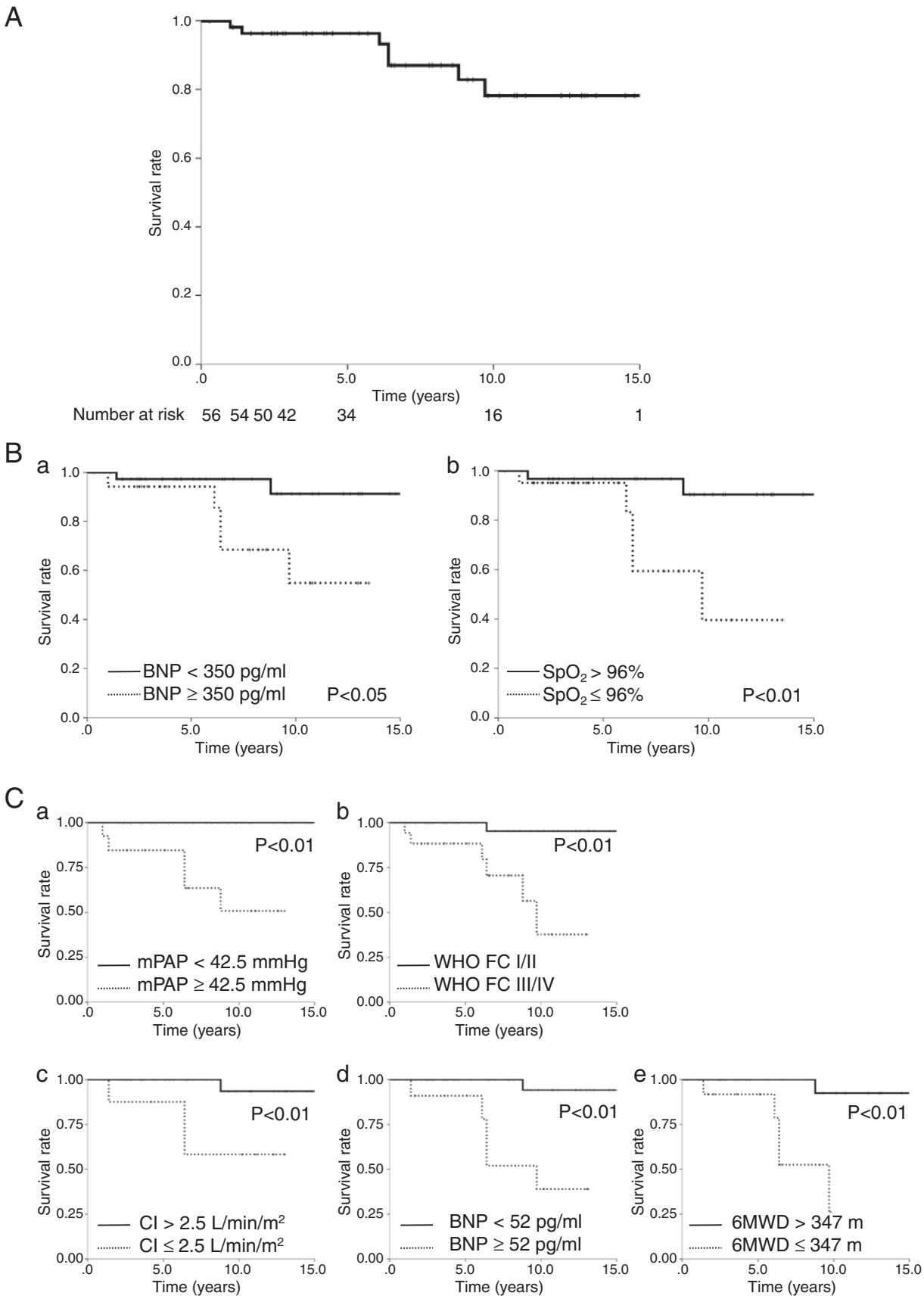

Fig. 1. (A) Mean survival time from the diagnosis was 14.9 ± 0.8 years (95% CI, 13.4–16.4 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 98, 96, 96, 96 and 78%, respectively. (B) Survival rate of patients stratified by parameters at baseline. a: Survival rate of patients with BNP ≥ 350 pg/mL at baseline was significantly worse than patients with BNP < 350 pg/mL ($P < 0.05$). b: Survival rate of patients with $SpO_2 \leq 96\%$ at baseline was significantly worse than patients with $SpO_2 > 96\%$ ($P < 0.01$). (C) Parameters significant in the univariate analysis (a: mPAP, b: WHO functional class (FC), c: cardiac index (CI), d: BNP, e: 6MWD) could be used to stratify the prognosis of patients ($P < 0.01$).

Please cite this article as: Ogawa A, et al, Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan, Life Sci (2014), http://dx.doi.org/10.1016/j.lfs.2014.01.077

Table 1
Clinical and hemodynamic data of survivors and non-survivors at baseline.

	Survivor ($n = 49$)	Non-survivor ($n = 7$)	P
Age, years	33 ± 18	25 ± 10	0.26
Male, *n* (%)	14 (29)	1 (14)	0.43
HPAH, *n* (%)	10 (20)	0 (0)	0.41
WHO functional class (I/II/III/IV)	3 (0/2/34/13)	4 (0/0/2/5)	<0.01
6MWD (m)	257 ± 166	103 ± 179	<0.05
BNP (pg/mL)	260 ± 307	705 ± 556	<0.01
Uric acid (mg/dL)	6.3 ± 2.0	6.7 ± 1.0	0.66
mPAP (mm Hg)	61 ± 17	62 ± 14	0.95
RAP (mm Hg)	8 ± 4	13 ± 9	<0.05
PCWP (mm Hg)	9 ± 3	10 ± 5	0.82
SvO_2 (%)	66.1 ± 8.7	65.4 ± 10.1	0.86
Cardiac index (L/min/m^2)	2.4 ± 0.9	2.4 ± 0.9	0.82
PVR (dyn·s/cm^5)	1391 ± 615	1375 ± 537	0.96
Heart rate (bpm)	74 ± 16	86 ± 15	0.07
SpO_2 (%)	97 ± 3	95 ± 3	0.08
Treatment			
Oral PGI_2	9 (18)	0 (0)	0.22
IV PGI_2	37 (76)	6 (86)	0.55
Dose of epoprostenol (ng/kg/min)	79.6 ± 43.2	54.0 ± 47.8	0.19
ERA	34 (69)	4 (57)	0.52
PDE5 inhibitor	28 (57)	1 (14)	<0.05
Monotherapy	10 (20)	3 (43)	0.24
Combination therapy	38 (78)	4 (57)	0.24
Number of PAH-targeted drugs: 2	16 (33)	4 (57)	0.21
Number of PAH-targeted drugs: 3	22 (45)	0 (0)	<0.05
Warfarin	11 (22)	2 (29)	0.72
Oxygen therapy	46 (94)	7 (100)	0.50

Values other than WHO functional class are expressed as mean ± SD. WHO functional class is presented as the median and number of patients in each class. HPAH: hereditary pulmonary arterial hypertension, 6MWD: 6-miute walk distance, BNP: brain natriuretic peptide, mPAP: mean pulmonary arterial pressure, RAP: right atrial pressure, PCWP: pulmonary capillary wedge pressure; SvO_2: mixed venous oxygen saturation; PVR: pulmonary vascular resistance, SpO_2: oxygen saturation, PGI_2: prostacyclin; IV: intravenous; ERA: endothelin receptor antagonist, and PDE5: phosphodiesterase type 5.

Hemodynamic parameters (mPAP, RAP, SvO_2, cardiac index, and PVR) were also significantly improved from those at baseline ($P < 0.01$).

Prognostic factors related to survival

The Cox proportional hazard model was used to estimate the risk factors for mortality based on the baseline data of patients. Age, sex or HPAH did not correlate with survival. Whether the patient was an incident case or prevalent case or time between the diagnosis and initiation of treatment or study enrollment was not related to survival. WHO functional class at diagnosis and at referral was not correlated with survival. BNP, RAP, and SpO_2 were important for predicting the prognosis in the univariate analysis. In the multivariate analysis, none of the baseline parameters were predictors of survival. ROC curves were constructed to determine optimal threshold values for baseline BNP, RAP, and SpO_2. The cutoff value for RAP was 10 mm Hg, but this could not be used to stratify survival. Patients with a BNP level ≥350 pg/mL and SpO_2 ≤96% at baseline had a significantly worse prognosis (Fig. 1B). Patients who died during the study period did not have any pulmonary diseases. They were severely ill with overt heart failure at referral and oxygen saturation dropped because of it.

With regard to follow-up data, WHO functional classes I and II (HR, 0.061; 95% CI, 0.007–0.512; P = 0.01), 6MWD (HR, 0.993; 95% CI, 0.989–0.998; P < 0.01), BNP (HR, 1.003; 95% CI, 1.001–1.005; P < 0.01), mPAP (HR, 1.101; 95% CI, 1.045–1.161; P < 0.01), RAP (HR, 1.297; 95% CI, 1.030–1.631; P = 0.03), and cardiac index (HR, 0.027; 95% CI, 0.001–0.650; P = 0.03) were important for predicting the prognosis in the univariate analysis. Neither PAH-targeted drug was associated with the prognosis. Based on the area under the curve (AUC) calculated from the ROC curves, cutoff values were calculated: mPAP (AUC, 0.956; cutoff value, 42.5 mm Hg), cardiac index (0.904; 2.5 L/min/m^2), BNP (0.885; 52 pg/mL), and 6MWD (0.883; 347 m). Cutoff values for these four parameters and WHO functional classes I and II/III and IV did stratify survival (Fig. 1C). However, none of these parameters at follow-up was a predictor of survival in the multivariate analysis.

Table 2
Clinical and hemodynamic data before and after treatment.

	Baseline	Follow-up	P
Age, years	32 ± 17		
WHO functional class (I/II/III/IV)	3 (0/1/38/17)	2 (0/38/15/3)	<0.01
6MWD (m)	234 ± 174	378 ± 114	<0.01
BNP (pg/mL)	313 ± 372	67 ± 156	<0.01
Uric acid (mg/dL)	6.4 ± 1.9	6.2 ± 1.7	0.70
mPAP (mm Hg)	63 ± 15	35 ± 10	<0.01
RAP (mm Hg)	8 ± 4	5 ± 4	<0.01
PCWP (mm Hg)	9 ± 3	8 ± 4	0.31
SvO_2 (%)	66.2 ± 8.9	77.2 ± 5.7	<0.01
Cardiac index (L/min/m^2)	2.3 ± 0.8	3.5 ± 0.9	<0.01
PVR (dyn·s/cm^5)	1473 ± 600	481 ± 421	<0.01
Heart rate (bpm)	76 ± 17	82 ± 18	0.09
SpO_2 (%)	97 ± 3	98 ± 3	0.14

Abbreviations are as stated in Table 1. Data were evaluated in 56 patients except for hemodynamic parameters, that were evaluated in 43 patients who underwent follow-up right-heart catheterization >3 months after initial catheterization at our hospital.

Discussion

The present study is the first report on the survival of Japanese patients with I/HPAH who would have benefitted from recent progress in the development of PAH-targeted drugs in the modern era. Each PAH-targeted drug has been reported to improve the prognosis or progression of PAH (Sitbon et al., 2002; McLaughlin et al., 2005; Rubin et al., 2011). There have been improvements compared with those in the National Institutes of Health (NIH) Registry (D'Alonzo et al., 1991) but overall survival has been reported to be unsatisfactory despite such improvements in treatment options (Humbert et al., 2010; Benza et al., 2012; Zhang et al., 2011).

Our data demonstrated that after treatment, hemodynamic parameters improved significantly. mPAP decreased significantly by 28 mm Hg from 63 ± 15 mm Hg with improved cardiac index. As a result, PVR was also improved significantly. These results are consistent with our reports showing that epoprostenol and bosentan can reduce mPAP (Akagi et al., 2008, 2010). The baseline hemodynamic parameters were comparable or even worse than those reported previously (Humbert et al., 2010; Lee et al., 2012; Zhang et al., 2011; Badesch et al., 2010), but the improvement was more significant. This difference could have led to a significantly better prognosis. None of the baseline hemodynamic parameters (mPAP, cardiac index, or PVR) was a prognostic factor for survival. This suggests that long-term survival can be achieved even if severe pulmonary hypertension is confirmed by hemodynamic means (high mPAP and PVR). With regard to follow-up data, WHO functional classes I and II, mPAP <42.5 mm Hg, cardiac index >2.5 L/min/m^2, BNP <52 pg/mL, and 6MWD >347 m were important for predicting the prognosis in the present study. A recent study demonstrated that changes in WHO functional class, cardiac index, SvO_2, and the level of N-terminal-pro BNP on follow-up data would be predictors of the prognosis (Nickel et al., 2012). In contrast to our study, mPAP was not included as a prognostic factor in their study, in which mPAP was unchanged despite the treatment. Considering that the initial abnormality of I/HPAH is a high mPAP, improvement of the mPAP would have led to improved survival of this cohort. In another type of pulmonary hypertension, chronic thromboembolic pulmonary hypertension, mPAP is indeed the determinant of the prognosis (Riedel et al., 1982; Lewczuk et al., 2001). In I/HPAH, reduction of mPAP might also be an important determinant for survival, as shown in Fig. 1C-a.

One distinct difference between our cohort and previous cohorts is the high prescription rate of PAH-targeted drugs. In Japan, there is an

Please cite this article as: Ogawa A, et al, Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan, Life Sci (2014), http://dx.doi.org/10.1016/j.lfs.2014.01.077

excellent national healthcare system that is supported by the government. Currently, PAH is allocated to a special program: the "Specified Disease Treatment Research Program". This program subsidizes medical care for patients with rare and intractable diseases. It also enables Japanese physicians to offer optimal treatment to patients. Epoprostenol has been reported to be the most potent vasodilator available, but it is expensive. In previous studies, the prescription rate of epoprostenol was not high; 0% in the NIH registry, 15% in a French registry, and 23% (prostanoids; not specified as epoprostenol) in a study examining the impact of follow-up data described above (Humbert et al., 2010; D'Alonzo et al., 1991; Nickel et al., 2012). In our cohort, epoprostenol was prescribed in 75% of patients. Based on a report stating a reduction of the mPAP of ≈9 mm Hg by a 1-year treatment with epoprostenol (Sitbon et al., 2002), the high prescription rate and long-term high dose of epoprostenol treatment and combination therapy including epoprostenol could have led to a large reduction in mPAP in our cohort. Combination therapy has been shown to be beneficial for patients, and upfront (rather than sequential combination) therapy is expected to be more beneficial (Vachiery & Gaine, 2012). However, upfront therapy is not always possible worldwide because of its high cost. Although a specific drug was not associated with the prognosis in the univariate Cox regression analysis in our cohort, there were significant differences in the prescription rate of PDE5 inhibitors and triple PAH-targeted therapy between survivors and non-survivors. In Japan, PDE5 inhibitors were approved relatively recently (in 2008). Non-survivors were mainly treated before that time, which could be one reason for this difference.

Another reason for the better overall survival could be a difference in ethnicity. One report from China showed better survival than that in Western countries (1- and 3-year survival estimates of 92.1% and 75.1%, respectively) (Zhang et al., 2011). This result is notable because patients often choose inexpensive medication or abandon treatment in China. Epoprostenol was not prescribed in this cohort. There might be a difference in the genetic background between Asians and Caucasians that leads to a different response to treatment.

Estimation of the risk factors for mortality using a univariate Cox proportional hazard model showed that BNP, RAP, and SpO_2 at baseline were important for the prediction of the prognosis. This result suggests that patients with I/HPAH cannot be treated successfully after establishment of severe heart failure, with BNP ≥350 pg/mL and SpO_2 ≤96% even at a referral center. This finding is consistent with reports stating that overt heart failure is a potent prognostic factor. It has also been reported that late referral to a pulmonary hypertension center is related to a delay in appropriate treatment that ultimately leads to heart failure and is a strong factor for mortality (Badagliacca et al., 2012).

The goal for treating patients with I/HPAH varies among physicians and is affected by the healthcare system of each country. Most clinical trials have set the end-point as an improvement in 6MWD. However, recently, the improvement of 6MWD has been shown not to be related to long-term survival (Savarese et al., 2012). In the present study, WHO functional class, mPAP, cardiac index, BNP, and 6MWD at follow-up were shown to be important for the prediction of the prognosis in univariate analysis. No parameters were shown to be significant in the multivariate analysis even though follow-up data (including hemodynamic parameters) were improved significantly compared with those at baseline. This finding might have been because our cohort was small and the number of events (disease-related death) was too small. Only seven (13%) subjects died out of all patients. This is a much lower number compared with those reported previously: 55% in the NIH registry, 29% in a French registry, and 49% in the study by Nickel et al. (Humbert et al., 2010; D'Alonzo et al., 1991; Nickel et al., 2012).

IPAH was originally reported to occur predominantly in younger women (D'Alonzo et al., 1991). Recently, it has been reported that in countries with aging populations, IPAH is diagnosed frequently in elderly patients (Hoeper et al., 2013). However, in the present study, patients were predominantly young women, similar to that reported in the NIH registry. Recently, it has also been reported that male patients with PAH have a worse prognosis (Humbert et al., 2010; Lee et al., 2012; Benza et al., 2012). However, our results showed that male sex was not a prognostic factor for survival.

This was a single-center retrospective study, so the possibility of selection bias and survivor bias could not be avoided. Our cohort involved 57% of prevalent cases, and this might be one reason why the survival seems better than that reported previously. The number of patients and events was small and there was variation in the follow-up period. These features could have affected the results of our study. A multicenter prospective study with scheduled repetitive catheterization is needed to confirm the importance of the improvement of hemodynamic data.

Conclusion

The present study revealed long-term survival of Japanese patients with I/HPAH treated at a single referral center. Patients with right-heart failure at referral had a poor prognosis. Hemodynamic parameters were improved significantly with treatment despite severe hemodynamic parameters at baseline. This observation could be related to the high prescription rates of PAH-targeted drugs in the present study. Further investigation with a multicenter registry is needed to reveal the prognostic factors in Japanese patients with I/HPAH.

Conflict of interest statement

H.M. received lecturer fees from GlaxoSmithKline, Actelion Pharmaceuticals Japan, and Nippon Shinyaku.

References

Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780–8.

McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galie N, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005;25:244–9.

Rubin LJ, Badesch DB, Fleming TR, Galie N, Simonneau G, Ghofrani HA, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 Study. Chest 2011;140:1274–83.

Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219–63.

Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156–63.

Lee WT, Ling Y, Sheares KK, Pepke-Zaba J, Peacock AJ, Johnson MK. Predicting survival in pulmonary arterial hypertension in the UK. Eur Respir J 2012;40:604–11.

Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012;142:448–56.

Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, et al. Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. Chest 2011;140:301–9.

D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343–9.

Akagi S, Matsubara H, Miyaji K, Ikeda E, Dan K, Tokunaga N, et al. Additional effects of bosentan in patients with idiopathic pulmonary arterial hypertension already treated with high-dose epoprostenol. Circ J 2008;72:1142–6.

Akagi S, Nakamura K, Miyaji K, Ogawa A, Kusano KF, Ito H, et al. Marked hemodynamic improvements by high-dose epoprostenol therapy in patients with idiopathic pulmonary arterial hypertension. Circ J 2010;74:2200–5.

Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010;137:376–87.

Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012;39:589–96.

Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest 1982;81:151–8.

Lewczuk J, Piszko P, Jagas J, Porada A, Wojciak S, Sobkowicz B, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 2001;119:818–23.

Please cite this article as: Ogawa A, et al, Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan, Life Sci (2014), http://dx.doi.org/10.1016/j.lfs.2014.01.077

Vachiery JL, Gaine S. Challenges in the diagnosis and treatment of pulmonary arterial hypertension. Eur Respir Rev 2012;21:313–20.
Badagliacca R, Pezzuto B, Poscia R, Mancone M, Papa S, Marcon S, et al. Prognostic factors in severe pulmonary hypertension patients who need parenteral prostanoid therapy: the impact of late referral. J Heart Lung Transplant 2012;31:364–72.
Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. J Am Coll Cardiol 2012;60:1192–201.
Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA Registry. Int J Cardiol 2013;168:871–80.

Please cite this article as: Ogawa A, et al, Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan, Life Sci (2014), http://dx.doi.org/10.1016/j.lfs.2014.01.077