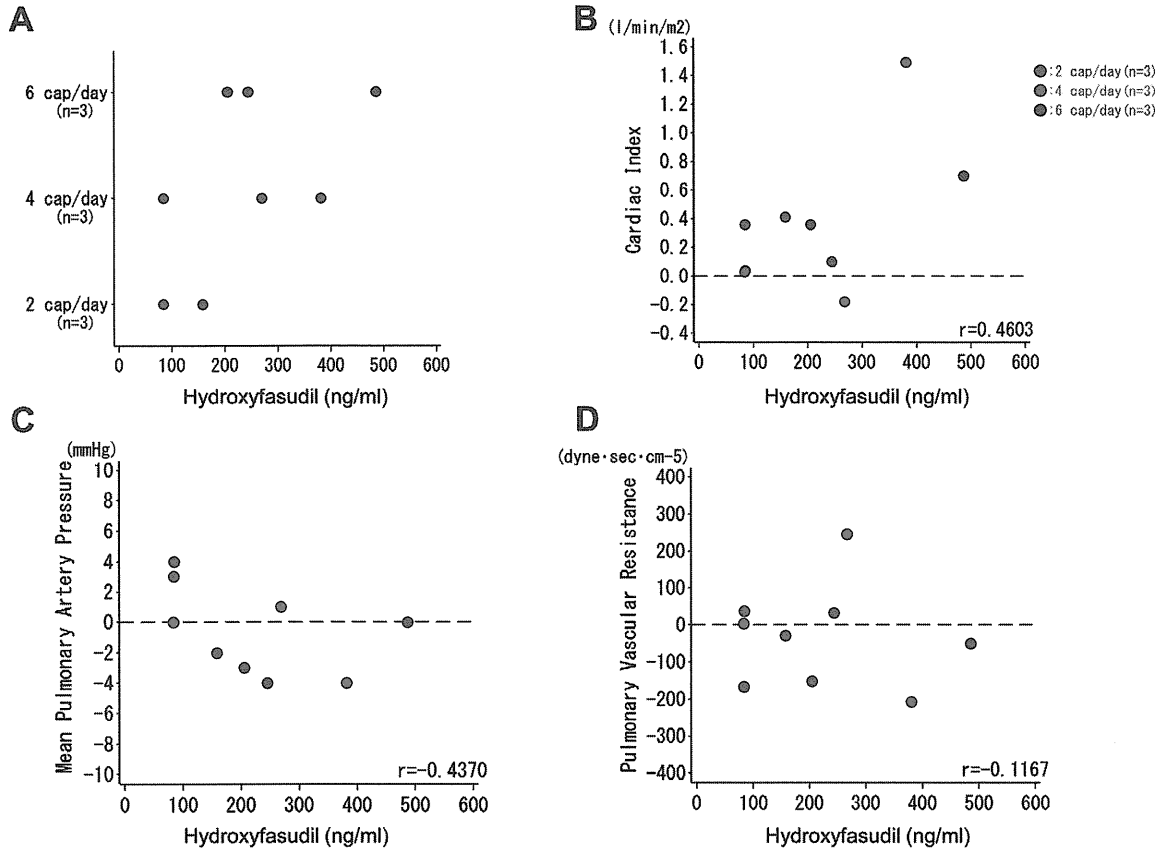

Figure. Serum levels of hydroxyfasudil and pulmonary hemodynamics. (**A**) Serum levels of hydroxyfasudil hydrochloride were dose-dependent of AT-877ER. (**B–D**) Serum levels of hydroxyfasudil tended to correlate with improvements in the cardiac index (**B**, r=–0.4370, P=0.2125) and mean pulmonary artery pressure (**C**, r=0.4603, P=0.2395), but not pulmonary vascular resistance (**D**, r=0.1167, P=0.7650). r, Spearman's rank correlation coefficient.

There were 3 discontinuations (2 in the AT-877ER group and 1 in the placebo group). The 2 discontinuations in the AT-877ER group included the patient who had cardiac failure, pulmonary edema and pleural effusion and eventually died, and 1 patient with renal impairment (increased BUN and creatinine levels, and positive proteinuria). The treatment was 3 capsules per dose for these patients, including the patient who discontinued the study because of renal impairment, which had recovered 13 days after discontinuation, and the patient in the placebo group who discontinued because of personal circumstances.

Discussion

The results of the present study showed that 3-month treatment with AT-877ER, a Rho-kinase inhibitor, significantly improved the CI in patients with PAH and that serum levels of AT-877ER tended to correlate with improvements in both CI and mean PAP. Importantly, all patients in the AT-877ER group had been maximally treated with pulmonary vasodilators, including 3 different vasodilators, beraprost, bosentan, and sildenafil.

Rho-Kinase and Inflammation

Inflammatory processes may be involved in the pathogenesis of PAH.[6,22] It has been demonstrated that Rho-kinase is up-regulated by inflammatory stimuli[14,23,24] and that Rho-kinase inhibition increases endothelial nitric oxide synthase (eNOS) expression and inhibits inflammatory cell migration and angiotensin II-induced upregulation of monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 in vivo or in vitro,[16] suggesting that the Rho-kinase pathway plays an important role in the pathogenesis of PAH.

Rho-Kinase Inhibitor

AT-877ER, fasudil, is a potent and selective inhibitor of Rho-kinase,[25] with its inhibitory effect on Rho-kinase being 100-fold and 1,000-fold more potent than on protein kinase C and myosin light chain kinase, respectively.[16] Several studies, including ours, have demonstrated in animal models that long-term inhibition of Rho-kinase with fasudil ameliorates monocrotaline-induced PAH and hypoxia-induced PAH.[6,17,19,26] Consistent with these findings, intravenous administration of fasudil also effectively reduces PVR in patients with PAH.[18]

Although beraprost sodium has no inhibitory effect on Rho-kinase, we have demonstrated that the combination of fasudil and beraprost is more effective than each monotherapy for ameliorating pulmonary hypertension in a rat model of monocrotaline-induced PAH.[27,28] Furthermore, it has been consistently demonstrated that IPAH patients under intravenous prostacyclin therapy show a favorable acute responses to

fasudil administration.[18,29]

Although inhibition of the ETA and ETB endothelin receptors is another effective strategy for the treatment of PAH,[30] endothelin and many other vasoactive substances (eg, serotonin, thrombin and platelet-derived growth factor) are involved in the pathogenesis of PAH, all of which could activate the Rho-kinase pathway.[14,16,24,31] Because Rho-kinase inhibitors could inhibit signal transductions initiated by all these vasoactive substances, it is highly possible that they exert more broadly beneficial effects than each single receptor antagonist.[14,16,24,31] Thus, the present clinical trial was designed to combine beraprost/sildenafil/bosentan with fasudil in order to develop additional and more beneficial treatment of PAH.

Enhanced Rho-Kinase Expression and Activity in PAH

The experimental studies using animal models have demonstrated that Rho-kinase activity in the pulmonary arteries is enhanced irrespective of etiology and that long-term treatment with Rho-kinase inhibitors ameliorates endothelial dysfunction and suppresses the hypercontraction and proliferation of VSMC and migration of inflammatory cells.[17,19,26] We and others have shown direct clinical evidence of Rho-kinase activation in patients with PAH, in whom Rho-kinase activity is enhanced in circulating neutrophils and the pulmonary arteries, resulting in hypercontraction of the pulmonary arteries[20] and thus supporting the previous findings in both animal models of PAH and patients with PAH.[14,17–19,26,29,32] Furthermore, we have demonstrated that endothelial vasodilator function is impaired and VSMC contraction is enhanced in the pulmonary arteries from patients with PAH,[20] and that inhibition of Rho-kinase abolishes hypercontraction of the VSMCs in the pulmonary arteries from IPAH patients,[20] which could explain the mechanism for the present findings.[18,29,32]

Study Limitations

Several limitations should be mentioned. First, the study group consisted of a small number of Japanese patients with PAH, demonstrating significant effects of AT-877ER on CO but not on pulmonary hemodynamics. Our calculation using the present results predicts that it would reach statistical significance for pulmonary hemodynamics if 100 patients could be recruited for each group. Thus, the present findings need to be confirmed in future studies with a large number of patients. Second, renal impairment occurred in some patients in the AT-877ER group, although a higher concentration of hydroxyfasudil seemed to be favorable for improving pulmonary hemodynamics. Thus, the appropriate dosage of AT-877ER remains to be determined in future trials. Third, the long-term effects of AT-877ER (ie, >3 months) remain to be examined in PAH patients in future clinical trials. Fourth, more male patients were enrolled in the AT-877ER group because there was no randomization by sex. The sex difference in Rho-kinase activity remains be examined in future studies with a larger number of patients. Fifth, the AT-877ER group had better pulmonary hemodynamics and more prevalence of congenital heart disease, which should be adjusted in future studies with a larger number of patients.

Conclusions

Treatment with AT-877ER, an oral form of Rho-kinase inhibitor, could be a new strategy in addition to the present medical treatment of PAH.

Acknowledgments

YF: analysis and interpretation of data, drafting of the manuscript. NY, HM, MM, KU, AY, YK, MK, HW, YT, TA, SO, NY, TI: acquisition of data. TN: analysis and interpretation of data; HS: study conception, design, and final approval of the manuscript.

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Disclosures

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Patient Consent

Obtained.

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Supplementary Files

Supplementary File 1

Figure S1. Study design.

Figure S2. Numbers of patients enrolled in the present study who underwent screening and randomization.

Table S1. Cardiac hemodynamics changes and adverse events in the placebo and the AT-877ER groups

Table S2. %Changes in cardiac hemodynamics and 6-min walk distance in the placebo and AT-877ER groups at week 12

Table S3. Adverse events

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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

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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).

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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).

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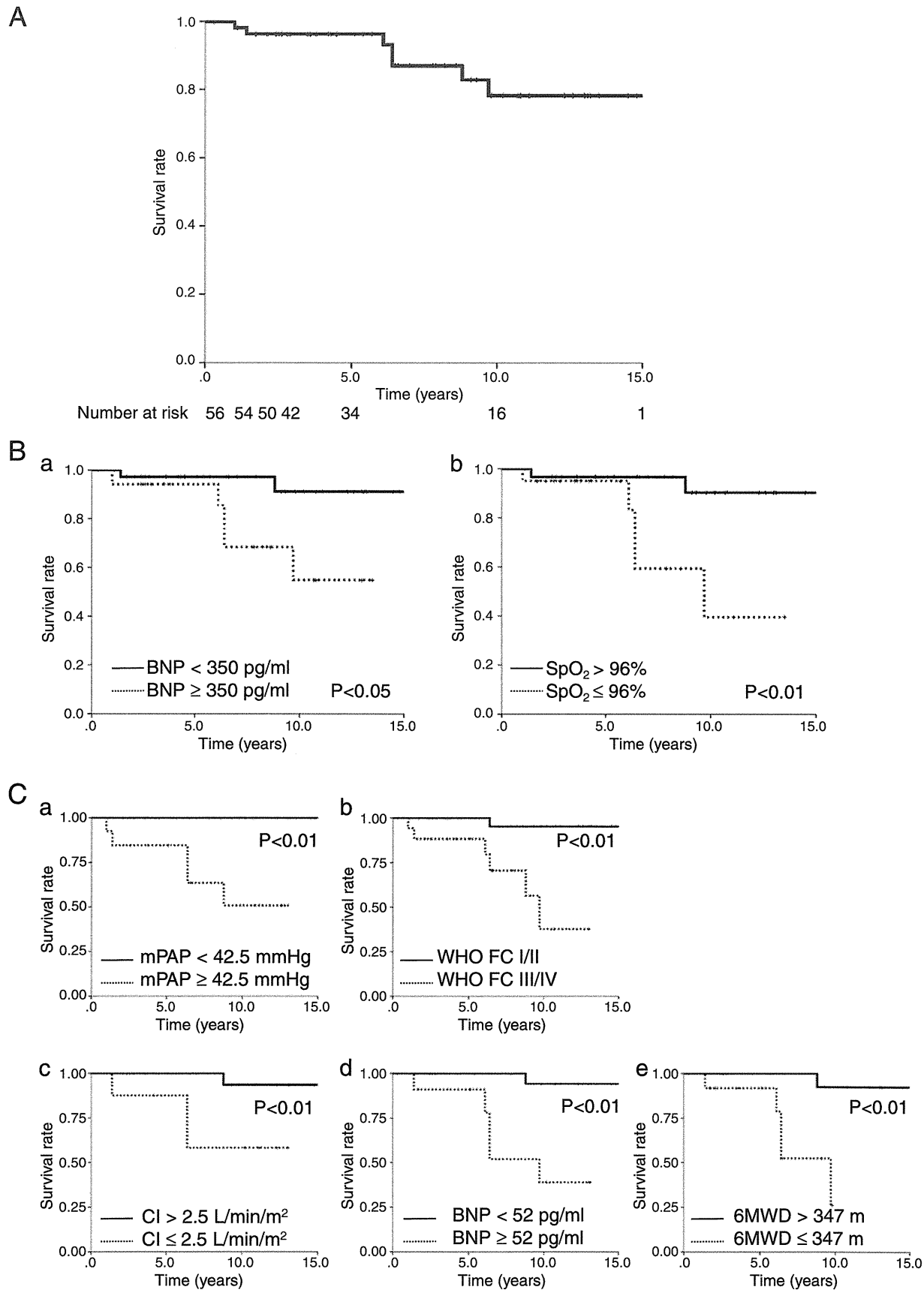

Fig. 1. (A) Mean survival time from the diagnosis was 14.9 ± 0.8 years (95% CI, 13.4–16.4 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 98, 96, 96, 96 and 78%, respectively. (B) Survival rate of patients stratified by parameters at baseline. a: Survival rate of patients with BNP ≥350 pg/mL 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 ($P < 0.01$).

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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.

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.

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.

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

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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.

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INTERNAL MEDICINE

□ CASE REPORT □

Imatinib is Partially Effective for the Treatment of Pulmonary Capillary Hemangiomatosis

Shiro Adachi[1], Akihiro Hirashiki[2], Takahisa Kondo[2], Masato Nakaguro[3], Aiko Ogawa[4], Katsumasa Miyaji[4], Hiromi Matsubara[4], Toyoharu Yokoi[5] and Toyoaki Murohara[1]

Abstract

A 43-year-old man presented with dyspnea on exertion. Right heart catheterization demonstrated pulmonary arterial hypertension (PAH). He was treated with bosentan, sildenafil and intravenous epoprostenol. Despite the administration of such intensive therapy, the patient's condition deteriorated to a World Health Organization functional class (WHO-FC) of IV. He participated in a clinical trial of imatinib for PAH. After three months of treatment with imatinib, the chest X-ray and echocardiography findings improved, and the WHO-FC class was III. One year after, however, the PAH worsened again, and the patient died 2.6 years after the first diagnosis. At autopsy, patchy capillary proliferation was observed in the lungs. The definitive diagnosis was pulmonary capillary hemangiomatosis.

Key words: pulmonary hypertension, pulmonary capillary hemangiomatosis, imatinib, tyrosine kinase inhibitor

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Introduction

Pulmonary capillary hemangiomatosis (PCH) is an extraordinarily rare cause of pulmonary arterial hypertension (PAH). In the Dana Point classification, both PCH and pulmonary veno-occlusive disease (PVOD) are classified as Group 1' PAH (1). Patients with PCH typically survive for only two to three years unless they undergo lung transplantation (2). The definitive diagnosis depends solely on pathological findings. We herein present a case of PCH that was resistant to conventional PAH therapy, including bosentan, sildenafil and intravenous epoprostenol, but responsive to imatinib, which enabled the patient to return home for one year until his final admission.

Case Report

A 43-year-old man presented with progressive dyspnea on exertion. He had worked as a carpenter two years earlier. His past medical and familial history were unremarkable. He had never smoked and denied any illicit drug use. On a physical examination, his blood pressure was 95/65 mmHg, his heart rate was 105 bpm and his respiratory rate was 22 breaths/min. An electrocardiogram showed right ventricular hypertrophy with ST changes. The level of plasma brain natriuretic peptide (BNP) was 202 pg/mL. A Doppler echocardiogram demonstrated a peak tricuspid regurgitation pressure gradient of 70 mmHg. Pulmonary function tests showed a normal forced vital capacity (FVC) (3.10 L, 83.6% of the predicted value), normal forced expiratory volume 1.0% (FEV 1) (2.76 L, 86.8% of the predicted value) and normal FEV1/FVC ratio (86%); however, the diffusing capacity for carbon monoxide (DL_{CO}) was severely decreased (6.19, 22.5% of the predicted value). High-resolution computed tomography (HRCT) of the chest revealed centrilobular ground glass opacity, septal thickening and mediastinal lymph node enlargement. Medical examinations indicated no

[1]Department of Cardiology, Nagoya University Graduate School of Medicine, Japan, [2]Department of Advanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine, Japan, [3]Department of Pathology, Nagoya University Graduate School of Medicine, Japan, [4]Department of Cardiology, National Hospital Organization Okayama Medical Center, Japan and [5]Department of Diagnostic Pathology, Aichi Medical University Hospital, Japan
Received for publication June 17, 2013; Accepted for publication September 18, 2013
Correspondence to Dr. Takahisa Kondo, takahisa@med.nagoya-u.ac.jp

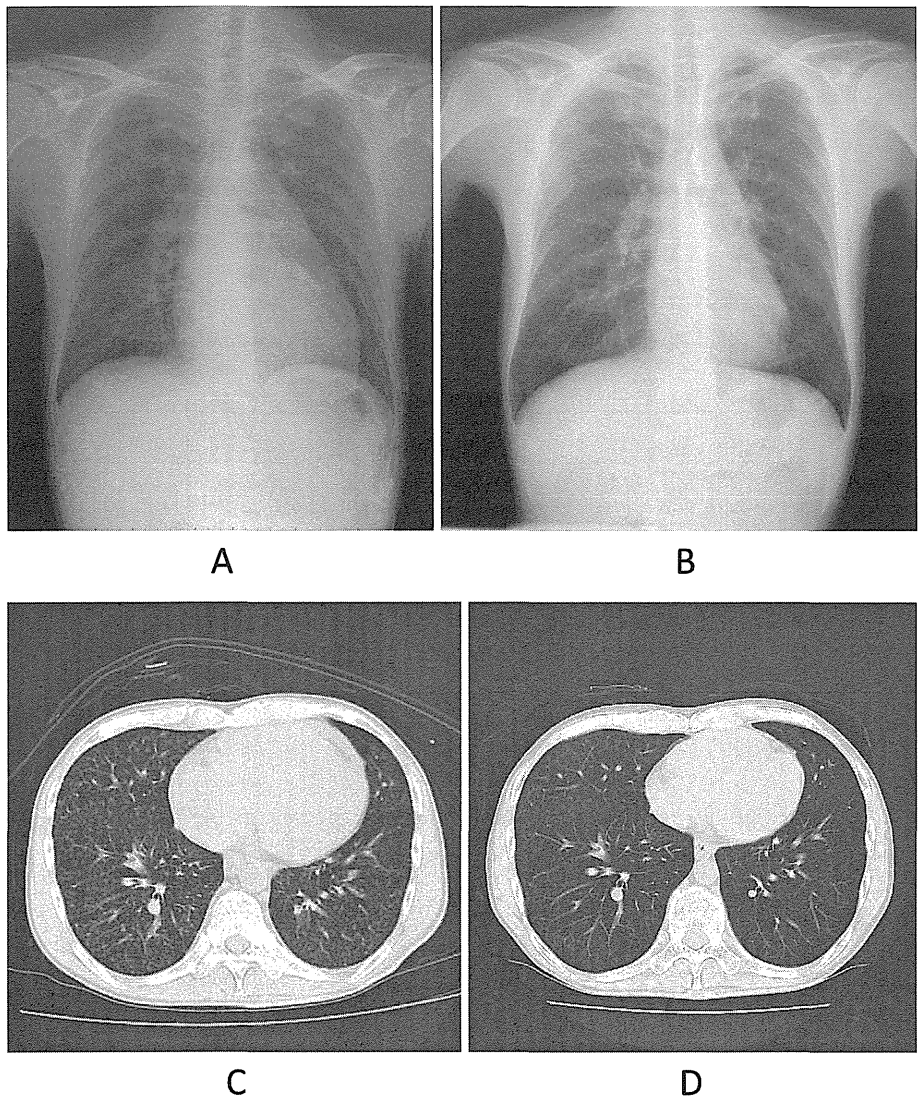

Figure 1. Chest X-ray and high-resolution computed tomography (HRCT) before and after imatinib treatment. A: A chest X-ray obtained before imatinib treatment showed dilation of the pulmonary artery trunk and cardiomegaly. B: A chest X-ray obtained after imatinib treatment showed improvements in the dilation of the pulmonary artery trunk and cardiomegaly. C: HRCT performed before imatinib treatment showed diffuse bilateral centrilobular ground glass opacity and septal thickening. D: HRCT performed after three months of imatinib treatment. The ground glass opacity and septal thickening had improved, and the pericardial effusion had decreased.

specific cause leading to pulmonary hypertension. Right heart catheterization demonstrated a pulmonary arterial pressure (PAP) of 64/22/35 mmHg (systolic/diastolic/mean) and a pulmonary capillary wedge pressure of 2 mmHg. The pulmonary vascular resistance (PVR) was 1,310 dynesec/cm^5. Perfusion lung scintigraphy did not show any abnormal perfusion defects. Therefore, we diagnosed the patient with idiopathic PAH or Group 1' PAH.

Treatment was initiated with bosentan, and both sildenafil and intravenous epoprostenol (maximum dose: 26 ng/kg/min) were carefully added. However, the patient's respiratory condition deteriorated with the development of pulmonary edema, and his arterial oxygen saturation on pulse oximetry (SpO_2) was 90.0% with inhalation of 10 L/min 100% oxygen using a face mask. He remained in World Health Organization functional class (WHO-FC) IV. Although lung transplantation was considered, the patient refused the procedure. Instead, we decided to administer imatinib after obtaining approval from the domestic ethics committee of the National Hospital Organization Okayama Medical Center. Soon after imatinib was started with an initial dose of 100 mg once per day, the patient's respiratory condition rapidly improved. The dose of imatinib was increased to 150 mg once per day, and the intravenous epoprostenol was tapered off. The patient's condition improved to WHO-FC III, with an SpO_2 of 98% with inhalation of 5 L of nasal oxygen. The cardiomegaly on chest X-rays and ground glass opacity and septal thickening on HRCT improved (Fig. 1). The degree of left ventricle compression was also reduced on an echocardiogram (Fig. 2). After three months of imatinib treat-

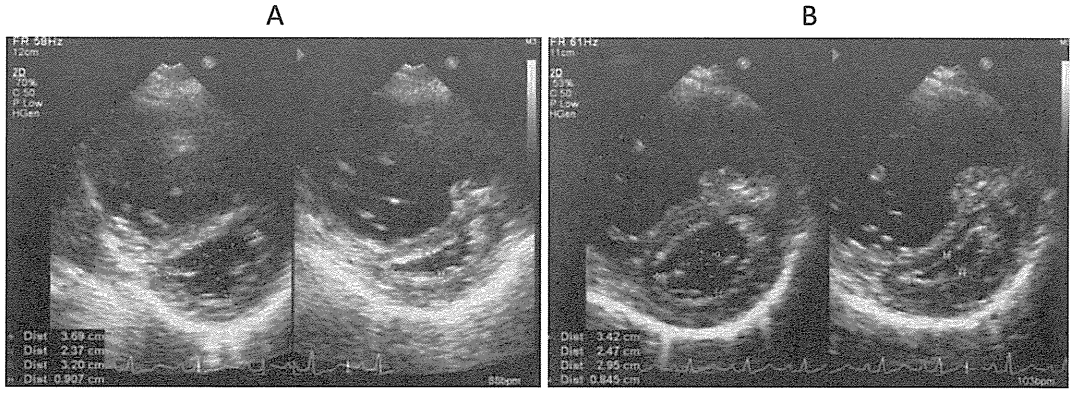

Figure 2. Parasternal short-axis view of an echocardiograms obtained before and after imatinib treatment. A: Before imatinib treatment. A flat septum and D-shaped left ventricle were observed. B: After three months of imatinib treatment. The flat septum and D-shaped left ventricle had improved.

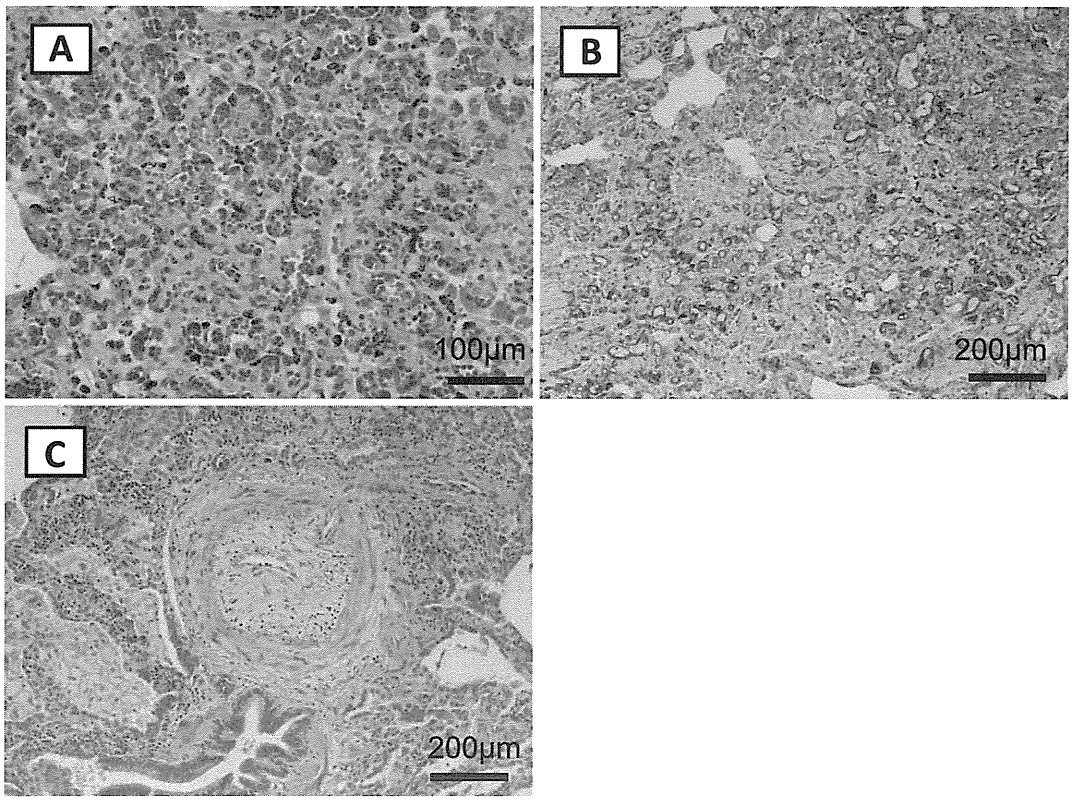

Figure 3. Histological findings of the pulmonary lesion. A: Nodular and hemangioma-like proliferation of capillaries in the alveolar walls. The capillaries are dilated and filled with red blood cells (Hematoxylin and Eosin staining; original magnification ×200). B: Immunostaining of CD34 highlighting proliferating capillaries (original magnification ×100). C: Some muscular arteries exhibited marked intimal fibrosis and occlusion of the lumen (Hematoxylin and Eosin staining; original magnification ×100).

ment, the patient was discharged home. He remained in WHO-FC class III, with a plasma BNP level of 71 pg/mL. One year after discharge, however, the dyspnea reappeared, and he again required hospitalization. The plasma BNP level increased to 1,037 pg/mL and the systolic PAP estimated on an echocardiogram increased to 135 mmHg. Right-sided heart failure rapidly progressed despite the initiation of catecholamine treatment for nine days after hospitalization, and the patient died 2.6 years after the first diagnosis. At autopsy, the pathological findings revealed dominant nodular and hemangioma-like proliferation of capillaries in the alveolar walls, and PCH was diagnosed (Fig. 3).

Discussion

Imatinib, a tyrosine kinase inhibitor, has been reported to

be effective in some cases of PAH (3-5); however, there are no precise case reports of PCH. In the present case, a diagnosis of PCH/PVOD was suspected based on the clinical, laboratory and HRCT findings (6, 7). The pathological findings revealed dominant patchy hemangioma-like capillary proliferation, although no venous fibrosis or occlusion were observed in any lobes of the lungs. The muscular arteries showed only mild intimal and medial thickening. Therefore, PCH was the definitive etiologic diagnosis in this patient.

In this case, the administration of imatinib rapidly improved the patient's symptoms, laboratory test results and echocardiography and HRCT findings. Among the medications prescribed for this patient, only imatinib proved effective enough to allow him to be discharged home and improved his quality of life. In a previous report of a case of PVOD, imatinib was added to diuretics, anticoagulants and epoprostenol, and neither bosentan nor sildenafil were used (3). However, in the present case, all PAH-targeted therapies were used. Therefore, it is clear that only imatinib was effective for this patient.

Imatinib may be specifically effective for PCH due to the inhibitory effects of several tyrosine kinase activities (3-5). Moreover, imatinib exhibits antiproliferative and pro-apoptotic effects on smooth muscle cells stimulated with platelet-derived growth factor (PDGF) in subjects with idiopathic PAH (8). There are several possible mechanisms by which imatinib may elicit pulmonary vasodilation. These include: (1) inhibition of PDGF receptor-mediated elevation of the intracellular Ca^{2+} levels (9); (2) inhibition of other off-target protein kinases, such as epidermal growth factor receptor, Src and protein kinase C (10-12); and (3) inhibition of c-Abl-mediated actin polymerization (13).

Imatinib may work in PAH patients with higher PVR values. In the International Multicentre PREvalence Study on Sepsis (IMPRESS) study, treatment with imatinib improved exercise capacity and hemodynamics in patients with advanced PAH already treated with two or more pulmonary vasodilators; however, serious adverse events and imatinib discontinuation were common (14). In particular, subdural hematomas developed in 4.2% of the patients treated with imatinib, all of which occurred in patients receiving concomitant anticoagulation. In the present case, the patient was not treated with oral anticoagulants, but rather with bosentan and sildenafil, and no obvious side effects caused by imatinib were observed.

Abe et al. reported that the administration of imatinib reduces a high right ventricular systolic pressure in pulmonary hypertensive rats (15). Imatinib therapy has also been reported to improve the arterial oxygen saturation (SaO_2), PVR and cardiac output, although the 6-minute walk distance as the primary end point did not change significantly (5). Meanwhile, a subanalysis showed that, among the patients with a PVR of ≥1,000 dynesec/cm^5 only, the pulmonary artery pressure, cardiac output and 6-minute walk distance significantly improved (6). These results suggest that the administration of imatinib in addition to other therapies, such as endothelin receptor blockers and phosphodiesterase-5 inhibitors, has the potential to be effective for severe pulmonary artery hypertension. In the present case, the PVR before treatment with imatinib was 1,310 dynesec/cm^5. Therefore, imatinib appeared to be effective for this patient.

Hatano M. et al. reported that treatment with imatinib improves the DL_{CO} because the medication decreases the serum PDGF concentration (16). However, it should be noted that the effects of imatinib were reduced after 1.5 years of treatment. Namely, the effects of imatinib may decrease with long-term treatment. Further studies are needed to investigate the long-term safety and efficacy of imatinib in patients with PCH.

In summary, imatinib was partially effective in a PCH patient who exhibited an inadequate response to bosentan, sildenafil and intravenous epoprostenol.

The authors state that they have no Conflict of Interest (COI).

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INTERNAL MEDICINE

□ CASE REPORT □

Pulmonary Tumor Thrombotic Microangiopathy with Circulatory Failure Treated with Imatinib

Aiko Ogawa[1], Ichiro Yamadori[2], Osamu Matsubara[3] and Hiromi Matsubara[1]

Abstract

Pulmonary tumor thrombotic microangiopathy is a lethal, yet difficult to diagnose, complication of gastrointestinal carcinoma. Even if properly diagnosed, there is no treatment, especially after a circulatory collapse. We herein report a case of pulmonary tumor thrombotic microangiopathy with circulatory failure due to pulmonary hypertension. The patient was temporarily successfully treated with imatinib, an inhibitor of the platelet-derived growth factor receptor. Pulmonary hypertension was dramatically ameliorated and the patient was able to be weaned from percutaneous cardiopulmonary support within 20 days of treatment. Imatinib may be effective for ameliorating pulmonary hypertension that is caused by pulmonary tumor thrombotic microangiopathy.

Key words: pulmonary tumor thrombotic microangiopathy, circulatory failure, treatment, imatinib

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) presents with rapidly progressive pulmonary hypertension related to carcinoma (1). The condition was originally reported in 1990, and since then, more than 50 cases have been pathologically diagnosed at autopsy. However, a clinical diagnosis of PTTM is difficult. In addition, there have not yet been any reported cases of patients who survived after the development of severe pulmonary hypertension with circulatory failure due to PTTM.

Case Report

A 47-year-old woman with no previous medical history was referred to our hospital for further treatment of pulmonary hypertension in August 2007. She had a three month history of dry cough, general fatigue and dyspnea upon effort. She visited a nearby hospital, was diagnosed with pulmonary hypertension and admitted to the hospital. Two days later, she presented with syncope and was transferred to our hospital. At the time of admission, a continuous infusion of dopamine (3 μg/kg/min) and dobutamine (3 μg/kg/min) was required. Her oxygen saturation was 99% with oxygen supplementation at 5 L/min. Electrocardiography showed sinus tachycardia with an SIQIIITIII pattern and negative T wave in V2 and V3, thus suggesting acute right ventricular overload (Fig. 1A). A chest radiography showed dilated pulmonary arteries, cardiomegaly and congestion (Fig. 1B). A high-resolution computed tomography (CT) scan demonstrated a nodular shadow and septal thickening with a slight amount of pleural effusion in the lung (Fig. 1C). A contrast-enhanced CT scan showed no tumor emboli to be present in the pulmonary arteries (Fig. 1D). Due to impaired hemodynamics, we could not perform either lung perfusion scintigraphy or pulmonary angiography at the time of admission. Echocardiography showed a dilated right atrium and ventricle. A right heart catheterization revealed an elevated pulmonary arterial pressure and a reduced cardiac output (Fig. 2). We immediately started bosentan and epoprostenol therapy in order to treat pulmonary hypertension. On Day 9, despite treatment with a continuous infusion of epoprostenol (3.8 ng/kg/min) with catecholamines, the hemodynamic data deteriorated. She manifested circulatory collapse and needed percutaneous cardiopulmonary support. Imatinib, an inhibi-

[1]Department of Clinical Science, National Hospital Organization Okayama Medical Center, Japan, [2]Department of Clinical Pathology, National Hospital Organization Okayama Medical Center, Japan and [3]Department of Pathology, Hiratsuka Kyosai Hospital, Japan
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Correspondence to Dr. Aiko Ogawa, aiko-oky@umin.ac.jp

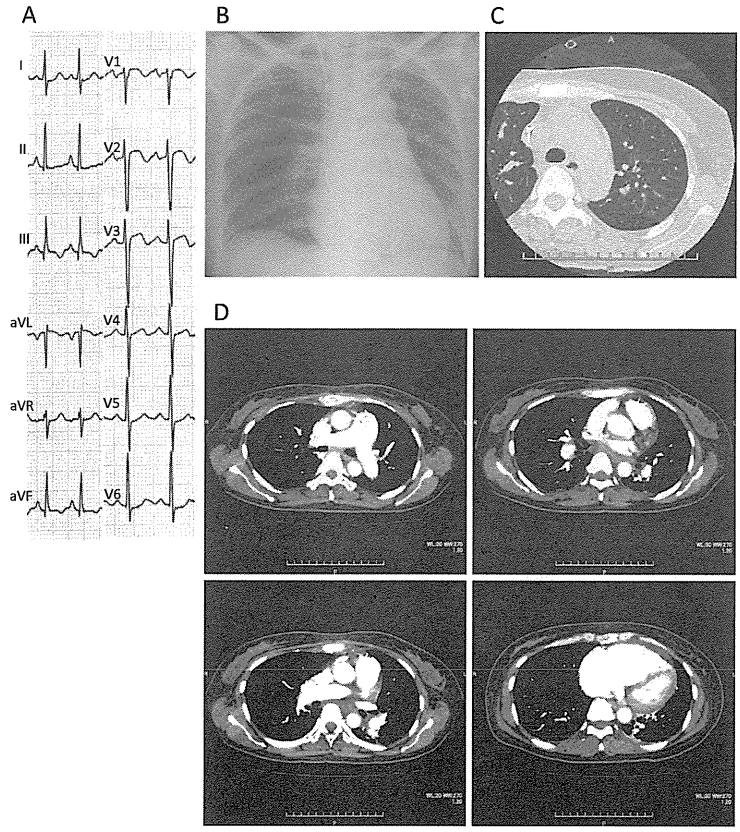

Figure 1. Images of the patient at admission. A: Electrocardiography shows sinus tachycardia with an SIQIIITIII pattern and negative T wave in V2 and V3. B: Chest radiography demonstrates dilated pulmonary arteries, cardiomegaly and congestion. C: High-resolution CT shows a nodular shadow and septal thickening with a slight amount of pleural effusion in the lung. D: A contrast-enhanced CT scan shows no tumor embolisms in the pulmonary arteries.

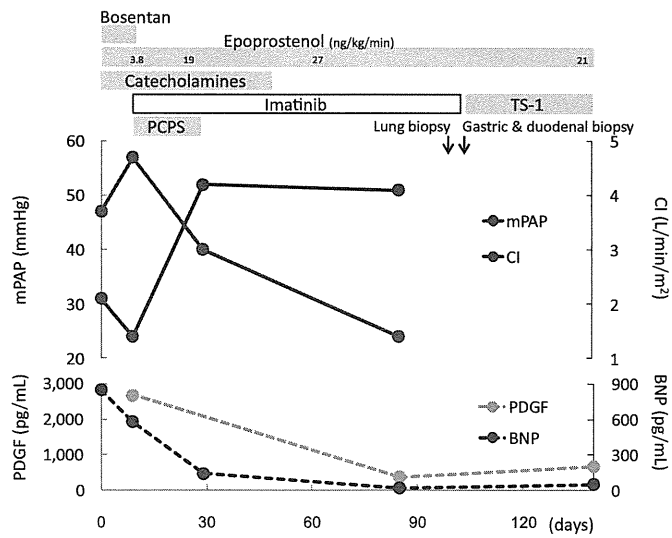

Figure 2. Time course of treatment. Mean pulmonary artery pressure (mPAP), cardiac index (CI) and plasma levels of platelet-derived growth factor (PDGF) and brain natriuretic peptide (BNP) are shown. Treatments including percutaneous cardiopulmonary support (PCPS) are also shown. The time points at which the biopsies were performed are indicated by arrows. Imatinib treatment successfully improved the hemodynamics, and PDGF decreased in parallel with the amelioration of mPAP.

tor of the tyrosine kinase receptor for platelet-derived growth factor (PDGF), was initiated (100 mg/day) and her pulmonary arterial pressure gradually decreased. She was successfully weaned from the percutaneous cardiopulmonary

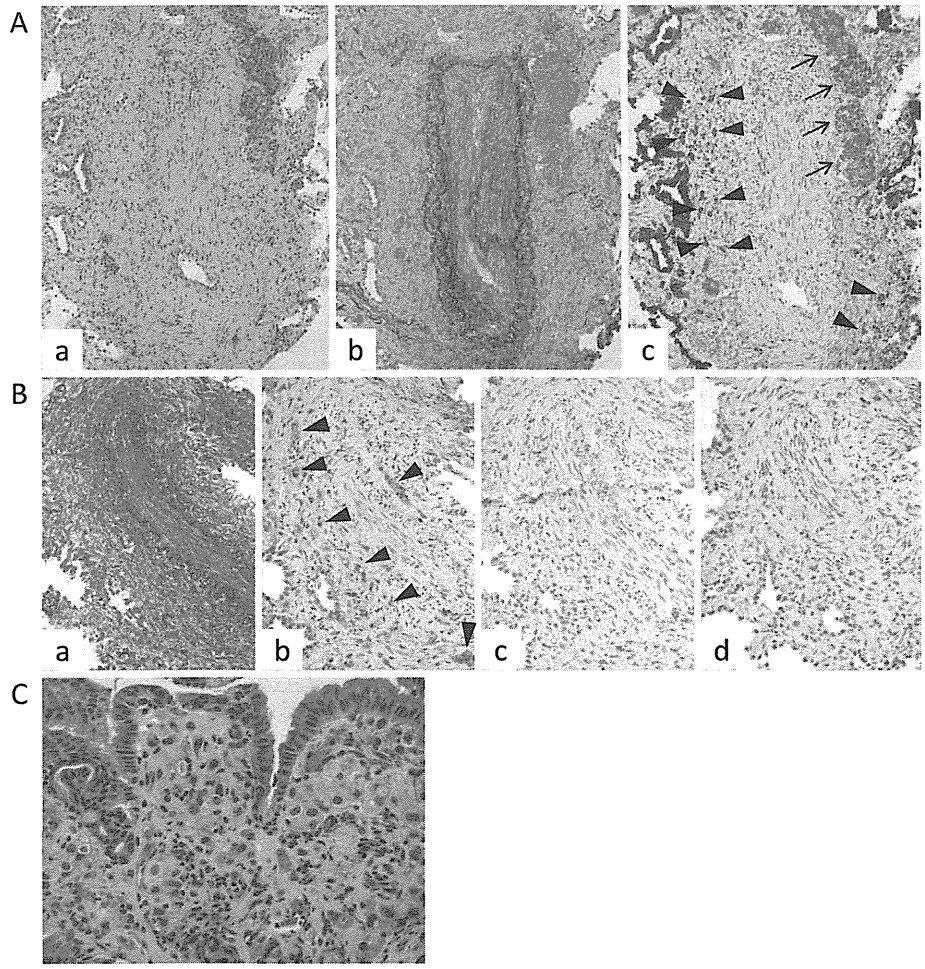

Figure 3. Histology of the lung and duodenal biopsy specimens. A: The lung biopsy specimen shows pronounced intimal thickening of a pulmonary artery (a: Hematoxylin and Eosin staining, b: elastica Masson stain). The tumor invasion can be observed in the parenchyma (arrowheads) and lymphatic vessels (arrows) (c: immunohistochemistry of cytokeratin 7). Note that the artery is stenosed, not by tumor embolism, but by a proliferation of vascular endothelial cells. B: The lung biopsy specimen shows a pulmonary artery that was stenosed by intimal thickening (a: elastica Masson stain). Vascular endothelial growth factor (b) is expressed in the tumor cells (arrowheads) that are scattered outside of the occluded vessel. PDGF-A (c) and PDGF-B (d) are not detected. C: The duodenal biopsy specimen shows the mucosa to be infiltrated by poorly differentiated adenocarcinoma.

support on Day 29. Her condition progressively improved and the hemodynamics nearly normalized by Day 85. Since we had never before observed such a rapid amelioration of pulmonary hypertension, a transbronchial lung biopsy was performed. The pathological examination revealed metastasized adenocarcinoma and PTTM (Fig. 3A). Vascular endothelial growth factor was expressed in the tumor cells, but not in the intimal cells (Fig. 3Ba and b). No expression of PDGF was detected in either type of cells (Fig. 3Bc and d). Screening for the primary focus revealed gastric and duodenal carcinoma (Fig. 3C). TS-1, an oral 5-fluorouracil derivative, was started on Day 104. Imatinib therapy was stopped because the hemodynamics had stabilized, and the patient was discharged on Day 140. A serial measurement of the plasma levels of PDGF showed a decrease in the PDGF levels in parallel with the amelioration of pulmonary hypertension (Fig. 2). She was followed up two months later, and the results of examinations suggested no evidence of pulmonary hypertension. She did not experience a recurrence of pulmonary hypertension. She died from the systemic metastasis of carcinoma approximately 9 months later. The family refused an autopsy; therefore, we could not obtain a histology sample of the lung.

Discussion

PTTM is generally related to gastrointestinal carcinoma and it triggers the development of advancing pulmonary hypertension. Pathologically, PTTM is caused by an obstruction of pulmonary arterioles by microembolisms of tumor cells, thrombus formation that is induced by the activation of thrombotic cascades on the surface of tumor embolisms and the abnormal proliferation of vascular endothelial cells caused by growth factors that are induced by tumors (2).

The clinical diagnosis of PTTM is extremely difficult (3). Even if PTTM is diagnosed, it is not treatable, and patients usually die within a couple of days.

Imatinib is a tyrosine kinase inhibitor that has been approved as an anticancer drug. The drug inhibits the phosphorylation of the PDGF receptor, and subsequently blocks many intracellular downstream signaling pathways. We originally decided to treat this patient with imatinib because of its possible efficacy in pulmonary arterial hypertension (4). However, a recent randomized study did not show significant improvement in the primary endpoint following the administration of imatinib (5) and in the present patient, the pathological diagnosis of PTTM was confirmed.

In our patient, the plasma levels of PDGF decreased in parallel with the amelioration of pulmonary hypertension following the administration of imatinib. Several tumor cells simultaneously produce PDGF and express PDGF receptors (6). The termination of the autocrine loop by imatinib may be one of the mechanisms of decreasing plasma PDGF levels. Imatinib down-regulates the expression of both PDGF and the PDGF receptor in tumor cells, thus resulting in increased apoptotic cell death and the inhibition of tumor angiogenesis, which even further decreases the production of PDGF by the tumor cells. In PTTM, PDGF and PDGF receptors are reportedly expressed in both carcinoma cells and endothelial cells (7). In the present case, PDGF was not detected in lung biopsy specimens of either the tumor cells or the initimal cells. Since the specimen was obtained only after the initiation of imatinib in this patient, we do not know whether PDGF was not expressed from the beginning or if the expression level was reduced to below detectable range following imatinib therapy. Considering the fact that the plasma PDGF levels were decreased following the imatinib treatment, it is possible that the expression level of PDGF could have been modified by imatinib therapy. Based on this limited information, it is difficult to determine which type of cells were affected by imatinib; namely, the tumor cells, the excessively-proliferated intimal cells or both.

We herein described a patient with PTTM who was at least temporarily successfully treated by imatinib. The patient's condition remarkably improved following the administration of imatinib. To the best of our knowledge, this is the first report of a case of PTTM with severe pulmonary hypertension that was successfully treated following a circulatory collapse. The findings from this case suggest that imatinib might have an ameliorative effect on pulmonary hypertension caused by PTTM, possibly by reducing the expression of PDGF. Further study is needed in order to elucidate the mechanism by which imatinib exerts its effect in PTTM.

Author's disclosure of potential Conflicts of Interest (COI).
Hiromi Matsubara: Honoraria, GlaxoSmithKline, Actelion Pharmaceuticals Japan, Nippon Shinyaku and Novartis Pharmaceuticals Corporation.

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治療の有効性と使用法 慢性血栓塞栓性肺高血圧症に対する肺動脈形成術

永吉信哉（国立病院機構岡山医療センター循環器科）
松原広己（国立病院機構岡山医療センター臨床研究部長）

Point

- 慢性血栓塞栓性肺高血圧症（CTEPH）に対しては、肺動脈内膜摘除術（PEA）、薬物治療、バルーン肺動脈形成術（BPA）が行われる。
- PEAでは術関連死が高く、薬物治療では大幅な予後や症状の改善が期待できない。BPAも合併症対策を含めていまだ完成された治療ではなく、CTEPH治療の第一選択はPEAであり、PEAとBPAは補完関係にある。
- BPAにおいて、最も重要な合併症は再灌流性肺障害である。その本態はBPAに伴う血管損傷、すなわち病変の過拡張・病変末梢の圧過負荷・ワイヤー損傷と考えられる。
- 病変・肺動脈圧によりバルーンサイズを選択・調整することで、過拡張や病変末梢の圧過負荷に伴う肺動脈壁損傷を軽減する。
- BPAにおいて、現状ではワイヤー損傷による出血を完全に抑えることはできていないため、起こった際に重症化させないことが重要である。

慢性血栓塞栓性肺高血圧症（chronic thromboembolic pulmonary hypertension；CTEPH）は、器質化血栓による肺動脈の狭窄・閉塞が原因となって肺血管抵抗が上昇して、肺高血圧をきたす疾患である。急性肺血栓塞栓症の3～4％程度がCTEPHに移行すると報告されている[1]。予後は非常に悪く、平均肺動脈圧が40mmHg以上では5年生存率は30％、50mmHgを超えると5年生存率は10％であると報告されている。

特定疾患受給者証の交付を受けている患者は2010年度で1,288人であったが、届け出のされていない患者も決して少なくはないので、実際の患者数はより多いものと推定される。

CTPEHの治療

肺動脈内膜摘除術（pulmonary endartetectomy；PEA）

肺動脈の器質化血栓を内膜ごと外科的に剥離するPEAは治療の第一選択とされ、国内外の限られた施設で行われている。

手術適応としては、
①平均肺動脈圧が30mmHg以上
②肺血管抵抗300dyne/秒/cm^{-5}以上

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③血栓が手術で到達しうる部位(区域枝より中枢)にあること
④重篤な合併症がないこと
などがあげられている。

薬物治療と比較し症状や血行動態の改善効果は大きいが、末梢病変に対しては術関連死が高い(21.4%)とされている[2]。

薬物治療

現在まで、手術不適応の症例やPEA術後で肺高血圧残存の症例に対して、薬物治療が行われてきた。最近では可溶性グアニル酸シクラーゼ刺激薬であるリオシグアトが6分間歩行距離を改善させたとの報告はあるものの[3]、いずれの薬物治療でも平均肺動脈圧の低下は軽微であり、大幅な予後や症状の改善が期待できるとは考えにくい[4,5]。

バルーン肺動脈形成術 (balloon pulmonary angioplasty ; BPA)

2001年にFeinsteinらが、PEAの適応のない18人のCTRPH患者に対してBPAを行い、肺動脈圧・自覚症状・6分間歩行距離の改善を報告している[6]。

当施設では2004年より、PEAに不適なCTEPH患者に対して、BPAを行ってきた。平均肺動脈圧を25mmHg以下にして、自覚症状の改善のみでなく、在宅酸素療法や血管拡張薬の減量および中止を目的とした。2013年7月現在まで168人の患者に対してのべ800回のBPAを行っており、良好な成績を収めてきた[7]。

当院でBPAを施行した1例を提示する。

【症例提示】
当院初診時50歳、女性
主訴：歩行時息切れ(WHO機能分類Ⅳ度)
経過：突然の胸痛や呼吸困難などの急性肺塞栓を示唆する所見なく、2008年6月ごろより息切れが出現。症状増悪し、前医受診。下肢静脈血栓症・肺塞栓の診断で、血栓溶解療法、後に抗凝固療法・在宅酸素療法導入。肺動脈圧が徐々に上昇し、血管拡張薬内服を順次追加するも改善なく、エポプロステノール持続静注開始。しかし自・他覚所見の改善乏しく、2009年10月当院紹介となった。来院時の胸部X線(図1A-1)・肺血流シンチ(図1B-1)を示す。
経過：計4回のBPAを施行し(図1C)、内服・点滴治療を中止ししたにもかかわらず、自・他覚所見(図1A-2、B-2)血行動態(図1D)の改善が得られた。

治療法の選択

より効果的かつ安全に行える方法が、最良の治療であることはいうまでもない。効果の点から考えればPEAが圧倒的に優れており、熟練した術者が行えば、単回の治療によりCTEPHを根治できる。従って、ことに近位肺動脈に器質化血栓を有するCTEPHにおいては、必ず検討されるべきと考える。

一方で、術死亡の可能性があるのも事実であり、わが国ではそのリスクをきらって薬物治療に偏る傾向があるようだ。確かに薬物治療においては、副作用・相互作用さえなければ大きなリスクは存在しないが、高価な薬剤を生涯服用し続ける必要があるにもかかわらず血行動態の改善効果は乏しく、PEAの適応を検討することなく安易に開始すべきものではない。

同様に、PEAの適応が有る症例に対して、手術リスク回避のためにBPAを検討すべきであろうか？　確かにわれわれの施設でのBPAの成績は、PEAと比肩しうるほどのものではある(表1)。しかしBPAでは肺動脈内の器質化血栓を摘除しているわけではないので、あまりにも多量の器質化血栓を有する肺動脈中枢部の治療には不適である。われわれの成績は、治療対象がPEAに不適である、主として末梢型のCTEPH患者であったがゆえに達成できたものであり、中枢型に対しても同様であると考えてはいけない。

さらに、カテーテル治療であることから漠然と低リスクと考えがちであるが、当院においても術関連死亡を2%程度認めており、加えて透視被爆や造影剤使用に伴うアレルギー・腎症などの問題もある。160人以上のCTEPH患者にBPAを行ってきたわれわれですら、合併症対策も含めてBPAはいまだ完成された治療とは考えておらず、CTEPH治療の第一選択はPEAであり、PEAとBPAは補完関係にあるものと理解している。

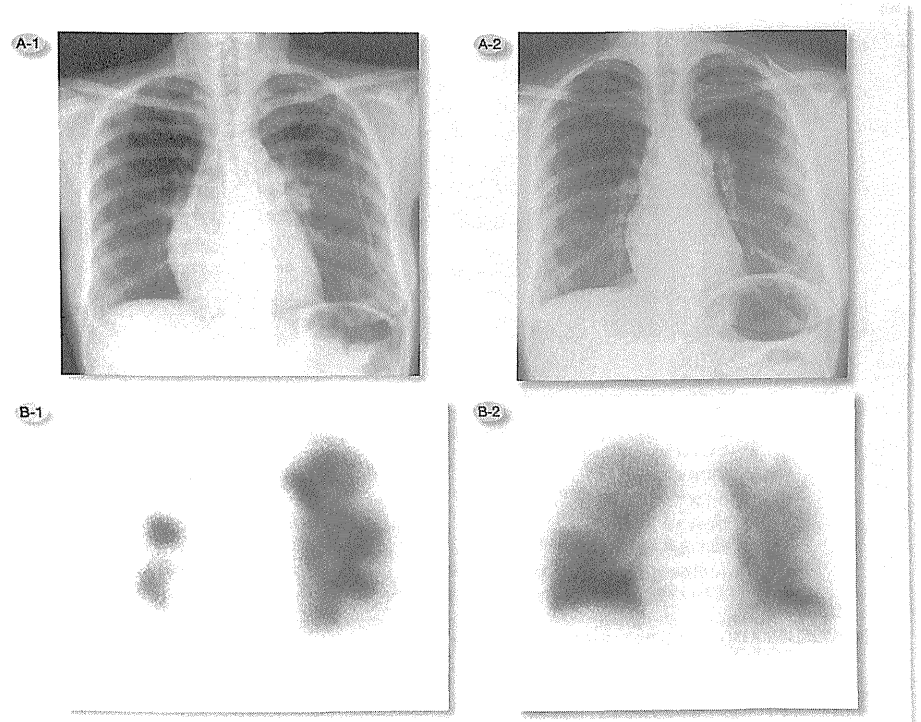

図1　【症例提示】胸部X線(A)、肺血流シンチ(B)、肺動脈造影(C)、血行動態・自覚症状(D)
A-1：2009年10月：心拡大・左右第2弓の突出・末梢肺動脈陰影の減少を認める。
A-2：2011年4月：心拡大の改善・左右第2弓突出改善。
B-1：2009年10月：肺血流シンチ：右上・中・下葉・左下葉を中心に血流欠損あり。
B-2：2011年6月：BPA後血流改善を認める。

(次項へ続く)