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The role of balloon pulmonary angioplasty and pulmonary endarterectomy: Is chronic thromboembolic pulmonary hypertension still a life-threatening disease?

Yu Taniguchi [a,*], Yoichiro Matsuoka [a], Hiroyuki Onishi [a], Kenichi Yanaka [a], Noriaki Emoto [a], Hidekazu Nakai [b], Kenji Okada [b], Kenichi Hirata [a]

[a] Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan
[b] Division of Cardiovascular Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Japan

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ABSTRACT

Background: The management of non-operable chronic thromboembolic pulmonary hypertension (CTEPH) has evolved with the availability of balloon pulmonary angioplasty (BPA) and pulmonary vasodilators. We launched the BPA program in 2011. The aim was to analyze the survival and treatment efficacy of our CTEPH treatment program in the modern management era.

Methods and results: We retrospectively reviewed data from 143 consecutive CTEPH patients diagnosed from January 2011 (i.e. after the availability of BPA) to December 2019. Of forty-one patients who underwent pulmonary endarterectomy (PEA), 25 underwent additional BPA (Combination group) and the others were treated with only PEA (PEA group). Ninety patients underwent BPA (BPA group). The remaining 12 patients did not undergo any interventional treatments.

The 1- and 5-year survival rates of operated patients ($n = 41$) were 97.4% and 90.0%, compared to 96.9% and 86.9% in not-operated patients ($n = 102$), respectively ($p = 0.579$). There was no mortality in the Combination group. Mean pulmonary artery pressure after treatments in the PEA only, Combination, and BPA only groups was 20.5 ± 6.7, 17.9 ± 4.9, and 20.7 ± 4.6 mmHg, respectively ($p = 0.067$, one-way ANOVA). Percent decrease of pulmonary vascular resistance in each treatment groups was −73.7 ± 11.3%, −74.3 ± 11.8%, and − 54.9 ± 22.5%, respectively ($p < 0.01$, one-way ANOVA).

Conclusion: There was no significant difference in long-term survival between operated and not-operated CTEPH. Moreover, the Combination approach might have the potential to introduce notable improvements in the prognosis of CTEPH. BPA and PEA appear to be mutually complementary therapies in the modern management era.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and the obstruction of pulmonary arteries with non-resolving organized thromboemboli, leading to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension (PH), right heart failure, and finally, death [1–3]. Historically, the prognosis of untreated patients with CTEPH is very poor, with a 5-year survival rate of less than 50% in those with a mean pulmonary artery pressure (PAP) greater than 30 mmHg, and 10% in those with a mean PAP greater than 50 mmHg [4]. Surgical pulmonary endarterectomy (PEA) remains the gold standard treatment in patients with CTEPH who are judged to be operable. Several reports show that operated patients have better long-term survival. Indeed, an international prospective registry from 27 European centers showed that not-operated patients had a significantly worse prognosis with a 3-year survival rate of 70%, while that of patients undergoing surgery was 89% [5,6]. However, 40–70% of CTEPH patients are judged as non-operable due to distal lesions or the presence of comorbidities [5,7]. Recently, the management for non-operable CTEPH has evolved with the availability of balloon pulmonary angioplasty (BPA) and the use of pulmonary arterial hypertension (PAH)-targeted medications. The short-term (16 weeks) randomized double-blind controlled CHEST trial showed that riociguat, a soluble guanylate cyclase stimulator, significantly improved exercise capacity (6-min walk distance) and pulmonary hemodynamics in patients with

Abbreviations: BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA-FC, New York Heart Association functional class; PAP, pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization.

* Corresponding author at: Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 6500017, Japan.
E-mail address: yutani@med.kobe-u.ac.jp (Y. Taniguchi).

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non-operable CTEPH or with persistent/residual PH after PEA [8,9]. Treprostinil, a prostacyclin analogue, also improved exercise capacity at 24 weeks in the randomized, double-blind controlled trial in non-operable CTEPH or persistent/residual PH after PEA [10]. Furthermore, BPA, an endovascular procedure to widen narrowed or obstructed pulmonary arteries, has emerged as an additional treatment option for patients with non-operable CTEPH. The first case series, reported by Feinstein et al. in 2001, demonstrated a reduction in mean pulmonary artery pressure (mean PAP) of 9 mmHg, but also reported that its mortality rate was 5.6% [11]. With refinements in the technique, several reports have succeeded in improving the efficacy and safety of BPA. These studies, mostly published since 2012, reported an overall reduction in mean PAP of 21 mmHg from baseline and a mortality rate of 1.5% after an average of four angioplasty sessions for each patient [12]. The efficacy and safety of BPA for non-operable cases were equivalent to those achieved using PEA for operable cases [13]. Until recently, reports on the efficacy and safety of BPA had been published mainly from Japan. However, with accumulation of evidence, attempts to treat non-operable CTEPH patients with BPA has spread to several countries outside Japan, even to countries where BPA was initially viewed with skepticism [14,15]. BPA should be considered as an established treatment strategy for non-operable patients. The recent 2018 World Symposium on pulmonary hypertension in Nice proposed and recommended PH targeted medical therapy and BPA for inoperable cases at the expert centers [16].

We aimed to clarify the long-term outcomes in patients with CTEPH in the modern management era from experience at Kobe University.

2. Methods

This retrospective study complied with the Declaration of Helsinki. This study was approved by the ethics committee of Kobe University (approval number B200125).

2.1. Patients

This observational study was carried out in all consecutive patients with CTEPH who were diagnosed, treated, and followed up at the Kobe University Hospital between January 2011 and December 2019; data were collected from hospital medical records. Hemodynamic characteristics (assessed by right heart catheterization [RHC]), functional status with the New York Heart Association functional class (NYHA-FC), and exercise capacity based on the 6-min walk distance were collected at baseline (i.e. time CTEPH diagnosis) and after the interventional treatment including PEA and BPA if applicable. Vital status was accessed at the last follow-up visit. For patients without any news for more than 3 months, mortality status was determined by telephone contact to patients.

2.2. Diagnosis and treatment of CTEPH

The diagnosis of CTEPH was established according to clinical guidelines that were current during the observational period [17]. Diagnosis was based on medical history, physical examination, ventilation-perfusion lung scan, multidetector computed tomography pulmonary angiography, RHC, and selective pulmonary angiography. Newly diagnosed patients were defined as those meeting the diagnostic criteria at the time of their first RHC, and follow-up time was calculated from this date. Since November 2001, we started surgical pulmonary endarterectomy for patients with operable CTEPH. Not-operated patients were treated with oral anticoagulants alone or with off-label use of PAH drugs including endothelin-receptor antagonists (ERA; bosentan, ambrisentan, macitentan), phosphodiesterase type-5 inhibitors (PDE-5i; sildenafil, tadalafil), and/or soluble guanylatecyclase stimulator (sGC stimulator; riociguat), according to patient clinical status, treatment availability, and physicians' decision. Beginning in March 2011, we launched a BPA program for non-operable CTEPH patients. Patients diagnosed since 2011 could undergo interventional treatments with PEA or BPA at an early stage following diagnosis. Operability was considered according to the accessibility and distribution of chronic thromboembolic lesions, hemodynamic severity and the presence of comorbidities that could increase surgical risk [6,18]. There was no clear criteria for indication or contraindication of BPA [19]; however, patients who refused, had too mild hemodynamics, extremely old age (>90 years old), chronic kidney disease stages 4–5, and patients with malignancy whose expected prognosis was less than 6 months, were not offered BPA. Combinations of PEA and BPA were performed on selected operable patients; additional BPA after PEA was considered for patients with residual PH (mean PAP >25 mmHg), or residual symptoms (>NYHA 2), regardless of normalized hemodynamics. Initial unilateral BPA to the lung with distal lesions, as well as secondary PEA to the lung with proximal lesions were planned for carefully selected patients with severe hemodynamics to reduce perioperative risk. The assessment of treatment strategies for all patients was made by a multidisciplinary team of experts including both experienced cardiologists and thoracic surgeons, as recommended by the guidelines [17].

The BPA procedure was considered in newly diagnosed patients as of March 2011, but also in patients who had been previously diagnosed and considered as non-operable. To avoid the bias regarding the impact of PEA or BPA in incident patients, consecutive patients with CTEPH diagnosed since 2011 after the availability of interventional treatments including both PEA and BPA were enrolled in this study.

2.3. Statistical analysis

The data supporting the findings of this study are available from the corresponding author upon reasonable request. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics 17.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) according to variable distribution. Differences in continuous variables, such as age, 6-min walk distance, and hemodynamic characteristics were compared using the independent Student's *t*-test for normally distributed variables and the Mann–Whitney *U* test for non-normally distributed variables. One-way analysis of variance (ANOVA) was used to compare multiple groups. Categorical variables, such as sex, NYHA-FC and use of PAH medications were expressed as number and percentage and were compared using the χ^2-test for independence. Analysis of overall survival was performed using an intention-to-treat approach. For the survival analysis, the date of diagnostic RHC was used as the start point to determine length of survival. The cut-off date was December 31, 2019. The Kaplan–Meier method was used to estimate overall survival. For all analyses, the level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient population

Between January 2011 and December 2019, a total of 143 patients were diagnosed with CTEPH at the Kobe University Hospital. Forty-seven patients were judged as operable and 41 ultimately underwent PEA after a median of 2.3 months (IQR: 1.5; 5.7 months) after diagnosis. Six patients had not undergone PEA because of patient's refusal ($n = 3$) or existence of comorbidities ($n = 3$). Ninety patients underwent BPA with a mean of 4.0 ± 1.5 sessions per patient after a median of 2.7 months (IQR: 1.2; 4.6 months) after diagnosis. Of these, two patients had operable form; however, they were treated with BPA due to comorbidities or advanced age (**BPA only group**). Twelve patients had not undergone any interventional treatment including PEA or BPA due to mainly patients' refusal, and extremely advanced age or severe comorbidities (**No intervention group**). In BPA, amount of contrast used per

session was 169.1 ± 20.1 mL, while radiation dose per session was 585 ± 221 mGy. When compared with not-operated patients, operated patients were younger (58.9 ± 13.8 years vs. 68.4 ± 12.7 years; $p < 0.001$), more frequently male (39.0% vs. 17.6%; $p = 0.009$), and had higher proportion of patients with a history of acute pulmonary embolism (46.3% vs. 26.5%; $p = 0.029$). Operated patients also had more severe baseline hemodynamics (mean PAP: 41.8 ± 8.6 mmHg vs. 36.0 ± 9.2 mmHg; $p < 0.001$; PVR: 874 ± 373 dynes.s.cm^{-5} vs. 696 ± 364 dynes.s.cm^{-5}; $p = 0.009$). In operated patients, 26 patients (63.4%) also received PAH drugs, while 62 patients (60.8%) received PAH drugs in not-operated patients. Among the operated patients, 16 underwent only PEA (**PEA only group**); the remaining 25 patients underwent 'combination therapy' by combining PEA and BPA, with 22 patients receiving additional BPA after PEA for residual PH or symptoms, and three patients receiving initial unilateral BPA to the lung with distal lesions and secondary PEA to the other lung with proximal lesions (**Combination group**).

The baseline clinical and hemodynamic characteristics and medical treatments at intervention or at last follow-up in each group are summarized in Table 1. Patients in the Combination group had more severe mean PAP and PVR than those of the BPA only group ($p = 0.003$, $p = 0.005$, respectively) or the No intervention group ($p = 0.029$, $p < 0.001$, respectively). A trend was observed where the hemodynamics of the No intervention group were milder than in other groups. Almost all patients in the PEA only or Combination groups discontinued medical treatments after interventional treatments, whereas more than half of patients in the BPA only group continued medications after BPA.

3.2. Effects of interventional treatments

Table 2 shows the treatment effects on symptoms, exercise capacity, and hemodynamics in each treatment group. *Re*-evaluation of hemodynamics with RHC was performed after a median of 17.7 days (IQR: 14.5; 21.3 days) following the date of PEA in the PEA only group, after a median of 78.1 days (IQR: 24.3; 95.1 days) following the date of the last intervention in the Combination Group, and after a median of 79.4 days (IQR: 12.4; 99.2 days) following the date of the last BPA. *Re*-evaluation data of mean PAP and PVR in the PEA only, Combination, and BPA only groups were 20.5 ± 6.7 mmHg, 17.9 ± 4.9 mmHg, 20.7 ± 4.6 mmHg ($p = 0.067$, one-way ANOVA), and 205 ± 129 dynes.s.cm^{-5}, 222 ± 76 dynes.s.cm^{-5}, 267 ± 126 dynes.s.cm^{-5} ($p = 0.082$, one-way ANOVA), respectively. Absolute change of mean PAP and % decrease of PVR from baseline in each group are −20.0 ± 9.3 mmHg, −24.5 ± 8.9 mmHg, −15.7 ± 9.4 mmHg, ($p = 0.145$: PEA only group vs Combination group; $p = 0.101$: PEA only group vs BPA only group;

Table 1
Baseline characteristics and treatments initiated after diagnosis nd treatments at last follow-up in each treatment group.

Variable	Operated $n = 41$		Not-operated $n = 102$		p value*
	PEA only $n = 16$	Combination (PEA + BPA) $n = 25$	BPA only $n = 90$	No intervention $n = 12$	
Baseline characteristics					
Age (years)	54.0 ± 14.7	62.0 ± 12.4	68.6 ± 12.1	67.1 ± 17.1	< 0.001
Male (n, %)	7 (43.8)	9 (36.0)	14 (15.6)	4 (33.3)	0.022
NYHA FC I,II / III,IV (%)	18.8 / 81.2	28.0 / 72.0	16.7 / 83.3	66.7 / 33.3	0.003
6MWD (m)	357 ± 170	343 ± 88	300 ± 97	343 ± 102	0.122
BNP (pg/mL)**	132 [557]	207 [445]	82 [176]	50 [81]	0.023
Baseline hemodynamics					
Mean RAP (mmHg)	7.2 ± 4.9	5.4 ± 2.7	5.2 ± 3.6	4.8 ± 4.4	0.253
Systolic PAP (mmHg)	69.6 ± 17.9	75.6 ± 16.8	64.0 ± 15.2	57.9 ± 22.2	0.006
Diastolic PAP (mmHg)	25.9 ± 5.9	25.3 ± 7.3	21.2 ± 6.0	20.4 ± 10.6	0.007
Mean PAP (mmHg)	40.9 ± 8.2	42.4 ± 9.0	36.3 ± 8.7	34.0 ± 13.2	0.007
PAWP (mmHg)	10.8 ± 3.1	8.3 ± 3.70	8.0 ± 3.5	7.2 ± 4.5	0.029
Cardiac output (L/min)	3.78 ± 1.55	3.09 ± 0.70	3.58 ± 1.18	4.40 ± 1.11	0.014
Cardiac index (L/min/m^2)	2.18 ± 0.70	1.93 ± 0.39	2.28 ± 0.70	2.73 ± 0.66	0.006
PVR (dynes.s.cm^{-5})	750 ± 403	954 ± 336	719 ± 369	527 ± 278	0.005
SvO_2 (%)	59.5 ± 11.2	61.9 ± 7.9	63.6 ± 8.1	66.1 ± 9.1	0.176
Anticoagulants					
Vitamin K antagonist	15 (93.7)	21 (84.0)	67 (74.4)	10 (83.3)	
Direct oral anticoagulants	1 (6.3)	4 (16.0)	23 (25.6)	2 (16.7)	
Medical treatment since diagnosis					
PAH-targeted drugs (n, %)	8 (50.0)	18 (72.0)	52 (57.8)	10 (83.3)	
sGC stimulator (n, %)	6 (37.5)	14 (56.0)	30 (33.3)	7 (58.3)	
ERA (n, %)	4 (25.0)	3 (12.0)	19 (21.1)	1 (8.3)	
PDE5-i (n, %)	0 (0.0)	1 (4.0)	8 (8.9)	2 (16.7)	
Prostacyclin analog (n, %)	1 (6.3)	3 (12.0)	4 (4.4)	0 (0.0)	
Home oxygen therapy (n, %)	6 (37.5)	11 (44.0)	47 (52.2)	6 (50.0)	
Medical treatment at last follow up					
PAH-targeted drugs (n, %)	2 (12.5)	2 (8.0)	30 (33.3)	10 (83.3)	
sGC stimulator (n, %)	2 (12.5)	2 (8.0)	26 (28.9)	7 (58.3)	
ERA (n, %)	0 (0.0)	0 (0.0)	3 (3.3)	1 (8.3)	
PDE5-i (n, %)	0 (0.0)	0 (0.0)	1 (1.1)	2 (16.7)	
Prostacyclin analog (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Home oxygen therapy (n, %)	2 (12.5)	4 (16.0)	28 (31.1)	6 (50.0)	

List of abbreviations: NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; RAP: right atrial pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation; PAH: pulmonary arterial hypertension; sGC: soluble guanylate cyclase; ERA: endothelin-receptor antagonists; PDE5-i: phosphodiesterase type-5 inhibitors.
Data are given as mean ± standard deviation or median [interquartile range].
* one-way ANOVA, comparison between PEA only, Combination, BPA only, and No intervention.

Table 2
Clinical and Hemodynamic Data at Baseline and *Re*-evaluation of each treatment group.

	Operated								Not-operated			
	PEA only Re-evaluation data available ($n = 15$)			Combination (PEA + BPA) Re-evaluation data available ($n = 24$)					BPA only Re-evaluation data available ($n = 81$)			
	Baseline	*p* value	Re-evaluation*	Baseline	*p* value	After 1st intervention	*p* value	Re-evaluation*	Baseline	*p* value	Re-evaluation*	*P* value*
Characteristics												
NYHA FC (I,II / III,IV) (%)	18.8 / 81.2	0.001	81.2 / 18.8	28.0 / 72.0	0.010	68.0 / 32.0	0.023	96.0 / 4.0	16.7 / 83.3	< 0.001	85.4 / 14.6	0.315
6MWD (m)	324 ± 194	0.018	452 ± 157	343 ± 88	0.709	347 ± 138	0.002	418 ± 105	311 ± 95	< 0.001	380 ± 110	0.174
BNP (pg/mL)**	133 [569]	0.116	96 [260]	207 [445]	0.006	114 [135]	0.003	53 [84]	70.8 [175.2]		24.5 [38.5]	< 0.001
SaO2 (%)	91.0 ± 5.8	0.007	95.6 ± 4.9	91.0 ± 4.0	0.261	92.2 ± 4.3	0.030	94.3 ± 2.8	90.5 ± 4.7	< 0.001	93.7 ± 2.9	0.003
Hemodynamics												
Systolic PAP (mmHg)	70.0 ± 18.9	< 0.001	32.9 ± 11.0	75.6 ± 16.8	< 0.001	48.7 ± 15.8	< 0.001	30.4 ± 8.4	64.1 ± 15.3	< 0.001	35.6 ± 7.7	0.025
Diastolic PAP (mmHg)	24.9 ± 5.2	< 0.001	13.3 ± 4.9	25.3 ± 7.3	< 0.001	16.8 ± 8.0	0.002	11.0 ± 4.4	21.3 ± 6.0	< 0.001	11.7 ± 3.8	0.236
Mean PAP (mmHg)	40.7 ± 8.7	< 0.001	20.5 ± 6.7	42.4 ± 9.0	< 0.001	27.4 ± 8.3	< 0.001	17.9 ± 4.9	36.4 ± 8.8	< 0.001	20.7 ± 4.6	0.067
Mean RAP (mmHg)	7.1 ± 5.2	0.956	7.2 ± 3.9	5.4 ± 2.7	0.523	5.9 ± 4.3	0.046	3.6 ± 3.4	5.1 ± 3.0	0.005	3.8 ± 2.9	0.002
PAWP (mmHg)	10.5 ± 3.4	0.785	10.1 ± 3.5	8.3 ± 3.7	0.622	8.8 ± 3.7	0.439	7.8 ± 3.4	8.2 ± 3.3	0.588	8.0 ± 3.2	0.087
Cardiac Output (L/min)	3.52 ± 1.60	0.001	5.02 ± 2.15	3.09 ± 0.70	< 0.001	3.70 ± 0.79	0.264	3.84 ± 0.84	3.64 ± 1.14	< 0.001	4.07 ± 1.03	0.007
Cardiac Index (L/min/m^2)	2.11 ± 0.72	0.006	3.06 ± 0.93	1.93 ± 0.39	< 0.001	2.36 ± 0.45	0.782	2.38 ± 0.41	2.30 ± 0.68	< 0.001	2.59 ± 0.58	0.003
PVR (dynes.s. cm^{-5})	833 ± 392	< 0.001	205 ± 129	954 ± 336	< 0.001	415 ± 161	< 0.001	222 ± 76	694 ± 347	< 0.001	267 ± 126	0.082
SvO2 (%)	58.9 ± 10.4	0.039	66.4 ± 7.2	61.9 ± 7.9	0.079	59.7 ± 7.6	< 0.001	66.3 ± 4.3	63.8 ± 8.0	< 0.001	68.2 ± 4.9	0.268
Absolute change of mean PAP from baseline (mmHg)			−20.0 ± 9.3			−15.0 ± 9.8		−24.5 ± 8.9			−15.7 ± 9.4	<0.001
% decrease of mean PAP from baseline (%)			−47.9 ± 17.1			−34.0 ± 19.4		−56.5 ± 11.9			−40.4 ± 17.1	<0.001
% decrease of PVR from baseline (%)			−73.7 ± 11.3			−54.5 ± 16.7		−74.3 ± 11.8			−54.9 ± 22.5	<0.001

List of abbreviations: NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; SaO2: arterial oxygen saturation; RAP: right atrial pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation;
* One-way ANOVA, comparison between re-evaluation data in PEA only, Combination, and BPA only.
** Median [interquartile range].

$p < 0.001$: Combination group vs BPA only group) and − 73.7 ± 11.3%, −74.3 ± 11.8%, −54.9 ± 22.5%, ($p = 0.899$: PEA only group vs Combination group; $p = 0.003$: PEA only group vs BPA only group; $p < 0.001$: Combination group vs BPA only group) respectively.

3.3. Survival

During a median follow-up period of 40.4 months (IQR: 17.0; 65.7 months), 14 of 143 patients (9.8%) passed away. The 1-, 3-, 5-year overall survival rates were 97.1%, 92.6%, 87.8%, respectively (Fig. 1). Fig. 2 shows the Kaplan-Meier estimates of survival in operated patients ($n = 41$; PEA only group: $n = 16$, Combination group: $n = 25$) and in not-operated patients ($n = 102$; BPA only group: $n = 90$, No intervention group: $n = 12$). The 1-, 3-, 5-year survival rates of operated patients were 97.4%, 90.0%, 90.0%, compared to 96.9%, 91.8%, 86.9% in not-operated patients ($p = 0.579$ by the Cox-Mantel log-rank test). Fig. 3 shows the Kaplan-Meier estimates of survival in each treatment group. The 1-, 3-, 5-year survival rates in the PEA only group were 92.9%, 85.1%, 74.5%, those in the BPA only group were 97.6%, 93.0%, 90.1%. There was no mortality in the Combination group. The cause of death in each treatment group are summarized in Table 3. Three patients died of right heart failure, whereas nine patients died of malignant disease after 26.4 ± 18.7 months after interventional treatments or diagnosis. In seven of these patients, malignancy had not been suspected at the time of CTEPH diagnosis.

4. Discussion

The present study describes one of the monocentric cohorts of CTEPH patients with long-term follow-up in the modern management era where more than 90% of CTEPH patients have undergone interventional treatments with PEA or BPA, or both. Almost normal hemodynamics could be achieved after these interventional treatments, and these hemodynamic improvements translate into excellent survival in not only operable CTEPH but also non-operable CTEPH. Additionally, combination therapy with PEA and BPA could improve hemodynamics dramatically, even though baseline hemodynamics were severe. BPA and PEA appear to be mutually complementary therapies for CTEPH patients.

The recent 2018 World Symposium on pulmonary hypertension in Nice proposed and recommended that treatment strategy should be assessed by an expert CTEPH team, and PEA for operable patients,

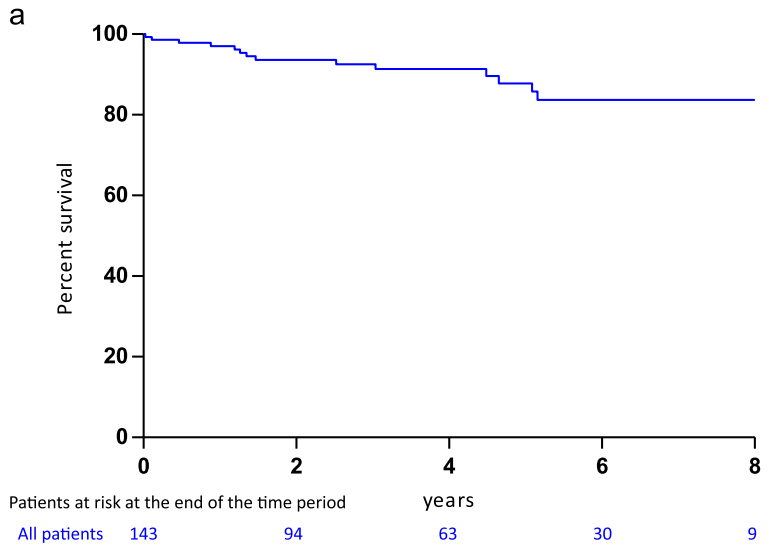

Fig. 1. Kaplan-Meier estimates of the 8-year survival in all patients with CTEPH diagnosed since 2011 ($n = 143$).

whereas PH targeted medical therapy with or without BPA for inoperable cases. The international prospective registry by Delcroix et al. from 27 European centers showed that of 679 CTEPH patients, 404 patients (59%) underwent PEA and 275 patients (41%) were not operated. Not-operated patients had not undergone BPA because BPA had not been established as an alternative treatment in European countries at that time [6]. Amsallem et al. reported that although the absolute number of PEA had not changed since initiation of the BPA program, the percentage of operated patients had decreased from 82% to 51% in the French National Reference Center [20]. Siennicka et al. also reported that the percentage of patients who underwent PEA had decreased from 59% to 19% since initiating the BPA program in Poland [21]. This suggested that the total number of CTEPH patients referred to PH expert centers had increased for interventional treatment since initiation of BPA. In our study, of 143 patients diagnosed with CTEPH since BPA era, 131 patients (91.6%) underwent interventional treatment with PEA ($n = 41$, 28.7%) and BPA ($n = 90$, 62.9%), and 25 out of 41 operated patients (61.0%) underwent combination therapy with PEA and BPA. The efficacy of these interventional therapies was satisfactory with a $-73.7 \pm 11.3\%$ decrease of PVR in the PEA only group, $-74.3 \pm 11.8\%$ decrease of PVR in the Combination group, and $-54.9 \pm 22.5\%$ decrease of PVR in the BPA only group. Almost normal hemodynamics had been achieved after these interventional treatments. A direct and simple comparison of clinical outcome between PEA and BPA is not appropriate. Baseline hemodynamics, pathological status, or characteristics of operable and non-operable might be different. Our results showed that operated patients were younger, more frequently male, and more history of acute pulmonary embolism in the Japanese patient cohort. Indeed these characteristics were consistent with those of the international CTEPH registry by Pepke-Zaba et al. [5].

The aforementioned international prospective CTEPH registry showed that not-operated CTEPH patients ($n = 275$) had a significantly worse prognosis with a 3-year survival rate of 70%, while that of patients undergoing surgery was 89% before BPA era [6]. In a Polish cohort study,

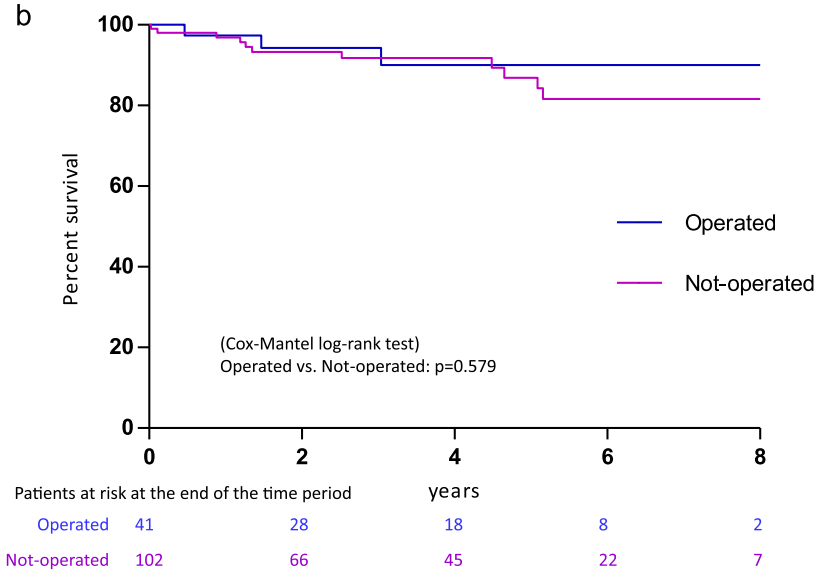

Fig. 2. Kaplan-Meier estimates of the 8-year survival in 41 operated patients (blue line) and 102 not-operated patients (red line); p = 0.579 (Cox-Mantel log-rank test).

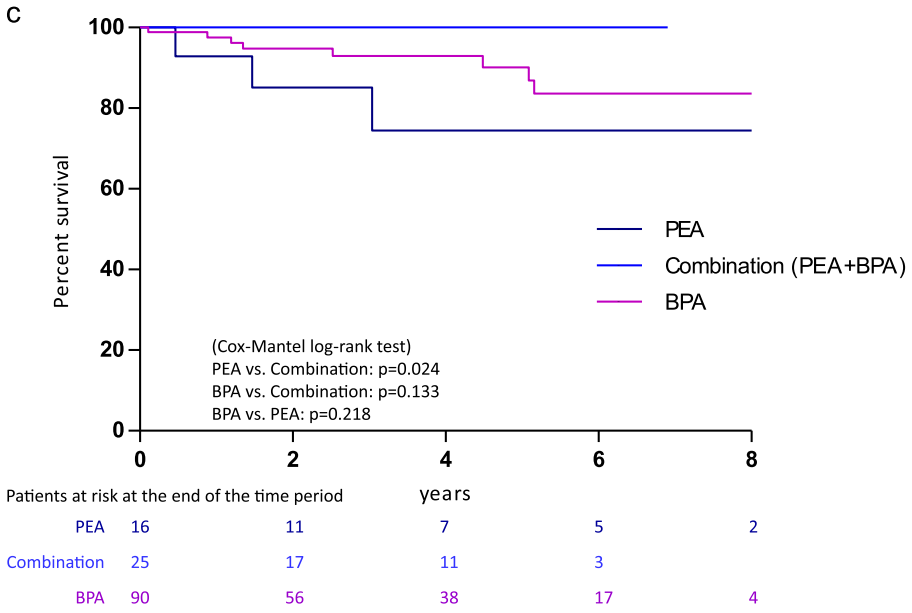

Fig. 3. Kaplan-Meier estimates of the 8-year survival in the PEA only group ($n = 16$: dark blue line), Combination group ($n = 25$: blue line), and BPA only group ($n = 90$: red line); $p = 0.024$ (PEA vs. Combination), $p = 0.133$ (BPA vs. Combination), $p = 0.218$ (BPA vs. PEA) (Cox-Mantel log-rank test).

Siennicka et al. reported that non-operable patients treated with BPA and PAH drugs exhibited better survival rates than those treated with PAH drugs alone (92% versus 79% at 2 years) [21]. Taniguchi et al. reported that the 1- and 3-year survival rates of not-operated patients ($n = 170$) were 91.6% and 85.0% in the recent management era after the availability of BPA from the French reports. In that study cohort, 80 of 170 not-operated patients (47.1%) underwent BPA, and BPA was independently associated to improve survival [22]. In the present study cohort, 90 of 102 not-operated patients (88.2%) had been treated with BPA, and concurrent use of PAH drugs in more than half the cases. Almost normal hemodynamics were achieved by BPA, resulting in excellent survival rates of not-operated patients with the 1-, 3-, and 5-year survival rate being 96.9%, 91.8%, and 86.9%. There was no longer significant difference in survival between operated and not-operated CTEPH patients.

Furthermore, "combination therapy" combining PEA and BPA is a possible treatment strategy. In our study, 22 out of 41 operated patients underwent additional BPA for residual pulmonary hypertension or symptoms, and 3 patients had antecedent BPA to decrease surgical risk before PEA. Our study demonstrated that combination approach with PEA and BPA could achieve dramatical improvements of hemodynamics and symptoms with no deaths, although baseline hemodynamics were severe. In a study of 15 patients, Araszkiewicz et al. reported that additional BPA could further improve the hemodynamics and exercise capacity of patients with residual or recurrent PH after PEA [23]. Yanaka et al. reported that although the hemodynamics were almost normalized after PEA, additional BPA for symptomatic patients (>NYHA 2) achieved further improvement of exercise capacity and symptoms compared to patients treated only by PEA in a study of 20 patients [24]. Although PEA should be considered as the first choice for operable patients, combination therapy consisting of initial unilateral BPA to the lung with distal lesions and secondary PEA to the other lung with proximal lesions for severe hemodynamic patients might be appealing; antecedent BPA could improve a very high PVR, a risk factor of perioperative mortality [25]. Secondary BPA after PEA could further improve hemodynamics,

Table 3
Cause of death for all non-survivors.

Treatments	Gender	Time from intervention to death	Cause of death	Any signs of malignancy at the time of CTEPH diagnosis
Post PEA	Female	5 months	Right heart failure	–
	Female	15 months	Uterus cancer	No
	Male	35 months	Lung cancer	No
Post BPA	Female	0.5 months	Right heart failure	–
	Female	25 months	Pneumonia	–
	Male	50 months	Leukemia	No
	Female	16 months	Bile duct cancer	No
	Female	61 months	Brest cancer	No
	Male	13 months	Lung cancer	No
	Female	27 months	Leukemia	No
	Female	6 months	Pancreas cancer	Yes
No interventions	Female	56 months from diagnosis	Advanced age	–
	Male	0.4 months from diagnosis	Right heart failure	–
	Male	15 months from diagnosis	Lung cancer	Yes

List of abbreviations: CTEPH: chronic thromboembolic pulmonary hypertension; PEA: pulmonary endarterectomy; BPA: balloon pulmonary angioplasty.

exercise capacity, and symptoms, while antecedent BPA before PEA could reduce perioperative risk. PEA and BPA would be mutually complementary therapies for CTEPH patients. Several reports already support the excellent results of specific patient cohorts who underwent PEA and BPA [12,13,15,25]; however, the present study indicated that almost all patients with CTEPH could be mechanically treated with either PEA or BPA in a CTEPH expert center, which would lead to a notable improvement in their prognosis in the modern management era. Therefore, CTEPH patients should be evaluated and treated in a CTEPH expert center.

Another finding of our study is that the most frequent cause of death in CTEPH patients was not right heart failure, but the development of malignant cancer during follow up. The risk of thrombosis in patients with malignant tumors is 6 times higher than in healthy person [26]. Cancer is a risk factor for the development of thrombosis [27]. However, most of the patients who passed away had no signs of malignant tumor at the time of CTEPH diagnosis in this study. CTEPH patients rarely die from right heart failure in the recent management era, however careful screening and follow-up might be required for early diagnosis of cancer. More work is still needed to better understand the relation between CTEPH and malignant cancer.

4.1. Limitations

There are several limitations of this study, the main one being the monocentric and retrospective observational nature of the study. Therefore, the occurrence of some missing values regarding characteristics, hemodynamics, or the re-evaluation of data was unavoidable; this lack of data might have influenced the treatment outcomes. Furthermore, although it is common across CTEPH treatment in Japan, the proportion of patients judged as operable was relatively lower and that of non-operable was higher, the eligibility for PEA or BPA might have biased the impact of these treatments on survival. Moreover, the periods between the intervention and the re-evaluation of hemodynamics were different between the PEA and other groups, which may have obscured the efficacy of PEA. Therefore, direct comparison of the clinical outcomes between treatments may not be appropriate. Additionally, the Combination group included patients who had undergone additional BPA after PEA, as well as patients who had undergone planned antecedent BPA before PEA; this heterogeneity required careful interpretation of the clinical outcomes of the Combination group. Another limitation was that we did not consider the impact of associated medical conditions (such as prior splenectomy or infected pacemaker) which may have been linked to the development of CTEPH. This is because of inconsistent information for these conditions in our hospital records until the most recent few years.

4.2. Conclusion

The present study describes one of the monocentric cohorts of CTEPH patients with long-term follow-up in the modern management era where most of CTEPH patients have undergone interventional treatments with PEA or BPA, or both. These interventional treatments and the concurrently increasing use of sGC stimulators improved hemodynamic dramatically, which translate into excellent survival not only in operable CTEPH but also in non-operable CTEPH. Additionally, combination therapy with PEA and BPA could improve hemodynamics dramatically even though baseline hemodynamics were severe, and it might contribute to improve outcomes. Both BPA and PEA appear to be mutually complementary therapies for CTEPH patients.

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Conflict of interest statement

Dr. Taniguchi reports a research grant in the field of pulmonary hypertension from Actelion Pharmaceuticals Ltd., as well as Nippon Shinyaku Ltd. Dr. Emoto reports a research grant in the field of pulmonary hypertension from Bayer Ltd., Actelion Pharmaceuticals Ltd., and Nippon Shinyaku Ltd. Dr. Hirata reports a research grant in the field of pulmonary hypertension from Actelion Pharmaceuticals Ltd., and Nippon Shinyaku Ltd. The other authors report no conflicts.

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