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Long-term advanced therapy with bosentan improves symptoms and prevents deterioration of inoperable chronic thromboembolic pulmonary hypertension

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ABSTRACT

Aims: Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating disease, and treating patients with CTEPH who are not eligible for pulmonary endarterectomy is particularly challenging. Short-term bosentan or phosphodiesterase type-5-inhibitor treatment can greatly improve symptoms and hemodynamics in these patients; however, the long-term benefits of advanced pulmonary vasodilators are not known. We retrospectively investigated the long-term effects of advanced pharmacological therapy in Japanese patients with inoperable CTEPH.

Main methods: Seven consecutive patients with inoperable CTEPH (five women; mean age, 62.6 ± 6.9 years) treated with bosentan were included. World Health Organization functional class (WHO-FC), hemodynamics, exercise capacity, and plasma B-type natriuretic peptide (BNP) concentration were evaluated at baseline and for more than 2 years. Time to clinical worsening was also examined during long-term follow-up.

Key findings: WHO-FC improved significantly, from 3.1 ± 0.4 to 2.1 ± 0.4 ($p = 0.005$). Significant improvement was also seen in pulmonary vascular resistance, which decreased from 786.9 ± 300.0 to 352.2 ± 210.7 dynes s cm^{-5} ($p < 0.05$). Plasma BNP concentration decreased significantly from 1160.0 ± 971.4 to 305.1 ± 285.9 pg/mL ($p < 0.05$). No patient required hospitalization during the follow-up period (mean, 896 ± 564 days).

Significance: Long-term advanced therapy with bosentan significantly improves symptoms, pulmonary vascular resistance, plasma BNP concentration, and time to clinical worsening in Japanese patients with inoperable CTEPH. We consider bosentan to be an essential treatment for these patients.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating disease. It has been reported that the 5-year survival rate in Japanese patients with CTEPH is almost 60%, and that median survival is only 6.8 years (Nakanishi et al., 1997; Kunieda et al., 1999). A mean pulmonary artery pressure (mPAP) greater than 30 mm Hg indicates a much worse prognosis than one less than 30 mm Hg (Nakanishi et al., 1997; Lewczuk et al., 2001). The only approved drug treatment for CTEPH is warfarin, which can improve the prognosis of these patients, while pulmonary endarterectomy (PEA) provides a potential cure and much better prognosis for patients with centrally damaged pulmonary arteries (Dartevelle et al., 2004). The treatment of patients who are not eligible for PEA because of the involvement of distal pulmonary arteries remains challenging.

In CTEPH the pathological lesions are organized thrombi tightly attached to the medial layer of elastic pulmonary arteries, replacing the normal intima. These may completely occlude the lumen or form areas of stenosis, webs, or bands. Interestingly, histological changes in the non-occluded pulmonary arteries are similar to those seen in pulmonary artery hypertension (PAH), such as medial hypertrophy and the intimal proliferative and fibrotic changes that include plexiform lesions (Galiè and Kim, 2006).

As the pathological changes in the pulmonary vasculature appear similar, new pulmonary vasodilating drugs used to treat PAH have also been used in CTEPH: prostanoids (Ono et al., 2003; Cabrol et al., 2007; Skoro-Sajer et al., 2007), endothelin-receptor antagonists (ERAs) (Becattini et al., 2010), and phosphodiesterase type-5 (PDE5) inhibitors (Suntharalingam et al., 2008) are reported to have hemodynamic and clinical benefits, although these have not been established in randomized, placebo-controlled trials. Nonetheless, the prognosis of Japanese patients with CTEPH is improving: it has recently been reported that

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the 5-year survival rate has risen to 87.3% as a result of the use of PAH-specific therapies by almost two-thirds of patients (Nishimura et al., 2013). Currently 37.9% of patients in a CTEPH international registry are recorded as receiving at least one PAH-targeted therapy (Pepke-Zaba et al., 2011).

Recently riociguat, a novel soluble guanylate cyclase stimulator licensed for the treatment of PAH, has been shown to significantly improve exercise capacity and pulmonary vascular resistance (PVR) in patients with inoperable CTEPH or persistent CTEPH after PEA over a 16-week period (Ghofrani et al., 2013). Riociguat appears to have the potential to become the gold standard therapy for CTEPH, although its long-term effects are not known and it is not yet available in Japan.

Of the other PAH-specific drugs, only bosentan can effect a significant reduction in PVR and plasma N-terminal fragment (NT-pro) B-type natriuretic peptide (BNP) concentrations, and a significant improvement in cardiac index (CI) (Jaïs et al., 2008). Importantly, however, BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a 16-week randomized, placebo-controlled clinical trial undertaken in patients with inoperable CTEPH or persistent CTEPH after PEA, reported no improvement in functional outcomes such as 6-minute walk distance (6MWD), World Health Organization functional class (WHO-FC), or time to clinical worsening. Bosentan may offer a therapeutic option for Japanese patients with inoperable CTEPH or persistent CTEPH after PEA, but again its long-term benefits are not known. We retrospectively investigated the effects of bosentan on the symptoms, hemodynamics, exercise capacity, plasma BNP concentrations and time to clinical worsening when it was used as part of a treatment strategy for pulmonary hypertension (PH) in Japanese patients with inoperable CTEPH over a 2-year period.

Patients and methods

The records of consecutive Japanese patients treated with bosentan for symptomatic, inoperable CTEPH at Jichi Medical University Hospital between May 2007 and April 2012 were analyzed retrospectively. All patients met the requirements for CTEPH as follows: pre-capillary PH reflected by a mean pulmonary artery pressure (mPAP) $\geq$25 mm Hg, pulmonary capillary wedge pressure $\leq$15 mm Hg and PVR >2 Wood units in patients with multiple chronic (>6 months) or organized occlusive thrombi or emboli in the elastic pulmonary arteries (Galiè et al., 2009) (Supplemental Table 2). Hemodynamic parameters were measured by right heart catheterization and pulmonary artery disease was detected by ventilation-perfusion lung scan and multirow computed tomography (CT). In five patients, pulmonary artery (PA) clots were successfully treated with warfarin for >1 year before bosentan was initiated. In one patient, no PA thrombus could be detected after a 4-month course of warfarin, and blood D-dimer concentrations were below the limit of detection. In the final patient, no PA thrombus was seen on CT angiography and the levels of D-dimer were in the normal range before warfarin was administered (Supplemental Table 6). All patients were considered to be inoperable because of peripheral PA stenosis. The WHO-FC, hemodynamic parameters, exercise capacity, and plasma BNP concentrations were evaluated at baseline and routinely during follow-up. Right heart catheterization was repeated just before or after initiation of bosentan (supplemental Table 4); on each occasion it was performed 6 to 8 h after the patient had taken their normal dose of bosentan, beraprost and/or sildenafil. Time to clinical worsening due to PH, defined as hospitalization, lung transplantation or death, was also recorded. No specific treatment algorithm was used. Advanced therapies such as prostanoids or PDE5 inhibitors were commenced at the discretion of the supervising physician.

All data are presented as mean $\pm$ standard deviation. A paired *t*-test was used to compare variables at baseline and during follow-up after initiation of bosentan. A p value of <0.05 was considered significant.

Results

Seven consecutive patients with symptomatic inoperable CTEPH were enrolled (two men, five women; mean age 62.6 $\pm$ 6.9 years). None had previously undergone PEA or balloon pulmonary angioplasty (BPA). Six were WHO-FC III and one was WHO-FC IV before the initiation of bosentan. Patient background information, including symptoms, laboratory values, and treatment regimens are presented in Table 1. Before the initiation of bosentan, all patients had been treated with warfarin, five had been treated with beraprost and four with sildenafil. Six patients were treated with diuretics (Supplemental Table 3). Comorbidities included diabetes mellitus in four patients, impaired glucose tolerance in one patient, hypercholesterolemia in two patients, renal dysfunction in two patients and hyperuricemia in five patients (Supplemental Table 1).

After bosentan was added to supplement standard PAH-specific therapy, WHO-FC significantly improved from IV to III in one patient and from III to II in 6 patients ($p = 0.005$). In three patients in whom right heart catheterization was performed just before or after initiation of bosentan (cases 4, 5 and 6 at 1 year, 9 months and 1 year 9 months after initiation of bosentan, respectively; Supplemental Table 4), mean PVR significantly decreased from 786.9 $\pm$ 300.0 dynes s cm^{-5} to 352.2 $\pm$ 210.7 dynes s cm^{-5} ($p < 0.05$) over 22 months. Mean plasma BNP concentration also decreased significantly, from 1160.0 $\pm$ 971.4 pg/mL to 305.1 $\pm$ 285.9 pg/mL ($p < 0.05$). We also observed several results that suggested a trend toward improvement, but did not reach statistical significance: 6MWD increased from 257.0 $\pm$ 151.0 m to 360.8 $\pm$ 80.4 m ($p = 0.11$, $n = 4$, follow-up 708 $\pm$ 120 days), mPAP decreased from 47.0 $\pm$ 7.6 mmHg to 41.3 $\pm$ 8.3 mm Hg and CI increased from 2.18 $\pm$ 0.39 L/min/m^2 to 3.59 $\pm$ 1.72 L/min/m^2 ($n = 3$, follow-up 671 $\pm$ 116 days; Fig. 1A–F). No patient's condition worsened and none required hospitalization during the follow-up period; notably one patient had required inpatient hospital treatment 11 times before bosentan was started (median follow-up period, ~28 months). The details of drugs used in the follow-up period are shown in the supplemental Tables 4 and 5.

Discussion

Our results show that advanced therapy with bosentan over 2 years improves WHO-FC, PVR, plasma BNP concentrations, and time to clinical

Table 1
Baseline clinical, functional, and hemodynamic characteristics.

Variable	
Age, yrs	62.6 $\pm$ 6.9
Male Female, *n*	2 5
Previous PEA, *n*	0
WHO-FC, II/III/IV, *n*	0/6/1
mPAP, mmHg ($n = 3$)	47.0 $\pm$ 7.6
PVR, dsc^{-5} ($n = 3$)	786.9 $\pm$ 300.0
CI, L/min/m^2 ($n = 3$)	2.18 $\pm$ 0.39
6MWD, m ($n = 4$)	257.0 $\pm$ 151.0
BNP, pg/mL	1160.0 $\pm$ 971.4
Medications	
Warfarin 2–6 mg, *n*	7
Beraprost 120 μg, *n*	5
Sildenafil 60 mg, *n*	4
Hypertension	1
Diabetes mellitus	4
Hyperlipidemia	2
Renal failure	2
Hyperuricemia	5

Data are presented as mean $\pm$ standard deviation unless otherwise indicated.
Abbreviations: BNP, plasma B-type natriuretic peptide; CI, cardiac index; WHO-FC, World Health Organization functional class; mPAP, mean pulmonary artery pressure; 6MWD, 6-minute walk distance; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance.

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