Long-term efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension

M.C. Post, H.W.M. Plokker, J.C. Kelder, R.J. Snijder

Background. Inoperable chronic thromboembolic pulmonary hypertension (CTEPH) is associated with a poor survival.

Objectives. To evaluate the long-term response to a dual endothelin receptor antagonist in patients with inoperable CTEPH.

Methods. All consecutive 18 patients (mean age 63 ± 14 years) treated with bosentan for symptomatic inoperable CTEPH were included. Efficacy was evaluated by the log value of serum levels of N-terminal-pro brain natriuretic peptide (log NT-pro BNP), New York Heart Association functional class (NYHA), and the six-minute walk test (6-MWT). All follow-up data (median 31 months) were compared with baseline and divided into: short-term (<12 months), mid-term (between 12 and 24 months), and long-term follow-up (>24 months).

Results. At baseline, 15 patients were in NYHA class III and three in NYHA class IV, mean log NT-pro BNP level was 7.2 ± 1.4 log pg/ml, and mean 6-MWT distance was 404 ± 125 m. During short-term follow-up ($n=18$), the NYHA class improved ($p=0.001$), 6-MWT distance increased by 33 m ($p=0.03$), and log NT-pro BNP decreased to 6.9 ± 1.4 log pg/ml ($p=0.007$). During mid-term follow-up ($n=17$), the NYHA class improved ($p<0.001$), the mean 6-MWT distance increased by 41 m ($p=0.01$), and log NT-pro BNP was 6.9 ± 1.4 log pg/ml ($p=0.31$). During late follow-up ($n=14$) the NYHA class was still improved

($p=0.03$), the 6-MWT distance decreased by 9 m ($p=0.73$), and log NT-pro BNP was 7.1 ± 1.5 log pg/ml ($p=0.91$). The overall four year survival rate was 88%.

Conclusion: Bosentan seems to be effective during long-term treatment in patients with inoperable CTEPH. (*Neth Heart J* 2009;17:329-33).

Keywords: pulmonary hypertension, bosentan, follow-up, thromboembolism

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious devastating disease with a markedly impaired survival.¹ It is characterised by obstruction of the pulmonary arteries with organised fibrotic material, presumed to be the consequence of incomplete resolution of pulmonary emboli. This results in a progressive increase in pulmonary vascular resistance and right ventricular dysfunction with severe exercise limitation and right-sided heart failure. Approximately 1.5% of the patients who survive a pulmonary thromboembolic event will develop CTEPH within the first two years following an acute embolus.² Left untreated, the prognosis is poor with a survival rate of 50% after five years.³

The treatment of choice is a pulmonary endarterectomy, providing a potential cure for the disease.⁴ In this procedure the fibrotic material is removed from the proximal pulmonary arteries. However, in some patients endarterectomy is not an option due to severe comorbidity or the predominant involvement of distal pulmonary arteries.

Bosentan, a dual receptor endothelin antagonist, has an established role in the management of patients with pulmonary arterial hypertension.^{5,6} The endothelin-1 levels are increased in patients with CTEPH and correlate with the clinical severity of the disease.⁷ In recent studies, bosentan has been demonstrated to improve function during short-term follow-up and may offer a therapeutic option for patients with inoperable CTEPH.⁸⁻¹⁰ The beneficial effect during long-term follow-up is largely unknown. The aim of the present study was to evaluate the efficacy of bosentan

M.C. Post

H.W.M. Plokker

J.C. Kelder

Department of Cardiology, St Antonius Hospital, Nieuwegein, the Netherlands

R.J. Snijder

Department of Pulmonology, St Antonius Hospital, Nieuwegein, the Netherlands

Correspondence to: M.C. Post

Department of Cardiology, St Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, the Netherlands
E-mail: m.post@antonius.net

during mid- and long-term follow-up in inoperable CTEPH.

Methods

Patient selection

The present study was conducted at the Pulmonary Hypertension Unit of the St Antonius Hospital in Nieuwegein. This centre is one of the largest referral centres for surgical treatment of CTEPH in the Netherlands. The diagnosis of CTEPH was based on a standardised assessment of all patients including ventilation-perfusion scanning, CT-angio of the chest, chest radiography, transthoracic echocardiography, pulmonary angiography and right-sided heart catheterisation, and arterial blood gas analysis at rest and exercise. Other aetiologies for pulmonary hypertension were excluded. A multidisciplinary panel including pulmonologists, radiologists, cardiologists, and cardiothoracic surgeons reviewed each case. Inoperability was based on the unfavourable distal distribution of the occlusive disease.

Study design

This is a retrospective case series of patients treated off-label with bosentan. All consecutive patients with inoperable CTEPH were enrolled between February 2003 and August 2006. Compassionate use of bosentan was approved for each patient, in accordance with the Declaration of Helsinki of 1975 and in adherence to the International Conference of Harmonisation Good Clinical Practice Guidelines. All patients were informed that they were receiving a novel drug for the management of CTEPH, with potential adverse effects.

All patients started the study with bosentan 62.5 mg twice daily for four weeks and continued with 125 mg twice daily. The study was approved by the local medical ethics committee.

Follow-up

Prior to bosentan treatment and during follow-up all patients underwent a 6-minute walk test (6-MWT) and blood samples were obtained for assessment of liver function, anticoagulation, and N-terminal-pro-brain natriuretic peptide (NT-pro BNP). After initiation of bosentan therapy patients were evaluated on an outpatient basis at four weeks, 12 weeks and thereafter every six months. The follow-up period was divided into short-term (less than 12 months), mid-term (between 12 and 24 months), and long-term follow-up (more than 24 months). Safety was assessed by monitoring liver enzymes, vital signs, and adverse events.

Efficacy

The efficacy endpoints at follow-up were compared with baseline, including exercise capacity using the 6-MWT, the New York Heart Association (NYHA) functional class, and the serum levels of NT-pro-BNP.

Statistical analysis

The data are expressed as mean and standard deviation. The NT-pro BNP levels were presented as log levels. Changes from baseline were evaluated with a paired *t* test for continuous variables and with a Wilcoxon rank-sum test or χ^2 test for ordinal variables if appropriate. Time to event data are presented as Kaplan-Meier curves. Significance was determined at $p < 0.05$; all reported *p* values were two tailed. All statistical analyses were performed by using SPSS software (SPSS Inc., version 14.0 for Windows; Chicago, IL).

Results

Patients characteristics

Eighteen patients (7 female, mean age 63 ± 14 years) were treated with bosentan for a mean period of 33 ± 15 months, median with range 31 (5 to 55) months. All patients had inoperable CTEPH due to the distal localisation of the disease. All patients were treated adequately with oral anticoagulants. None of the patients had elevated liver enzymes prior to the start of bosentan. The interval between the diagnosis of inoperable CTEPH and the start of bosentan was less than six months in 14 patients, between six and 12 months in three patients and more than 12 months in one patient. The characteristics of the patients at baseline are summarised in table 1.

Table 1. Characteristics at baseline of the inoperable CTEPH patients before treatment with bosentan.

Characteristics at baseline	Data
Female/male (n)	7/11
Age (years)	63.2 ± 13.5
Body mass index (kg/m^2)	25.9 ± 3.2
Systolic blood pressure (mmHg)	123 ± 15
Diastolic blood pressure (mmHg)	75 ± 11
NYHA class III/IV (n)	15/3
Log NT-pro BNP (log pg/ml)	7.2 ± 1.4
6-MWT (m)	405 ± 125
Catheterisation	
- Systolic PAP (mmHg)	75 ± 17
- Diastolic PAP (mmHg)	22 ± 8
- Mean PAP (mmHg)	41 ± 11
- PVR (dyn.s.cm^{-5})	625 ± 298
- CO (l)	4.7 ± 1.2
Arterial blood gas	
- PaO_2 (kPa)	8.7 ± 1.8
- Saturation (%)	92 ± 7.8
Follow-up (months)	33 ± 15

NYHA=New York Heart Association functional class, NT-pro BNP=N-terminal-pro brain natriuretic peptide, 6-MWT=six-minute walk test, PAP=pulmonary artery pressure, PVR=pulmonary vascular resistance, CO=cardiac output, PaO_2 =partial oxygen pressure. Data are presented as mean $\pm$ standard deviation.

Efficacy and safety during follow-up

None of the patients developed a significant increase in liver enzymes or adverse events during the entire follow-up. Three patients (17%) died during follow-up. A 70-year-old female died seven months after the start of bosentan due to progressive CTEPH (NYHA class IV and a mean PAP of 64 mmHg at baseline), despite the institution of epoprostenol. A 58-year-old man died more than four years after the start of bosentan due to progression of CTEPH (NYHA class III and a mean PAP of 58 mmHg at baseline), despite the institution of epoprostenol. A 77-year-old man died 18 months after the start of bosentan due to cancer. The one-year survival rate was 94%, and the four-year survival rate 88%. The Kaplan-Meier curve for overall survival is shown in figure 1.

The short-term follow-up data were present for all patients (less than 12 months). The mean difference in 6-MWT distance was +32.6 m (95% CI 3.1 to 62.2; $p=0.03$). The mean difference in log NT-pro BNP was -0.30 log pg/ml (95% CI -0.10 to -0.50 ; $p=0.007$). The NYHA functional class improved compared with baseline. The NYHA functional class did not worsen in any of the patients.

The mid-term follow-up data were present for 17 patients (between 12 and 24 months). The mean difference in 6-MWT distance was +41.3 m (95% CI 10.7 to 71.9; $p=0.01$). The log levels of NT-pro BNP showed a non-significant decrease with a mean difference of -0.21 log pg/ml (95% CI -0.65 to 0.22 ; $p=0.31$). The NYHA functional class significantly improved compared with baseline. The NYHA functional class did not increase compared with baseline in any of the patients.

Fourteen patients were treated with bosentan for more than 24 months. The mean difference in 6-MWT was -8.8 m (95% CI -63.6 to 45.9 ; $p=0.73$). The mean difference in log NT-pro BNP levels was -0.03 log pg/ml (95% CI -0.55 to 0.49 ; $p=0.91$). The NYHA functional class showed a significant improvement compared with baseline. All these data are summarised in table 2, and figures 2 and 3.

Figure 1. Kaplan-Meier survival curve for patients with inoperable CTEPH treated with bosentan.

Figure 2. Difference in NYHA functional class during treatment with bosentan in inoperable CTEPH. NYHA=New York Heart Association functional class, CTEPH=chronic thromboembolic pulmonary hypertension; p values are compared with baseline.

Table 2. Difference in 6-MWT, NT-pro BNP and functional class during follow-up.

Characteristics	Baseline	<12 months	p	12-24 months	p	>24 months	p
Number	18	18	-	17	-	14	-
Female/male	7/11	7/11	-	6/11	-	6/8	-
6-MWT (m)	405±125	437±120	0.03	465±93	0.01	401±125	0.73
Log NT-pro BNP (log pg/ml)	7.2±1.4	6.9±1.4	0.007	6.9±1.4	0.31	7.1±1.5	0.91
NYHA II/III/IV	0/15/3	7/10/1	0.001	10/7/0	<0.001	6/7/1	0.03

NYHA=New York Heart Association functional class, NT-pro BNP=N-terminal-pro brain natriuretic peptide, 6-MWT=six-minute walk test, PAP=pulmonary artery pressure, p values are compared with baseline.

Figure 3. Box-plot presenting the difference in 6-MWT distance during follow-up. 6-MWT=six-minute walk test; p values are compared with baseline.

Discussion

This is one of the first studies to determine efficacy and safety of bosentan during a long-term follow-up of more than two years in inoperable CTEPH patients. This observational study shows an improvement in exercise capacity, NYHA functional class during short-term and mid-term follow-up after the treatment with bosentan. The disease seems to stabilise at long-term follow-up. The four-year survival rate was 88% in our patients with inoperable CTEPH treated with bosentan.

The short-term efficacy of bosentan in this group of patients has been described in a few, non-placebo controlled and mainly retrospective studies.⁸⁻¹¹ Bonderman et al. described the short-term efficacy and safety of bosentan in 16 inoperable CTEPH patients with a mean age of 70 years, a mean PAP of 52 mmHg, and an NYHA functional class of II in two, III in nine, and IV in the remaining five patients. After a follow-up of six months, they found a significant improvement in the NYHA functional class, an increase in the mean 6-MWT distance from 299 m to 391 m, and a significant decrease in the serum levels of NT-pro BNP.⁸ Similar findings were reported by Hoepfer et al. during a three-month follow-up period of 19 inoperable CTEPH patients with a mean age of 60 years, a mean PAP of 48 mmHg and an NYHA functional class of II in two, III in 14, and IV in two patients. The 6-MWT distance increased from a mean of 340 m before to 413 m after treatment with bosentan. A right-sided heart catheterisation at three-month follow-up was performed and showed a significant decrease in the mean pulmonary artery pressure to 42 mmHg and pulmonary vascular resistance, and an increase in the cardiac index.⁹ In an observational study by Hughes et

al., 20 patients with inoperable CTEPH could be included. The NYHA classification was II in five, III in 14, and IV in one patient, and the mean PAP was 48 mmHg. After at least three months of treatment with bosentan, they also found a significant improvement in NYHA classification, 6-MWT distance from 262 m before to 307 m after bosentan, the pulmonary vascular resistance and the cardiac index.¹¹ We describe similar findings in our 18 patients (mean PAP was 41 mmHg and NYHA classification was III in 15, and IV in three) with inoperable CTEPH at short-term follow-up after bosentan therapy, including a significant improvement in NT-pro BNP, NYHA functional class, and a mean increase in 6-MWT distance of 33 m. However, we did not perform a right-sided heart catheterisation during follow-up. A positive correlation has been described between the BNP levels and pulmonary vascular resistance and pulmonary arterial pressure.¹² It may serve as a non-invasive prognostic indicator for pulmonary arterial hypertension.¹³

Until now, only two studies have described the efficacy of bosentan in inoperable CTEPH after one or more years. Firstly, the study by Hughes et al. described 47 patients with a mean age of 60 years and a mean PAP of 51 mmHg. The NYHA functional class was II in ten, III in 32, and IV in five patients. After one year of treatment they found a significant increase in mean 6-MWT distance from 312 m to 364 m. A repeated right-sided heart catheterisation took place in 28 patients and showed a decrease in total pulmonary resistance and an increase in the cardiac index. The one-year survival rate was 96% and during a mean duration of exposure to bosentan of 20 months the overall survival rate was 89%.¹⁰ Secondly, the study by Seyfarth et al. studied the long-term efficacy of bosentan in the same group of patients. They included 12 patients with a mean age of 57 years, a mean PAP of 48 mmHg and an NYHA functional class of III in all patients. The mean 6-MWT distance increased from 319 m before to 402 m at 12 months and 381 m at 24 months after initiation of bosentan treatment. The NYHA functional class improved in these patients until a follow-up of 24 months, and none of the patients died in their registry. The right ventricular function, based on Doppler echocardiography, improved during the entire follow-up period of 24 months.¹⁴ We found a persistent increase in the 6-MWT, improvement in the NYHA classification and serum levels of NT-pro BNP during mid-term follow-up, and found the greatest magnitude of improvement within two years after the start of treatment with bosentan. During a follow-up of more than two years the disease seems to stabilise in comparison with the baseline findings. The one-year survival rate in our study was 94% and the four-year survival rate was 88%. In contrast to the historical data, where a four-year survival rate of 30% has been reported in non-treated patients with a mean PAP between 40 and 50 mmHg.³

Bosentan seems to be safe in the treatment of inoperable CTEPH. The different studies, mentioned above, described an elevation in liver enzymes in 0 to 2% of the patients and none of them developed major adverse events. Our data confirmed these findings.

Our study has limitations. Firstly, our and other described studies were uncontrolled, without a blinded randomised design. Secondly, it is a single centre observation describing a small number of patients. Therefore our study needs to be carefully interpreted.

Despite these limitations, our study demonstrates the usefulness of bosentan during long-term follow-up of more than two years. The exercise capacity, functional class and serum levels of NT-pro BNP seem to improve in this otherwise devastating progressive disease. Bosentan may offer an effective therapeutic option for patients with inoperable CTEPH. However, randomised placebo-controlled trials are necessary to confirm our findings. ■

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