Bosentan for treatment of pulmonary arterial hypertension (I)

Sabina A Antoniu
University of Medicine and Pharmacy, Clinic of Pulmonary Disease, 62 Costache Negri St, Bl.C2, Sc.A, Et.5, Ap.19, 700070 Iasi, Romania
Tel.: +40 232 219 694
Fax: +40 232 211 500
sabinaantoniu@excite.com

Evaluation of: McLaughlin VV., Sitbon O., Badesch DB. *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur. Respir. J.* 25, 244–249 (2005).

Primary pulmonary hypertension is a rare life-threatening form of pulmonary arterial hypertension. Several pharmacologic classes have recently become available for primary pulmonary hypertension treatment – prostacyclin and prostacyclin derivatives, endothelin receptor antagonists and phosphodiesterase inhibitors. Bosentan (Tracleer®) is an oral dual-endothelin receptor antagonist approved in Europe and North America for the treatment of pulmonary arterial hypertension. Several studies focused on the efficacy and safety of bosentan as an add-on or first-line therapy in primary pulmonary hypertension and pulmonary arterial hypertension related with connective tissue diseases. The current study assesses the impact of first-line bosentan therapy on the survival of primary pulmonary hypertension patients, compares it with a predicted hemodynamic survival also and focuses on the detection of predictors of survival.

Pulmonary hypertension (PH) is defined as an increase of mean pulmonary artery pressure of more than 25 mmHg at rest or 30 mmHg during exercise [1]. The revised 2003 Venice Classification of Pulmonary Hypertension classifies the various forms of PH according to the main pathophysiologic mechanism. Pulmonary arterial hypertension (PAH) encompasses the so-called 'primary' pulmonary hypertension (PPH) as well as 'secondary' PAH – associated with collagen disease, portal hypertension, HIV infection, drugs (e.g anorexigens) and toxins [2].

PPH is a rare life-threatening disease with sporadic (idiopathic PAH) or familial occurrence and an incidence of one to two in 1,000,000 individuals [1]. Mutations in the bone morphogenetic protein receptor II are now considered to trigger the pathogenic mechanism of PPH production, mostly in familial PPH and partly in the sporadic form of PPH [3]. The common pathogenic denominator of PAH is represented by a dysfunction of endothelial cells in the small pulmonary arteries leading to increased pulmonary vascular resistance and subsequently to right-ventricular failure and death [4].

Recently, the role of endothelin (ET) in the pathogenesis of PAH has been demonstrated. ET-1 is synthesized by endothelial and smooth muscle cells in pulmonary arteries and exerts its vasomodulating activities by binding with ET-A and B receptors. Through the ET-A receptors on vascular smooth muscle cells, ET-1 mediates vasoconstriction and triggers smooth muscle cell proliferation and subsequent vascular remodeling. On the contrary, if bound to ET-B receptors on endothelial cells, it stimulates nitric oxide (NO) release and vasodilation [5,6].

PPH clinical assessment includes functional classification and noninvasive and invasive cardiopulmonary tests. Of particular importance in the latter category is the acute reversibility testing (vasodilator testing) to NO, prostacycline or adenosine – a positive vasodilation response is considered when there are decreases of 20% or more in mean pulmonary artery pressure and pulmonary vascular resistance index [7].

This complex diagnostic work-up yields the main outcome measures used as efficacy end points: functional class (i.e., clinical severity), exercise capacity, hemodynamic parameters, quality of life or biologic markers (e.g., of endothelial dysfunction or heart failure) [8]. Among them, the strongest predictors of poor prognosis are considered advanced functional class, low walk distance and presence of pericardial effusion [9].

The natural history of PPH in the absence of any treatment is dominated by rapidly progressive right heart failure symptoms (including dyspnea), and the median survival in untreated PPH is estimated to be approximately 3 years [10]. Calcium channel blockers (CCBs), prostacyclin and prostanoids, anticoagulants, cardiac glycosides, diuretics and oxygen are used in PPH therapy [5]. Diuretics and oxygen are occasionally used for edema and dyspnea relief respectively, whereas digoxin, although indicated

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in PPH with heart failure and atrial fibrillation, has unclear efficacy in this context [5]. Although CCB's are not specifically approved in Europe or the USA for PPH treatment, they are recommended in patients with vasodilator reversibility [5].

A study performed in patients with PPH given high doses of CCBs demonstrated a significantly improved 5-year survival in responders with vasodilation response, compared with nonresponders or historic controls. In the same study it was shown that warfarin given in nonresponders may also improve survival [11]. Prostacyclin and its derivatives form another pharmacologic class of vasodilators with proven efficacy in the PAH and PPH subsets. Epoprostenol (Flolan®) administered via a central venous catheter reduced clinical severity and improved exercise capacity and hemodynamics in both PAH and PPH patients in the short term, as well as survival on a long-term basis [12–14]. However, the efficacy is somehow counterbalanced by problems arising from the necessity of continuous supply, modality of administration (via a central venous catheter) or side effects. Consequently, prostacyclin derivatives with improved pharmacokinetic profiles, such as subcutaneous-use treprostinil (Remodulin®), oral-use beraprost and inhaled-use iloprost (Ventavis®) have demonstrated their efficacy in improving exercise capacity or hemodynamics during PAH and PPH treatment [15–17]. Inhaled NO, L-arginine and vasoactive intestinal peptide have also been assessed in PAH/PPH, but their real efficacy remains unclear [5].

ET-receptor antagonists and phosphodiesterase (PDE)-5 inhibitors are among the pharmacologic classes currently under investigation for PAH treatment. Bosentan (Tracleer®) is an oral dual (ET-A and -B) receptor antagonist currently approved in both Europe and North America for the treatment of World Health Organization (WHO) Class III and IV PAH. The efficacy of bosentan as an add-on or first-line therapy in PPH/PAH was assessed in several studies. In a pilot study performed in severe PPH (New York Heart Association [NYHA] Class III or IV), the addition of bosentan to oral beraprost or inhaled iloprost produced a significant improvement in exercise capacity over a 3-month period [18]. In another study, the Bosentan: Randomized trial of Endothelin-receptor Antagonist THErapy (BREATHE)-2, the efficacy and safety of combining bosentan with epoprostenol in PAH treatment has been investigated and found a nonsignificant improvement in hemodynamics, exercise capacity and functional class in the bosentan/epoprostenol group, compared with the placebo/epoprostenol group [19]. Data contained in the survival analysis below came from two multicenter, randomized, placebo-controlled studies, in which the short-term efficacy of bosentan as a first-line treatment in PAH was assessed [20–21]. The same efficacy and survival outcomes were assessed subsequently during the open-label extensions [22].

In the first study of 32 patients with PAH (primary or associated with scleroderma), the efficacy and safety of bosentan (62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for at least 12 weeks) was compared with placebo. The primary end point was exercise capacity and the secondary end points were cardiopulmonary hemodynamics, Borg dyspnea index, WHO functional class and withdrawal due to clinical worsening assessed at 12 weeks. Bosentan significantly improved exercise capacity and cardiac hemodynamics and reduced dyspnea and clinical severity. More withdrawals due to clinical worsening were reported in placebo compared with the bosentan group and there was no intergroup difference in terms of severe adverse events [20].

The second study, BREATHE-1, had a similar randomized, placebo-controlled design and assessed the efficacy of two bosentan doses (125 and 250 mg twice daily) having the same primary and secondary end points of dyspnea, functional class and time to clinical worsening in PAH patients, assessed at 16 weeks. This study also enrolled severe PAH patients (WHO Class IV). Exercise capacity, dyspnea and functional class were improved in combined bosentan groups compared with the placebo group. Time to clinical worsening significantly increased in the combined bosentan group compared with placebo. Although in the bosentan higher-dose group, the above mentioned outcomes tended to be more improved compared with those of the bosentan lower-dose group, no dose–effect relationship could be found [21].

The current study is aimed at assessing the impact of bosentan given as first-line treatment and then potentially combined with other therapies in survival of PPH patients. It also compares bosentan treatment with the survival rates predicted using a formula established on hemodynamic data from the National Institutes of Health (NIH) PPH patients registry [10,22].

Methods & results

Survival data and the main outcome measures were analyzed in a subgroup of 169 severe symptomatic PPH patients (WHO Class III–IV) enrolled in the two randomized studies and subsequently followed-up during their open-label extensions. During the extension periods, the target bosentan dose was 125 mg twice daily, with the possibility of being titrated up to 250 mg twice daily should the physician detect clinical worsening. Prostanoids, or other oral therapies, could be administered as an add-on therapy during the open-label extensions. Baseline data were recorded at the start of bosentan therapy if possible, and included gender, age, WHO functional class, time from diagnosis (months), cardiopulmonary hemodynamics and exercise capacity (6 min walking distance). These data were compared with those of PPH patients included in the NIH registry (on which the predicting formula was established) and were analyzed *post hoc* as predictors of survival using the Cox proportional hazards model. Survival was estimated from the start of bosentan treatment until death or data cut-off and compared with predicted survival using the D'Alonzo formula – a predicting formula based on several hemodynamic parameters such as:

- Mean pulmonary artery pressure
- Mean right atrial pressure
- Cardiac index

Outcomes were represented by duration of observation for survival, patients lost to follow-up, lung transplantations, deaths, transfer to or additions of other therapies and discontinuation of bosentan without other events or treatment. The incidence of adverse events, as well as time to first threefold increase (above the upper limit) of liver transaminases were estimated using the Kaplan–Meier method, and the observation period included the placebo-controlled study durations plus open label extensions.

Baseline characteristics in bosentan-treated PPH patients were similar with those in the NIH PPH registry in terms of patients gender and age, walk distance and time from diagnosis (months) and cardiac hemodynamics – although a higher number of less severe PPH patients (Class II WHO) were found in the registry.

Most of the bosentan-treated PPH patients (77.4%) were receiving bosentan 125 mg twice daily at the time of the last observation. Mean follow-up duration was 2.1 ± 0.5 years and one patient was lost to follow-up (considered dead at the time of last contact). A total of 19 deaths (20 including the lost patient) and three lung transplantations were reported, and 39 patients were considered as receiving additional or replacement therapies (such as epoprostenol) during the observational period.

Estimated survival (Kaplan–Meier) in PPH patients receiving first-line bosentan therapy at each 6-month interval was significantly better than predicted (D'Alonzo equation). The 1-year estimated survival was 96% compared with 69% predicted, and the 2-year estimated survival was 89% compared with 57% predicted. The annual death rate was 5.5%. In terms of the therapeutic regimen, 85% of patients at 12 months and 70% of patients at 24 months follow-up were still on monotherapy. Furthermore, 78% of patients alive at 12 months and 55% alive at 24 months were on monotherapy. A total of 7% of the patients alive at 12 and 24 months were receiving add-on therapies.

Negative predictors of outcome were functional class and walk test, whereas cardiac hemodynamics only correlated with a trend towards a worse outcome. Adverse events were observed over a median period of 77 weeks (78 ± 28 weeks) and 14.9% of patients were found with three times the upper normal limit of hepatic transaminases, with approxiamately 90% of these cases being reported during the first 26 weeks of bosentan treatment.

Discussion & significance

Estimated versus predicted survival

The current survival analysis demonstrates that first-line bosentan treatment improves survival in PPH patients. Estimated 1- and 2-year survival rates were superior to predicted values obtained with NIH registry formula. However the predictive formula takes into account hemodynamic variables only and, according to the current analysis [22] and previous findings [9], these are not always found to be the strongest predictors of survival when compared with other predictors such as functional class or walk distance. Moreover, PPH population in the NIH Registry (observed during the 1980s) on whom the predictive formula was established, had a different battery of diagnostic tests and therapeutic regimens.

In a previous study it was shown that warfarin could improve survival in PPH patients without vasoactive response [11] but given the design limitations of the study, the data have to be interpreted cautiously. Therefore, it can be inferred that the method of comparison, predicted

survival, can be seen in this context as a 'worst-case scenario', which can be used as a surrogate in the absence of placebo. Moreover, the authors refrained from using a placebo group as a term of comparison. The use of historic controls from the NIH registry was also not considered despite the relative homogeneity of the two populations, probably owing to the differences in diagnosis and therapy strategies that could lead to biased results.

The safety profile of bosentan was assessed over a median duration of 77 weeks, which is lower than the observation time for survival analysis. Elevation of hepatic enzymes at least three-times the upper limit was reported in 14.9% of patients and the mean time to the first reported elevation was 26 weeks. However, these two variables were not analyzed as predictors of survival, probably due to different observation periods.

Impact of epoprostenol on primary pulmonary hypertension survival

Two studies assessed the impact of epoprostenol on survival in PPH patients. In one study, 162 PPH patients treated with epoprostenol were followed-up for a mean period of 36.3 months [13]. Observed survival with epoprostenol therapy was 87.8% at 1 year, 76.3% at 2 years and 62.8% at 3 years, and was significantly greater than survival data from the historic controls. Baseline predictors of survival included exercise tolerance, functional class, hemodynamic parameters and vasodilator response to adenosine. Predictors of survival after the first year of therapy included improved functional class, exercise tolerance and hemodynamics.

In another study, performed in 178 PPH patients treated with epoprostenol, the survival rates at 1, 2, 3 and 5 years were 85, 70, 63 and 55%. Among the predictors of survival were baseline severity and therapeutic response after 3 months of treatment [23].

Highlights

- Primary pulmonary hypertension is a rare form of pulmonary arterial hypertension with limited survival without appropriate therapy.
- Bosentan is a dual endothelin-receptor antagonist currently authorized in Europe and North America for the treatment of pulmonary arterial hypertension (including primary pulmonary hypertension).
- Bosentan used as first-line or add-on therapy in pulmonary arterial hypertension can improve clinical severity (functional class), cardiopulmonary hemodynamics and exercise capacity.
- In patients with primary pulmonary hypertension, bosentan can prolong survival and postpone the introduction of prostanoid vasodilators.

Survival in primary pulmonary hypertension: bosentan versus epoprostenol

According to the current analysis, first-line bosentan increases survival in PPH patients without precluding the subsequent addition of other therapies, for example epoprostenol. Regarding the relationship between bosentan monotherapy persistence and survival, most patients alive at 1 and 2 years were on bosentan monotherapy. Another issue that was not discussed in this analysis is the role of vasoactivity testing in predicting survival.

What happens when prostanoids are given as first-line therapy and bosentan is added further on? In the BREATHE-2 study, only the short-term efficacy of adding bosentan to epoprostenol has been assessed, and currently no survival data related with this study are available [19].

In a recent study, survival in idiopathic PPH functional Class III patients (WHO) receiving bosentan as first-line therapy was compared with survival in a historical cohort of idiopathic PPH functional Class III (WHO) started with epoprostenol. Estimated 1- and 2-year survival rates in the bosentan cohort were higher than in epoprostenol, but the latter had more severely affected patients. When patients in the bosentan cohort were compared with matched patients in the epoprostenol cohort, survival rates were almost identical [24].

Expert commentary & outlook

The current analysis demonstrates that first-line bosentan therapy could reshape the natural history of PPH by prolonging survival and postponing the introduction of prostanoid vasodilators. The therapeutic effect of first-line bosentan on survival was assessed in PPH patients and then compared with predicted survival based on the hemodynamic equation, and therefore the differences between estimated and predicted rates found may reflect this approach (especially in 1-year rates). It is also possible that during the natural history of the disease, the hierarchy of survival predictors changes so that for the more severely affected patients, hemodynamic measures are stronger predictors of survival. As an analysis of survival predictors according to disease severity in PPH patients without any therapies is not ethically possible, survival analysis such as that discussed above, performed with existing and upcoming therapies, provides indirect information on tailoring a therapeutic regimen, which could provide for maximum survival in PPH patients.

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Affiliation

Sabina A Antoniu, MD
University of Medicine and Pharmacy,
Clinic of Pulmonary Disease,
62 Costache Negri St,
Bl.C2, Sc.A, Et.5, Ap.19,
700070 Iasi, Romania
Tel.: +40 232 219 694
Fax: +40 232 211 500
sabinaantoniu@excite.com