Primary pulmonary hypertension (PPH) is a rare and progressive fatal disease. PPH is a diagnosis of exclusion, and median survival from the time of diagnosis is 2.8 years, if without treatment. Current options for treatment include oxygen, anticoagulation, diuretics, digoxin, calcium channel blockers, prostacyclin, and inhaled nitric oxide. However, endothelin-1 receptor antagonist (ERA) is less mentioned. We address a 19-year-old female who presented progressive dyspnea and exercise intolerance for 2 months. After series of studies, severe PPH was diagnosed. She hesitated to receive lung transplantation. Because of worsening of congestive heart failure (CHF), she started treatment with bosentan, an ERA. After 16 weeks of treatment, she experienced a great improvement of CHF and exercise capacity.

Key Words: Primary pulmonary hypertension • Endothelin receptor antagonist • Bosentan

INTRODUCTION

Primary pulmonary hypertension (PPH) is characterized by persistent pulmonary artery hypertension (PAH) of unexplained etiology.1 PPH is relatively rare, with an estimated incidence of 1 to 2 per million in the general population.2 The median survival of PPH from the time of diagnosis is 2.8 years, if without treatment.3 Many options for treatment exist, such as oxygen, anticoagulation, diuretics, digoxin, calcium channel blockers (CCBs), prostacyclin, and inhaled nitric oxide (NO). However, bosentan, an endothelin-1 receptor antagonist (ERA) which is approved in the treatment of PPH recently, is less reported. We herein narrate a young female with intractable severe pulmonary hypertension, who responded well to short-term treatment with bosentan.

CASE REPORT

A 19-year-old female, suspected of bronchial asthma but unresponsive to bronchodilators, was referred to our Cardiology Clinic owing to exertional dyspnea (New York Heart Association [NYHA] functional class II) for 2 months. Her body height and weight were 148 cm and 47 kg, respectively. She denied hypertension, diabetes mellitus, drug abuse, operation or other major systemic disease history. Her mother died suddenly at 26 years old of unknown cause. Her blood pressure and respiratory rate were 110/70 mmHg and 20/min, respectively. Her physical examinations were unremarkable except bilateral jugular venous engorgement, accentuated P2 and grade III/VI pansystolic murmurs at the left lower sternal border on cardiac auscultation. The arterial blood analysis in room air revealed hypoxemia (pH: 7.469, PaO₂: 64.8 mmHg, PaCO₂: 20.2 mmHg, HCO₃⁻: 14.4 meq/dL, oxygen saturation: 94.4%). The 12-lead electrocardiog-
raphy (ECG) revealed sinus rhythm, right axis deviation, and right ventricular hypertrophy [Figure 1A]. The chest x-ray showed enlarged right ventricle (RV) with prominent pulmonary vascular trunk [Figure 1B]. The echocardiography (UCG) demonstrated dilated RV with interventricular septal paradox as well as severe tricuspid regurgitation (TR) with an estimated pulmonary artery systolic pressure (PASP) of approximately 88 mmHg. The left ventricle (LV) function was normal (LV ejection fraction 67%). There were no increased thickness of pericardium, no pericardial effusion and no intra- or extra-cardiac shunting demonstrated by 2-dimensional and color Doppler UCG.

A series of examinations such as ventilation/perfusion lung scan, pulmonary function test, abdominal sonography and laboratory studies showed no evidence of pulmonary embolism, obstructive or restrictive pulmonary disease, portal hypertension, connective tissue disease or HIV infection. A right cardiac catheterization study demonstrated as follows: pulmonary capillary wedge pressure (PCWP) 13 mm Hg, main pulmonary artery pressure (PAP) 83/42 mmHg (mean 58 mmHg), RV 86/9 mmHg, mean right atrium (RA) pressure 14 mmHg, cardiac output (CO) 4.3 L/min, cardiac index (CI) 3.1 L/min, and main pulmonary artery oxygen saturation 75%. The patient’s PAP did not reduce after administration of nifedipine (10 mg) or nitroglycerin (0.6 mg).

Also, pulmonary angiography showed neither pulmonary arterial/venous occlusive disease nor congenital cardiac anomalies. On the basis of above findings, she was confirmed to have PPH. Lung transplantation was suggested, but she declined. High dosage of CCBs, such as nifedipine (30 mg/day) and diltiazem (90 mg/day) had been used but discontinued owing to hypotension. Therefore, she was treated with oral anticoagulant, warfarin (10 mg/day) and adjusted to keep the international normalized ratio between 2 and 3. Nocturnal oxygen (3 L/min) was also supplied. Unfortunately, severe dyspnea (NYHA functional class IV; WHO classification of PAH, functional class IV) happened after 2-year follow-up. Repeat UCG showed conspicuous RV and small LV (40 mm and 16 mm in end-diastole, respectively) and very high PASP (136 mmHg) [Figure 2A]. The patient still hesitated to undergo lung transplantation. After discussion, she agreed to take oral ERA, bosentan at a dose of 62.5 mg twice daily for the first month, then 125 mg twice daily for the next 3 months, starting June 4, 2005. After the first-month treatment, she got a significant improvement of dyspnea on exertion (NYHA functional class IV to class II) and completed the following course without adverse effects. Liver function tests and hematocrit were checked monthly and were within the normal ranges. After treatment for 4 months, the UCG also showed increased LV size in concordance with reduced RV size (36 mm and 32 mm in end-diastole, respectively), reduced PASP (from 136 to 120 mmHg) and severity of TR (from grade 4 to 1), and RA size (from 30 to 24 mm) (LV ejection fraction 70%) [Figure 2B]. Follow-up right cardiac catheterization revealed a significant lowering of mean RA pressure to 6 mmHg (from 14 to 6 mmHg), but no significant change.

Figure 1. A. The 12-lead ECG reveals sinus rhythm, right axis deviation, and right ventricular hypertrophy. B. The chest x-ray shows enlarged RV with prominent pulmonary vascular trunk.
of the PAP (117/43, mean 67 mmHg), RV pressure (127/12 mmHg), PCWP (14 mmHg), CO (3.6 L/min), CI (2.7 L/min). Therefore, bosentan has been continuously given.

DISCUSSION

PPH is defined clinically as the presence of PAH (mean PAP > 25 mmHg at rest, or > 30 mmHg with exercise), associated with a normal PCWP and the absence of secondary etiology.1-3 The first complaint of most patients is dyspnea. Other symptoms include fatigue (19-47%; along the course of the disease), palpitations (5-33%), syncope (8-36%), leg edema (3-37%), and chest pain (5-47%).4 Conditions such as thromboembolic disease, collagen disease, congenital heart disease, valvular heart disease, underlying lung disease, and liver disease must be excluded. Drug history, such as usage of appetite-suppressant drug (fenfluramine), should also be obtained. The workup studies should include chest x-ray, ECG, UCG, pulmonary function tests, ventilation perfusion lung scan, the tests for collagen vascular disease (antinuclear antibodies, anti-double strain DNA, etc.), liver function test, HIV testing, and cardiac catheterization.5

Currently, treatment options for PPH include diuretics, digoxin, CCBs, prostacyclin and its analogues, inhaled NO, ERAs, and adjunctive therapies, such as anticoagulants and oxygen. Poor response has been documented with diuretics, digoxin, and CCBs.6-8 Additionally, intravenous prostacyclin and inhaled NO must given via continuous infusion and inhalation device, respectively.9-10 Patients with pulmonary hypertension were reported to have high concentrations of endothelin-1 (ET-1) in the plasma and lungs.11 ET-1 is a potent vasoconstrictor as well as smooth-muscle mitogen. Two separate receptors of ET-1 exist. ET-A receptors, mainly found in vascular smooth muscle cells, can induce vasoconstriction by increasing intracellular calcium. On the other hand, ET-B receptors, mainly expressed by endothelial cells, can stimulate the release of vasodilating agents, such as nitric oxide and prostacyclin. Either selective blocking of ET-A receptors alone or non-selective blocking of both receptors can dilate the local vessels.11-15 Bosentan (TracleerTM, Actelion, Switzerland), a non-selective antagonist administrated orally, has been approved for the
treatment of PPH in humans. The cost of each dose (either 62.5 mg or 125 mg) is NT$1,892, and the total cost for our patient is about NT$1,380,000 each year. The recommended dose of bosentan is initially 62.5 mg twice daily for 4 weeks, followed by a maintenance dose of 125 mg twice daily. The adverse effects of bosentan include serious hepatotoxicity and fetal damage. It is contraindicated in patients with moderate to severe liver impairment and pregnancy. Other side effects are headache, nasopharyngitis, flushing, edema, hypotension, palpitation, fatigue, and pruritis. Decreased hemoglobin level was also reported. Furthermore, up to 7% of patients in clinical trials developed a drug-related hepatitis that required dose reduction or cessation of therapy. Therefore, liver function tests and hemoglobin/hematocrit must be monitored monthly.

The effect of bosentan on cardiopulmonary hemodynamics includes a decrease in pulmonary vascular resistance, which may account for the improved 6-minute walking distance and symptoms of CHF. Bosentan also reduces the rate of clinical worsening. Regarding our patient, after 4-month treatment with bosentan, CHF symptoms and exercise capacity improved in association with significant decrease in RV size (40 to 32 mm), RA pressure (14 to 6 mmHg), the severity of TR (grade 4 to 1), and increase in LV size (16 to 36 mm).

Survival of PPH is directly related to NYHA functional class. It tends to have a worse prognosis if RA pressure is greater than 20 mmHg, mean PAP greater than 85 mmHg, and CI less than 2 L/min/M². However, in recent studies of PPH, the duration of bosentan used was only 12 to 16 weeks, which was not sufficient to test for survival. Larger and longer-term studies are required.

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原發性肺動脈高壓是一種罕見和持續性惡化與致命的疾病。在臨床上呈現持續性的高肺動脈
壓而無其它的致病因素。它的診斷是利用排除法。如果沒有治療的話，從診斷確定開始，
平均存活約 2.8 年。目前治療的方法包括氧氣輔助、使用抗凝血劑、利尿劑、毛地黃、鈣
離子阻斷劑、前列腺素和吸入性一氧化氮；然而，內皮素-1 受體拮抗劑較少被報告。我們
提出一位 19 歲的女性表現二個月持續性呼吸困難和運動不能，經過一系列的檢查之後，診
斷為重度原發性肺動脈高壓。建議接受肺移植手術，但病人猶豫不決。因為心臟衰竭愈來
愈惡化，開始接受內皮素-1 受體拮抗剤 Bosentan 治療。經過 16 週的治療後，病人的心臟
衰竭症狀和運動功能有明顯改善。

關鍵詞：原發性肺動脈高壓、內皮素拮抗剤、Bosentan。