Imatinib is Partially Effective for the Treatment of Pulmonary Capillary Hemangiomatosis

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Abstract

A 43-year-old man presented with dyspnea on exertion. Right heart catheterization demonstrated pulmonary arterial hypertension (PAH). He was treated with bosentan, sildenafil and intravenous epoprostenol. Despite the administration of such intensive therapy, the patient’s condition deteriorated to a World Health Organization functional class (WHO-FC) of IV. He participated in a clinical trial of imatinib for PAH. After three months of treatment with imatinib, the chest X-ray and echocardiography findings improved, and the WHO-FC class was III. One year after, however, the PAH worsened again, and the patient died 2.6 years after the first diagnosis. At autopsy, patchy capillary proliferation was observed in the lungs. The definitive diagnosis was pulmonary capillary hemangiomatosis.

Key words: pulmonary hypertension, pulmonary capillary hemangiomatosis, imatinib, tyrosine kinase inhibitor


Introduction

Pulmonary capillary hemangiomatosis (PCH) is an extraordinarily rare cause of pulmonary arterial hypertension (PAH). In the Dana Point classification, both PCH and pulmonary veno-occlusive disease (PVOD) are classified as Group 1’ PAH (1). Patients with PCH typically survive for only two to three years unless they undergo lung transplantation (2). The definitive diagnosis depends solely on pathological findings. We herein present a case of PCH that was resistant to conventional PAH therapy, including bosentan, sildenafil and intravenous epoprostenol, but responsive to imatinib, which enabled the patient to return home for one year until his final admission.

Case Report

A 43-year-old man presented with progressive dyspnea on exertion. He had worked as a carpenter two years earlier. His past medical and familial history were unremarkable. He had never smoked and denied any illicit drug use. On a physical examination, his blood pressure was 95/65 mmHg, his heart rate was 105 bpm and his respiratory rate was 22 breaths/min. An electrocardiogram showed right ventricular hypertrophy with ST changes. The level of plasma brain natriuretic peptide (BNP) was 202 pg/mL. A Doppler echocardiogram demonstrated a peak tricuspid regurgitation pressure gradient of 70 mmHg. Pulmonary function tests showed a normal forced vital capacity (FVC) (3.10 L, 83.6% of the predicted value), normal forced expiratory volume 1.0% (FEV1) (2.76 L, 86.8% of the predicted value) and normal FEV1/FVC ratio (86%); however, the diffusing capacity for carbon monoxide (DLco) was severely decreased (6.19, 22.5% of the predicted value). High-resolution computed tomography (HRCT) of the chest revealed centrilobular ground glass opacity, septal thickening and mediastinal lymph node enlargement. Medical examinations indicated no
specific cause leading to pulmonary hypertension. Right heart catheterization demonstrated a pulmonary arterial pressure (PAP) of 64/22/35 mmHg (systolic/diastolic/mean) and a pulmonary capillary wedge pressure of 2 mmHg. The pulmonary vascular resistance (PVR) was 1,310 dyne/sec/cm². Perfusion lung scintigraphy did not show any abnormal perfusion defects. Therefore, we diagnosed the patient with idiopathic PAH or Group 1 PAH.

Treatment was initiated with bosentan, and both sildenafil and intravenous epoprostenol (maximum dose: 26 ng/kg/min) were carefully added. However, the patient’s respiratory condition deteriorated with the development of pulmonary edema, and his arterial oxygen saturation on pulse oximetry (SpO₂) was 90.0% with inhalation of 10 L/min 100% oxygen using a face mask. He remained in World Health Organization functional class (WHO-FC) IV. Although lung transplantation was considered, the patient refused the procedure. Instead, we decided to administer imatinib after obtaining approval from the domestic ethics committee of the National Hospital Organization Okayama Medical Center. Soon after imatinib was started with an initial dose of 100 mg once per day, the patient’s respiratory condition rapidly improved. The dose of imatinib was increased to 150 mg once per day, and the intravenous epoprostenol was tapered off. The patient’s condition improved to WHO-FC III, with an SpO₂ of 98% with inhalation of 5 L of nasal oxygen. The cardiomegaly on chest X-rays and ground glass opacity and septal thickening on HRCT improved (Fig. 1). The degree of left ventricle compression was also reduced on an echocardiogram (Fig. 2). After three months of imatinib treat-
Figure 2. Parasternal short-axis view of an echocardiograms obtained before and after imatinib treatment. A: Before imatinib treatment. A flat septum and D-shaped left ventricle were observed. B: After three months of imatinib treatment. The flat septum and D-shaped left ventricle had improved.

Figure 3. Histological findings of the pulmonary lesion. A: Nodular and hemangioma-like proliferation of capillaries in the alveolar walls. The capillaries are dilated and filled with red blood cells (Hematoxylin and Eosin staining; original magnification ×200). B: Immunostaining of CD34 highlighting proliferating capillaries (original magnification ×100). C: Some muscular arteries exhibited marked intimal fibrosis and occlusion of the lumen (Hematoxylin and Eosin staining; original magnification ×100).

ment, the patient was discharged home. He remained in WHO-FC class III, with a plasma BNP level of 71 pg/mL. One year after discharge, however, the dyspnea reappeared, and he again required hospitalization. The plasma BNP level increased to 1,037 pg/mL and the systolic PAP estimated on an echocardiogram increased to 135 mmHg. Right-sided heart failure rapidly progressed despite the initiation of catecholamine treatment for nine days after hospitalization, and the patient died 2.6 years after the first diagnosis. At autopsy, the pathological findings revealed dominant nodular and hemangioma-like proliferation of capillaries in the alveolar walls, and PCH was diagnosed (Fig. 3).

Discussion

Imatinib, a tyrosine kinase inhibitor, has been reported to
be effective in some cases of PAH (3-5); however, there are no precise case reports of PCH. In the present case, a diagnosis of PCH/PVOD was suspected based on the clinical, laboratory and HRCT findings (6, 7). The pathological findings revealed dominant patchy hemangioma-like capillary proliferation, although no venous fibrosis or occlusion were observed in any lobes of the lungs. The muscular arteries showed only mild intimal and medial thickening. Therefore, PCH was the definitive etiologic diagnosis in this patient.

In this case, the administration of imatinib rapidly improved the patient’s symptoms, laboratory test results and echocardiography and HRCT findings. Among the medications prescribed for this patient, only imatinib proved effective enough to allow him to be discharged home and improved his quality of life. In a previous report of a case of PVOD, imatinib was added to diuretics, anticoagulants and epoprostenol, and neither bosentan nor sildenafil were used (3). However, in the present case, all PAH-targeted therapies were used. Therefore, it is clear that only imatinib was effective for this patient.

Imatinib may be specifically effective for PCH due to the inhibitory effects of several tyrosine kinase activities (3-5). Moreover, imatinib exhibits antiproliferative and pro-apoptotic effects on smooth muscle cells stimulated with platelet-derived growth factor (PDGF) in subjects with idiopathic PAH (8). There are several possible mechanisms by which imatinib may elicit pulmonary vasodilation. These include: (1) inhibition of PDGF receptor-mediated elevation of the intracellular Ca$^{2+}$ levels (9); (2) inhibition of other off-target protein kinases, such as epidermal growth factor receptor, Src and protein kinase C (10-12); and (3) inhibition of c-Abl-mediated actin polymerization (13).

Imatinib may work in PAH patients with higher PVR values. In the International Multicentre PREvAlence Study on Sepsis (IMPRESS) study, treatment with imatinib improved exercise capacity and hemodynamics in patients with advanced PAH already treated with two or more pulmonary vasodilators; however, serious adverse events and imatinib discontinuation were common (14). In particular, subdural hematomas developed in 4.2% of the patients treated with imatinib, all of which occurred in patients receiving concomitant antiagulation. In the present case, the patient was not treated with oral antiagulants, but rather with bosentan and sildenafil, and no obvious side effects caused by imatinib were observed.

Abe et al. reported that the administration of imatinib reduces a high right ventricular systolic pressure in pulmonary hypertensive rats (15). Imatinib therapy has also been reported to improve the arterial oxygen saturation ($\text{SaO}_2$), PVR and cardiac output, although the 6-minute walk distance as the primary end point did not change significantly (5). Meanwhile, a subanalysis showed that, among the patients with a PVR of $\geq$1,000 dynsec/cm$^2$ only, the pulmonary artery pressure, cardiac output and 6-minute walk distance significantly improved (6). These results suggest that the administration of imatinib in addition to other therapies, such as endothelin receptor blockers and phosphodiesterase-5 inhibitors, has the potential to be effective for severe pulmonary artery hypertension. In the present case, the PVR before treatment with imatinib was 1,310 dynsec/cm$^2$. Therefore, imatinib appeared to be effective for this patient.

Hatano M. et al. reported that treatment with imatinib improves the DL$_{CO}$ because the medication decreases the serum PDGF concentration (16). However, it should be noted that the effects of imatinib were reduced after 1.5 years of treatment. Namely, the effects of imatinib may decrease with long-term treatment. Further studies are needed to investigate the long-term safety and efficacy of imatinib in patients with PCH.

In summary, imatinib was partially effective in a PCH patient who exhibited an inadequate response to bosentan, sildenafil and intravenous epoprostenol.

The authors state that they have no Conflict of Interest (COI).

References


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