Imatinib for the Treatment of Pulmonary Arterial Hypertension Due to the Late Closure of Patent Ductus Arteriosus: A Case Report

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Purpose: Pulmonary arterial hypertension (PAH) may occur as complication of a wide range of conditions, particularly in grown-up congenital heart diseases (GUCHD). Despite currently available therapy its prognosis remains poor. Platelet-derived growth factor (PDGF) and its receptor (PDGFR) have been implicated in the pathogenesis of PAH. Imatinib is a PDGFR inhibitor which may be beneficial in the treatment of PAH. We report the case of a 27-year-old man, who developed PAH despite a late surgical closure of patent ductus arteriosus (PDA) in whom the additional therapy with imatinib may be beneficial, with an improvement of hemodynamics, functional status and clinical features.

Introduction: Pulmonary arterial hypertension (PAH) is a progressive life-threatening condition which leads to an increase in pulmonary vascular resistance (PVR) and to right-sided heart failure. Among several diseases involved in developing PAH, grown-up congenital heart diseases (GUCH) are implicated in 5-10% of total cases. Imatinib is a platelet-derived growth factor receptor (PDGF-R) antagonist, whose role in the treatment of PAH may be efficacious because of its anti-proliferative activity.

Case Description: We report the case of a 27-year-old Romanian man who underwent surgical closure of patent ductus arteriosus (PDA) at the age of 9. In September 2008 he presented to our attention for the first time. He was mildly symptomatic for exertional dyspnea (World Health Organization functional class [WHO-FC] II). Transthoracic echocardiography (TTE) revealed a non-dilated and hypertrophic right ventricle, with tricuspid annular plane systolic excursion (TAPSE): 18 mm and systolic pulmonary arterial pressure (sPAP): 64 mmHg. 6-minute walking distance (6MWD) was 420 m. Right heart catheterization (RHC) confirmed diagnosis of severe pre-capillary PAH (mean PAP [mPAP]: 47 mmHg; post-capillary wedge pressure [PCWP]: 10 mmHg; PVR: 813.2 dyn/sec/cm$^5$; cardiac index [CI]: 2.20 l/min/m$^2$). The patient started therapy with bosentan (62.5 mg bid, titled at 125 mg bid after 4 weeks). However, over the 12 months he experienced worsening dyspnea which required hospitalization. TTE showed a dilated right ventricle with a D-shaped left ventricle; significantly increased sPAP (72 mmHg) and moderate pericardial effusion (figure 1). 6MWD has been early interrupted at 4’50” for exertional dyspnea, with a significantly reduced walking distance (280 m). RHC revealed a significant worsening of PAH (mPAP: 52 mmHg; PCWP: 13 mmHg; PVR: 1006.4 dyn/sec/cm$^5$; CI: 1.83 l/min/m$^2$). A sequential combination therapy with inhaled iloprost (5 μg/inhalation for 9 times daily) plus sildenafil (40 mg tid) was subsequently added to bosentan. However, in April 2011 the patient experienced an episode of acute heart failure, apparently triggered by a respiratory infection: TTE showed a biventricular hypertrophy with sPAP: 68 mmHg and TAPSE: 11 mm. Treatment with imatinib (200 mg daily) was added to the previous combination therapy, with significant clinical benefit. After a follow-up of 12 months, TTE revealed a decrease of sPAP (57 mmHg), and a mild increase of TAPSE (13 mm), while 6MWD showed an increase of walking distance (325 m). The improvement in pulmonary function was confirmed by RHC values (mPAP: 44 mmHg; PCWP: 12 mmHg; PVR: 780.5 dyn/sec/cm$^5$ CI: 1.94 l/min/m$^2$).

Discussion: The case we proposed underlines the potential for safe and efficacious use of imatinib in PAH due to GUCH as an additional treatment in patients without response besides maximal combination therapy. The rationale for the use of imatinib in PAH is the potential to reverse pulmonary vascular remodeling and vessels-cell proliferation, because of its anti-proliferative and pro-apoptotic effect on pulmonary artery smooth muscle cells. For these reasons it may contribute to a progressive improvement in hemodynamics with clinical and functional benefits and increased survival.

Conclusion: The case we have reported underlines the potential for safe and efficacious use of imatinib in PAH due to the late surgical closure of PDA, as an additional treatment in patients without response besides maximal combination therapy.