Dasatinib-induced pulmonary hypertension in acute lymphoblastic leukemia: case report

Akut lenfoblastik lösemili hastada dasatinib kullanımına bağlı pulmoner hipertansiyon: Olgu sunumu

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Summary– Pulmonary hypertension (PHT) is a pathological condition determined as an increase in mean pulmonary arterial pressure ≥25 mmHg. Pulmonary arterial hypertension (PAH) is precapillary PHT and a life-threatening disease group which consists of different etiologies with the same pathological and clinical findings, and which is characterized by elevated pulmonary vascular resistance. Dasatinib is a dual Src/Abl kinase inhibitor associated with higher affinity for BCR/ABL kinase than imatinib, and is used in the treatment of chronic myelocytic leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL). We describe a case with ALL, in whom dasatinib treatment induced PAH, and who recovered with bosentan treatment.

Özet– Pulmoner hipertansiyon (HT) ortalama pulmoner arter basıncının 25 mmHg'nin üzerine çıktığı patolojik durumdur. Pulmoner arteriyel hipertansiyon ise prekapiller pulmoner HT tipi olup, farklı etiyolojik nedenlere bağlı ortaya çıkan, benzer patolojik ve klinik bulgulara neden olan hayatı tehdit eden, pulmoner vasküler direncin yükselmesi ile karakterize bir durumdur. Dasatinib ikili Src/Abl kinaz inhibitörüdür ve imatinibe göre BCR/ABL kinaz afinitesi daha yüksektir ve kronik myelositik lösemide ve Filadelfiya kromozomu pozitif olan akut lenfoblastik lösemide (ALL) kullanılmaktadır. Biz ALL tedavisinde dasatinib kullanımına bağlı olarak pulmoner HT gelişen ve bosentan kullanımı ile düzelen olguyu tartışmayı amaçladık.

Pulmonary hypertension (PHT) is pathological, and is defined as an increase ≥25 mmHg in mean pulmonary arterial pressure (PAP). Pulmonary arterial hypertension (PAH) is precapillary PHT and is characterized by elevated pulmonary vascular resistance. It is a life-endangering disease group, which consists of different etiologies with the same pathological and clinical findings.[1] Dasatinib is a dual Src/Abl kinase inhibitor linked with higher affinity for BCR/ABL kinase than imatinib. It is used in the treatment of chronic myelocytic leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL).[2]

Abbreviations:

ALL	*Acute lymphoblastic leukemia*
PAP	*Pulmonary arterial pressure*
PHT	*Pulmonary hypertension*
TAPSE	*Tricuspid annular plane systolic excursion*

Here, a case with ALL is described. The patient, in whom dasatinib treatment induced PAH, recovered with bosentan treatment.

CASE REPORT

A 50-year-old male had been diagnosed with ALL 6 years previously. There were no known previous cardiac or respiratory conditions, and no other significant disease. He was a smoker for 30 years. He received a hyperCVAD regimen (cyclophosphamide, vincristine, doxorubicin dexamethasone, methotrexate and cytarabine)[3] and imatinib (400 mg/day-4 months) as remission induction therapy. Due to relapse, after 2 cycles the treatment was switched to a FLAG-Ida regimen (fludarabine, cytarabine, idarubicin and G-CSF) [4] and dasatinib (140 mg/day) as salvage treatment.

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After a second complete remission, he received 3 cycle FLAG-Ida and Dasatinib regimen as consolidation treatment. Thereafter, POMP (6-mercaptopurine, vincristine, methotrexate, and prednisone) and dasatinib were used as maintenance treatment for 2 years. Dasatinib maintenance was continued alone at a dose of 140 mg/day until manifestation of pulmonary vascular toxicity occurred in September 2012. He was admitted to the outpatient clinic with complaints of exertional dyspnea and fatigue on October 2012. Due to the NCI grade IV pulmonary and cardiac toxicity, dasatinib was switched to nilotinib (2x400 mg/day). In addition he received furosemid (40 mg/on alternate days) and prednisolone (20 mg/on alternate days) for 3 weeks. Due to impaired clinical condition and increased symptoms, he was hospitalized on November 2012. Physical examination revealed blood pressure 100/70 mmHg, heart rate regular and 100 beats/min, a 2/6 systolic murmur in left sternal border without radiation, tachycardia at rest, jugular venous distension, hepatomegaly and peripheral oedema. Electrocardiography (ECG) demonstrated right axis, right bundle branch block. A chest-X-ray showed cardiomegaly with bilateral pleural effusion. Transthoracic echocardiography revealed normal left heart chambers and function with enlarged right heart dimensions (Right ventricle basal diameter 44 mm, right atrial area 20 cm^2). Systolic pulmonary artery pressure was measured as 70 mmHg. A short-axis view demonstrated D-shape caused by septal motion towards the left ventricle due to increased PAP (Figure 1a). Tricuspid annular plane systolic excursion (TAPSE), which correlates with right ventricle systolic function, was 14 mm due to impaired right ventricle function. He had a functional capacity class III according to NYHA.

Table 1. Findings of right heart catheterization

PCWP (mmHg)	7
RA (mmHg)	12
RV (mmHg)	67/0/24
PA (mmHg)	64/16/36
CO (l/min)	4.3
CI (l/min/m^2)	2.7

PCWP: Pulmonary capillary wedge pressure; RA: Right atrial pressure; RV: Right ventricular pressure; PA: Pulmonary artery pressure; CO: Cardiac output; CI: Cardiac index.

Right heart catheterization revealed severe precapillary PAH (Table 1). The vasoreactivity test with adenosine was negative. Normal wedge pressure excluded drug-induced cardiomyopathy and other left heart diseases. Parenchymal lung diseases, pulmonary embolism, and other reasons were ruled out with diagnostic imaging methods. Laboratory screening tests for HIV and systemic rheumatic diseases were negative. Pro BNP level was 1280 pg/L. His 6-min walking distance was 120 meters. PAH possibly related to dasatinib therapy was diagnosed. Dasatinib was discontinued and dosage of furosemide treatment was increased. As PAH specific treatment, bosentan was initiated with 2x62.5 mg/day. Liver enzymes and hemoglobin level were evaluated in 2 weeks, and bosentan dosage increased to 2x125 mg/day. After 9 months, the patient's functional capacity was significantly improved. His 6 min walking distance was 750 meters and pro BNP level was <60 pg/L. His transthoracic echocardiographic examination demonstrated normal systolic pulmonary artery pressure, normal right ventricular function and dimension (Figure 1b)

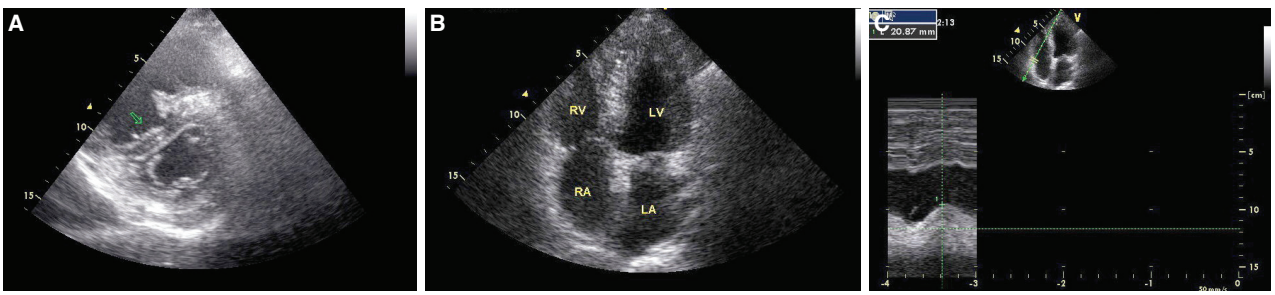

Figure 1. **(A)** Short-axis window in transthoracic echocardiography (TTE) demonstrates interventricular septal shift due to increased pulmonary artery pressure. **(B)** Apical window in TTE demonstrates normal left and right heart dimensions after dasatinib withdrawal and bosentan treatment. **(C)** Apical window in TTE demonstrates normal TAPSE (tricuspid annular plane systolic excursion) after dasatinib withdrawal and bosentan treatment.

and improved TAPSE (Figure 1c). The patient refused right heart catheterization. 2 months after drug cessation, the patient was asymptomatic with functional capacity NYHA class I.

DISCUSSION

In this case report we described recovery from dasatinib-induced PAH with bosentan treatment in a patient with ALL. There are some case reports in whom transient PAH occurred due to dasatinib treatment. Dasatinib has a broad range of activity in multiple biological processes, which may partially explain its enhanced antileukemic activity.[5,6] Dasatinib potency is 300-fold that of imatinib, and pleural effusion is a common side effect. Quintás-Cardama et al. demonstrated that right ventricular systolic pressure increased in 18 patients and normalised in 10 patients after dasatinib cessation.[2] The pathobiological mechanism of PAH induction with dasatinib treatment is not clear yet. The risk of PAH appearance is 0.45% in patients undergoing chronic dasatinib treatment.[7]

Imatinib, dasatinib and nilotinib have different molecular mechanism actions and target profiles with different side effects. There are case reports in which imatinib treatment was shown to reverse advanced pulmonary vascular disease and prolong survival in PAH. Imatinib acted as PDGFR inhibitor, and case reports show that a possible alternative mechanism caused PAH in patients who recieved dasatinib. Dingli et al. reported concomitant diagnosis of myeloproliferative disease and PAH.[8] Our patient's symptoms disappeared and PAP decreased after diasatinib discontinuation with Bosentan treatment. Therefore, in our patient ALL-induced PAH was unlikely.

Until now, five cases with reversible dasatinib-induced PAH have been described.[9-11] Montani et al. demonstrated that in 9 patients dasatinib caused PAH, with specific effect on pulmonary vessels. Improvement was seen after drug cessation. In that report, only one patient with ALL was diagnosed with PAH, and the disease appeared earlier than in patients with CML.[7,12]

Chronic treatment with dasatinib may cause severe, life-threatening PAH, right ventricular failure and death. Although pulmonary pressure improves after drug cessation, normalization doesn't occur in all patients. We therefore suggest that dasatinib should be carefully used in patients with myeloproliferative disease and closely-followed right ventricular systolic pressure, with echocardiography as an excellent non-invasive imaging modality for PAH.

Conflict-of-interest issues regarding the authorship or article: None declared.

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Key words: Acute lymphoblastic leukemia; dasatinib; hypertension, pulmonary.

Anahtar sözcükler: Akut lenfoblastik lösemi; dasatinib; hipertansiyon, pulmoner.