



Imatinib-induced decompensated heart failure in an elderly patient with chronic myeloid leukemia: case report and literature review

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Abstract

Because it is safe and well tolerated, imatinib is a standard first-line therapy for chronic myeloid leukemia (CML). Although there have been sporadic reports of imatinib-induced cardiotoxicity, including left ventricle (LV) dysfunction and heart failure, the evidence for it is contradictory. Here, we reported a case of an 88-year-old male patient with CML developed decompensated heart failure following imatinib therapy. Four days after the initiation of imatinib, the patient developed orthopnea, edema and a pleural effusion accompanied by abdominal distension, nausea and vomiting. The chest X-ray film showed an enlarged cardiac profile. The echocardiogram demonstrated a decreased LV ejection fraction and enlarged left-side cardiac chambers. B-type natriuretic peptide concentrations were markedly increased. The patient recovered soon after the withdrawal of imatinib and introduction of comprehensive therapy for heart failure. Imatinib-induced cardiotoxicity in elderly patients is a potentially serious complication that merits further evaluation.

J Geriatr Cardiol 2012; 9: 411–414. doi: 10.3724/SP.J.1263.2012.05251

Keywords: Heart failure; Chronic myeloid leukemia; Imatinib

1 Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder caused by an acquired mutation of hematopoietic stem cells. This mutation results in a reciprocal translocation between chromosomes 9 and 22 termed the Philadelphia chromosome (t[9;22][q34;q11]) and generates a novel fusion gene, BCR-ABL, which encodes tyrosine kinase.^[1] Imatinib mesylate (Gleevec, Novartis), a small-molecule inhibitor of multiple tyrosine kinases, selectively prevents phosphorylation of BCR-ABL and inhibits downstream signaling and growth of BCR-ABL-positive cells. Since May 2001, when the U.S. Food and Drug Administration approved imatinib for treatment of CML, this drug has been a standard first-line therapy for CML, revolutionizing its treatment. Both IRIS and TARGET investigators have confirmed a good cardiac safety profile and efficacy in patients with CML receiving imatinib.^[2–4] Imatinib has resulted in 90% of CML patients remaining in the chronic phase for at least five years.^[5]

Imatinib-induced cardiotoxicity, including LV dysfunction and heart failure, has received much attention in recent years.^[6,7] However, Van Glabbeke *et al.*^[8] analyzed a EORTC-ISG-AGITG study and found no instances of imatinib-related LV failure in patients with gastrointestinal stromal tumors patients. A recent prospective assessment of 59 CML patients found no clinically significant cardiotoxicity during 12 months follow-up; the researchers concluded that specific consideration of imatinib-induced cardiotoxicity is not necessary when assessing candidates for imatinib treatment.^[9] Ribeiro *et al.*^[10] studied 103 consecutive patients with CML receiving imatinib and found no evidence for systematic deterioration of cardiac function; however, these researchers pointed out that there is a possibility of isolated cases of cardiotoxicity. Here, we report an 88-year-old man with CML who developed decompensated heart failure four days after commencing imatinib treatment.

2 Case report

An 88-year-old male with CML was admitted to our hospital on August 24, 2010 because of significantly high white blood cell and platelet counts. He had been diagnosed with MDS-U in September 2009 and CML in August 2010. Cytogenetic studies had shown positive results for the t(9;22) PDGFR fusion gene and BCR-ABL (12.2% b2a2). His me-

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Received: May 25, 2012 **Revised:** September 24, 2012

Accepted: October 31, 2012 **Published online:** November 30, 2012

dical history included hypertension (well controlled), type 2 diabetes mellitus (well controlled), and permanent atrial fibrillation with a satisfactory heart rate. On admission, B-type natriuretic peptide (BNP) concentrations were 2,467 pg/mL and a chest X-ray film was normal (Figure 1A). An ECG revealed T-wave inversion and ST-segment depression in I, aVL, V₅ and V₆. An echocardiogram showed left and right atrial enlargement (Table 1).

On physical examination, the patient was in good general condition and his vital signs were within the normal range. No orthopnea or jugular venous distension was detected. Clear breath sounds were heard bilaterally; no rales were heard. There was no cardiac enlargement and the rhythm was irregular (heart rate, 86 beats/min). The first heart sound at the apex was faint, no cardiac murmurs were heard. There was no hepatomegaly or edema of the lower limbs.

On August 25, 2010, oral imatinib mesylate monotherapy (Gleevec, Novartis, 400 mg once daily) was started. The patient complained of mild abdominal distension. On the 2nd day after the initiation of therapy, he developed nausea and vomiting. His dose of imatinib was reduced to 200 mg daily and his gastrointestinal symptoms improved slightly. On day 4 of imatinib therapy, the patient complained of orthopnea and moderate edema was found in both legs. Biochemical test showed a plasma BNP concentration of 14,228 pg/mL. Plasma TnI, blood urea nitrogen and serum creatinine were in the normal range (Table 2). An echocardiogram showed a slightly decreased LV ejection fraction (EF) and enlarged left atrial and ventricular chambers (Table 1). A chest X-ray film revealed an enlarged cardiac profile and a pleural effusion (Figure 1B). His ECG was similar before and after imatinib treatment. A diagnosis of acute heart failure was made and imatinib discontinued. He was prescribed comprehensive therapy including oxygen inhalation, diuretics and vasodilators according to the ACC/AHA 2009 guidelines for the diagnosis and management of heart failure in adults. By September 11, 2010, the patient's symptoms and signs of heart failure had resolved and findings of biochemical tests, chest X-ray film and echocardiogram were all consistent with recovery.

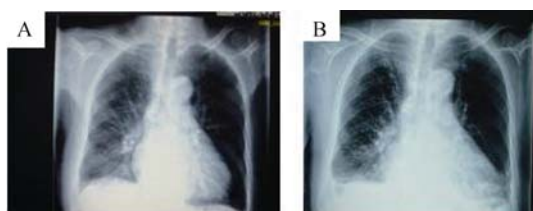


Figure 1. Chest X-ray films. (A): On admission and (B) when the patient had decompensated heart failure. An enlarged cardiac profile and pleural effusion are visible in Figure 1B.

Table 1. Echocardiographic data on admission, day 4 of imatinib treatment (decompensated heart failure), and after discontinuation of imatinib (recovered from heart failure).

	On admission	HF	Recovery from HF
LVEF (%)	53	46	61
LVEDD (mm)	52	59	54
LVSD (mm)	37	42	36
LA (mm)	39	46	41
RA (mm)	45	50	47

HF: heart failure; LA: left atrium; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic dimension; RA: right atrium.

Table 2. Biochemical data on admission, day 4 of imatinib treatment (decompensated heart failure), and after discontinuation of imatinib (recovered from heart failure).

	On admission	HF	Recovery from HF
BNP (pg/mL)	3,502.6	14,228	5,322.7
TnI (ng/mL)	0.02	0.02	0.01
CK (U/L)	30	50.5	20
CK-MB (U/L)	21.2	31.2	26
LDH (U/L)	588.2	1248.5	403

BNP: B-type natriuretic peptide; CK: creatine kinase; CK-MB: MB isoenzyme of creatine kinase; HF: heart failure; LDH: lactate dehydrogenase; TnI: troponin I.

3 Discussion

We present here a case of an elderly patient with CML who developed decompensated heart failure after only four days of imatinib mesylate treatment.

Imatinib mesylate, a targeted drug for tyrosine kinases, has revolutionized the treatment of CML. In a phase III, randomized, open-label IRIS trial, there were no instances of disease progression to an accelerated phase or blast crisis. The cumulative best complete cytogenetic response rate was 82%; 63% of all patients randomized to receive imatinib and still on study treatment were still in best complete cytogenetic response at last assessment. The estimated event-free survival at 6 years was 83% and estimated rate of freedom from progression to accelerated phase and blast crisis 93%.^[3]

Although imatinib is less toxic and better tolerated than traditional chemotherapy drugs, it can cause serious cardiotoxicity. Imatinib is reportedly not cardiotoxic at clinically relevant concentrations.^[11] High-dose imatinib has a greater potential for severe cardiotoxicity than does standard-dose imatinib.^[12,13] Although imatinib 400 mg (b.i.d.) reportedly results in more rapid reduction in tumor burden than does imatinib 400 mg/d,^[14] cardiotoxicity related to high dosage must be considered. Several publications have focused on the cardiotoxicity of imatinib mesylate. Although it can occur

at any age, the incidence increases with age. Imatinib-induced cardiotoxicity, which ranges from asymptomatic mild LV dysfunction to congestive heart failure,^[15] may be facilitated by the presence of relevant comorbidities such as pre-existing cardiovascular disease or renal failure.^[7] BNP is a cardiac neurohormone that is secreted by membrane granules in the cardiac ventricles in response to ventricular volume expansion and pressure overload. BNP concentrations are reflective of LV diastolic filling pressures and are reportedly increased in patients with symptomatic LV dysfunction. In the present case, the concentration of BNP increased from 2467 pg/mL to 14,228 pg/mL after initiation of imatinib, reflecting deterioration in cardiac function and decompensated heart failure. After withdrawal of imatinib, not only were the symptoms relieved, but also the BNP concentration decreased significantly, which implied that decompensated heart failure in this patient was imatinib-related. Similarly to the present patient, a patient with hypereosinophilic syndrome after receiving imatinib treatment for one week developed severe LV dysfunction that resolved after prompt drug withdrawal.^[16]

However, the above-described relationships between BNP or left ventricle EF and imatinib treatment duration and dose are not supported by recent evidence.^[17,18] A retrospective analysis of 219 consecutive patients treated with imatinib mesylate^[19] found that cardiotoxic adverse events occurred in 8.2% of them. These events were manageable with medical therapy and infrequently required dose reduction or discontinuation of imatinib mesylate. Heart failure is uncommon, occurring in less than 1% of treated patients. There was no statistical difference regarding cardiac symptoms and signs, BNP concentrations and echocardiographic measurements between imatinib and control groups.^[10] Atallah *et al.*^[20] summarized all the available reported serious cardiac adverse events occurring in patients on clinical trials involving imatinib and reported that 22 (1.7%) of 1276 patients developed systolic cardiac failure, 18 of whom had previous predisposing conditions such as cardiac failure, diabetes mellitus, hypertension, coronary artery disease, arrhythmia and cardiomyopathy. The EORTC-ISG-AGITG study also failed to confirm previous suggestions of imatinib-induced cardiac toxicity.^[8] Our patient had the predisposing conditions of hypertension, type 2 diabetes mellitus and permanent atrial fibrillation. However, although he had a relatively high concentration of BNP and abnormal cardiac chambers, his New York Cardiac Function Classification was good. The significant increase in BNP concentration and corresponding changes in echocardiographic index following imatinib treatment indicated decompensated heart failure in this patient.

In summary, imatinib therapy uncommonly causes heart failure and mainly occurs in elderly patients with preexis-

ting cardiovascular conditions. We recommend that if such patients develop symptoms suggestive of heart failure, they be monitored closely and treated aggressively with standard medical therapy, including diuretics. In addition, imatinib mesylate should be discontinued or the dosage reduced. Although imatinib-induced cardiotoxicity is uncommon in CML patients, even during long-term treatment,^[21] we strongly recommend standard cardiac monitoring of patients, especially the elderly, with a history of cardiovascular disease.

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