A Case Report of Imatinib-induced Acute Heart Failure and Literature Review

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ABSTRACT

Patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML), gastrointestinal stromal tumors (GISTs) or acute lymphoblastic leukemia (ALL) are appropriate candidates for medical treatment using imatinib. Here, we report a case of imatinib-induced acute heart failure in a patient with ALL and retrospectively analyse the adverse reactions of imatinib. The patient was a 45-year man with Ph+ and bcr-abl positive (bcr-abl+) ALL. He was treated with imatinib approximately four months ago. At that time, he had no risk factors for cardiac disease, and his heart function was normal. Then, four months after starting imatinib, he manifested signs of acute heart failure. A retrospective analysis of the adverse reactions in 100 cases of leukemia patients, who took imatinib in the past three years, indicated a rare incidence of congestive heart failure among those patients. Our experience in treating the patient suggests that brain natriuretic peptide levels and cardiac doppler examinations should be monitored closely in these patients.

Key Words: *Imatinib, Acute lymphoid leukemia, Acute heart failure.*

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INTRODUCTION

Imatinib mesylate is a type of oral tyrosine kinase inhibitor (TKI) that is used in the treatment of Philadelphia chromosome-positive (Ph+) blood malignant cancers, such as Ph+ CML, Ph+ ALL, and malignant gastrointestinal stromal tumors (GISTs).[1] Imatinib may cause neutropenia, thrombocytopenia, anemia, edema, *etc.*[2] Some experts have also reported that the use of imatinib is associated with the risk of congestive heart failure.[3,4] However, there has never been a report of imatinib-induced heart failure from China. We report a case of imatinib-induced acute heart failure and fatal thrombocytopenia; and review the adverse reactions in 100 cases of leukemia patients taking imatinib in the past three years.

CASE REPORT

A 45-year male patient presented with confirmed ALL for four months and fatigue for 10 days, to the Department of Hematopathology of our hospital on March 7th, 2019.

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He was diagnosed as ALL-(BCR/ABL+) by bone marrow biopsy, karyotyping and fusion gene analysis; and treated with imatinib four months ago. Prior to receiving imatinib treatment, the patient had no history of cardiovascular disease, and his heart function was normal. After receiving imatinib, he experienced some relief. Ten days later, he felt progressive aggravation of fatigue and gradually anasarca appeared, which was more apparent in the legs, as well as insomnia, shortness of breath, and poor appetite, without fever, nausea and vomiting.

On physical examination, he was conscious, but had edema, moderate anemia, and both limbs showed visible and scattered petechiae. Bilateral breath sounds were audible but unclear, scattered and wet; there was no pleural rub. The heart rate was 120 times/min with sinus rhythm, but valvular insufficiency murmur. The laboratory tests revealed white blood cells to be 211×10^9/ L, hemoglobin 80 g/L, and platelets 2×10^9 / L. Liver functions showed ALT of 100 U/L and AST 120 U/ L. Serum LDH-L was 151 U/L, proBNP 2000 ng/L, PCT 1.1 µg/L, e CRP 117.36 mg/L, and CK – MB 3.32 ng/ml.

We treated the patient concurrently with large-volume leukapheresis, liver protectant, diuresis, anti-infection and one dose of platelets. After three days, the patient's condition worsened. He experienced severe dyspnea and his heart showed signs of exhaustion after slight activity. The cardiac Doppler revealed the ejection fraction to be 28%; he had generalised cardiomegaly, severe tricuspid regurgitation, and moderate mitral valve regurgitation. But, before the patient received the imatinib

treatment, his atria and ventricles were normal, and the interventricular septum and the posterior wall of the left ventricle were normal in thickness and amplitude (Figure 1). Immediately, we stopped imatinib treatment and gave the patient diuretics and cardiac medications. The patient's symptoms were relieved, but he died of cerebral hemorrhage, caused by thrombocytopenia after two days.

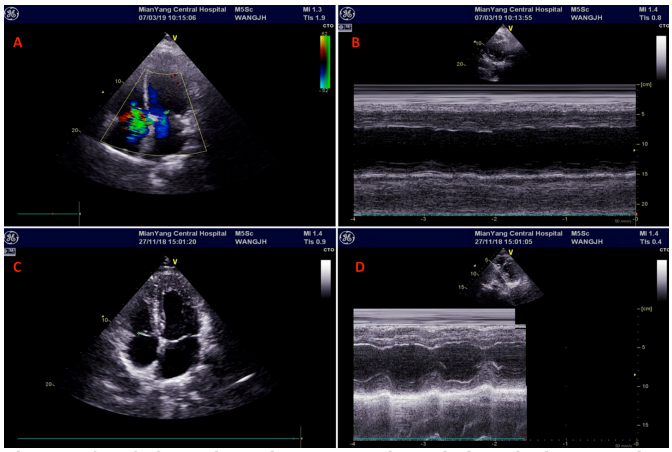

Figure 1: (A, B) The patient's heart was enlarged, the valvular regurgitation was severe, the ventricular wall thinner, and flexibility decreased after imatinib use. The anterior and posterior diameter of the left ventricle was 61 mm, the thickness of the left ventricular wall was 5 mm, and the ejection fraction was 28%. (C, D) The atria and ventricles were normal, and the interventricular septum and the posterior wall of the left ventricle were normal in thickness and amplitude before imatinib use. The anterior and posterior diameter of the left ventricle was 46 mm, the thickness of the left ventricular wall was 9 mm, and the ejection fraction was 62%.

Imatinib-induced heart failure is rare, and we retrospectively reviewed the adverse reactions of 100 leukemia patients with imatinib treatment in the past three years. The results showed that the main adverse reactions to imatinib occurred in the blood system, such as leukopenia, erythropenia and thrombocytopenia. Non-hematological adverse reactions included edema, water and sodium retention, digestive symptoms, muscle aches and cramps, and abnormal liver and kidney function (Table I). The condition of almost all those patients were not serious and the adverse reactions were tolerable.

Table I: Organs and systems involved in the adverse reactions to imatinib.

Organs and systems	n	Composition ratio (%)	Clinical manifestations
Blood	65	65%	Reduction in white blood cells, hemoglobin, and platelets
Liver and kidney	13	13%	Elevated transaminases, bilirubin, creatinine, and uric acid
Digestive system	33	33%	Nausea, constipation, diarrhea
Skin	9	9%	Multiple serous effusions, skin edema
Circulatory system	0	0	Palpitations, irregular heartbeat, heart failure
Muscle	30	30%	Muscle soreness and cramps
Other	15	15%	Fatigue, poor appetite, insomnia

DISCUSSION

Imatinib inhibits the fusion protein product of the fusion gene BCR/ABL, which is formed by reciprocal translocation of ABL proto-oncogene on chromosome 9 with BCR gene on chromosome 22 of human cells. Imatinib, in particular, inhibits the active binding site for adenosine triphosphate (ATP) on the fusion protein; thus, inhibiting the phosphorylation of the abl tyrosine kinase. This, in turn, inhibits the cell proliferation and increases apoptosis.[1] This patient had the fusion gene BCR/ABL, which conformed to the use of imatinib chemotherapy. The preclinical findings suggest that imatinib remains a potential cardiotoxin. Trent *et al.* recommend treating the risk factors for cardiovascular disease in imatinib-treated patients in accordance with the American Heart Association (AHA) guidelines for the prevention and treatment of heart failure.[5]

Cardiac toxicity can be caused by the tyrosine kinase inhibitors, like imatinib mesylate, dasatinib, nilotinib, sunitinib, sorafenib and lapatinib. The cardiotoxic events may range from asymptomatic subclinical abnormalities such as electrocardiographic changes and left ventricular ejection fraction decline to life-threatening events, such as congestive heart failure and acute coronary syndromes.[6] The mechanisms behind toxic cardiomyopathy are complex and multifactorial, but include interference with the myocardial cell bioenergetics and intracellular calcium pathways, the generation of reactive oxygen species (ROS), neurohormonal stress, and the induction of apoptosis.[6] Zhifei *et al.* revealed that high-mobility group box 1 protein-mediated necroptosis contributes to dasatinib-induced cardiotoxicity.[7]

The incidence of cardiotoxicity was cited to be similar to that of the onset of heart failure in the general population, estimated at 0.2% per year, as evidenced by new-onset heart failure or left ventricular dysfunction.[8] Ghias *et al.* reported a case of rapidly progressive dyspnea and heart failure in an elderly male with metastatic GIST, who received imatinib for just two weeks.[9] However, imatinib-induced severe acute heart failure and fatal thrombocytopenia have not been reported in China.

Considering the aforementioned case summary and toxic cardiomyopathy pathogenesis, we presume that this complication in the patient may be due to the long-term use of imatinib and a myocardial structural defect. Thus, this case report raises awareness about the accelerated cardiotoxicity profile of imatinib. Further prospective studies with multidisciplinary input are needed to further establish this association.

Imatinib is generally a safe and effective drug; and most adverse reactions are mild and tolerable. Although myocardial damage is rare, it is still worthy of attention. The potential risk of heart disease should be evaluated before and during the use of imatinib, such as routine blood test, heart color Doppler ultrasound examination, and brain natriuretic peptide levels.

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PATIENT'S CONSENT:
Informed consent was obtained from the patient's family for publication of this case report and accompanying images.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTIONS:
ZL, WQ: Treated the patient.

XZ, YL: Drafted the manuscript.

XH, JW: Performed data retrieval; and statistical analysis; and helped draft the manuscript.

All authors read and approved the final manuscript for publication.

REFERENCES

1. Waller CF. Imatinib Mesylate. *Recent Results Cancel Res* 2018; **212**:1-27. doi:10.1007/978-3-319-91439-8_1.
2. Francisco ARG , Alves D , David C, Guerra L, Pinto FJ, Almeida AG. Cardiotoxicity in hematological diseases: Are the tyrosine kinase inhibitors imatinib and nilotinib safe. *Cardiovasc Toxicol* 2018; **18(5)**:431-5. doi: 10.1007/s12012-018-9453-3.
3. Savi M, Frati C, Cavalli S, Graiani G, Galati S, Buschini A, *et al.* Imatinib mesylate-induced cardiomyopathy involves resident cardiac progenitors. *Pharmacol Res* 2018; **127**: 15-25. doi: 10.1016/j. phrs.2017.09.020.
4. Chambers TP, Santiesteban L, Gomez D, Chambers JW. Sab mediates mitochondrial dysfunction involved in imatinib mesylate-induced cardiotoxicity. *Toxicol* 2017; **382**:24-35. doi: 10.1016/j.tox.2017.03.006.
5. Trent JC, Patel SS, Zhang J, Araujo DM, Plana JC, Lenihan DJ, *et al*. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. *Cancer* 2010; **116(1)**:184-92. doi: 10.1002/cncr.24683.
6. Hantson P. Mechanisms of toxic cardiomyopathy. *Clin Toxicol (Phila).* 2019; **57(1)**:1-9. doi:10.1080/15563650.2018.1497172.
7. Zhifei X, Ying J, Hao Y, Gao Z, Xu B, Yang B, *et al*. High-mobility group box 1 protein-mediated necroptosis contributes to dasatinib-induced cardiotoxicity. *Toxicol Lett* 2018; **296**:39-47. doi: 10.1016/j.toxlet.2018.08.003.
8. Kim KW, Shinagare AB, Krajewski KM, Pyo J, Tirumani SH, Jagannathan JP, *et al.* Fluid retention associated with imatinib treatment in patients with gastrointestinal stromal tumor: Quantitative radiologic assessment and implications for management. *Korean J Radiol* 2015; **16(2)**:304-13. doi: 10.3348/kjr.2015.16.2.304.
9. Ghias AAP, Bhayani S, Gemmel DJ, Garg SK. Rapidly progressive dyspnea in gastrointestinal stromal tumor (GIST) with imatinib cardiac toxicity. *J Community Hospital Intern Med Perspectives* 2018; **8(2)**:87-91. doi: 10.1080/20009666.2018.1454787.