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). Imatinib may cause neutropenia, thrombocytopenia, anemia, edema, etc. Some experts have also reported that the use of imatinib is associated with the risk of congestive heart failure. 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 review the adverse reactions in 100 cases of leukemia patients taking imatinib in the past three years.

CASE REPORT
A 45-year-old 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. 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

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 211×10⁹/L, hemoglobin 80 g/L, and platelets 2×10¹¹/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 atraa and ventricles were normal, and the inter-
ventricular septum and the posterior wall of the left ventricle
were normal in thickness and amplitude (Figure 1). Immedi-
ately, 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.

![Image](image_url)

**Figure 1:** (A, B) The patient's heart was enlarged, the valvular regur-
gitation 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, erythrocytopenia and thrombocy-
topenia. 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.

| 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 chromo-
some 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. 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 accord-
ance with the American Heart Association (AHA) guidelines for
the prevention and treatment of heart failure.

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 asympto-
matic 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. The mechanisms behind toxic cardiomyo-
pathy 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. Zhifei et
al. revealed that high-mobility group box 1 protein-mediated
necroptosis contributes to dasatinib-induced cardiotoxicity.

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. 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. 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 complica-
tion 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 ultra-
sound 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.

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