To the editor:

Serum concentration of cardiac Troponin T in patients with hypereosinophilic syndrome treated with imatinib is predictive of adverse outcomes

We read with great interest the recent article by Pardanani et al.1 on serum concentration of cardiac Troponin T (cTnT) in patients with hypereosinophilic syndrome (HES) and other chronic myeloid disorders associated with eosinophilia (eos-CMD) by imatinib mesylate (Gleevec). In their experience, 2 pts with HES and 1 with eos-CMD achieved a complete clinical remission, and 1 additional patient with HES, a partial remission. Although the drug was welltolerated by most patients, a previously unrecognized treatment toxicity of acute left ventricular dysfunction occurred in a responding patient with HES within the first week of treatment with imatinib. A myocardial biopsy revealed eosinophilic infiltration and degranulation associated with myocyte damage.

A comparable experience has been observed by us in 2 of 5 pts with HES after starting treatment with imatinib. In our series of pts, the measurement of serum concentrations of cardiac Troponin T before treatment and then every 24 hours for almost 7 days accurately predicts the development of myocyte injury and the risk of adverse cardiac events. These 5 pts with HES, all men, median age 48 years, were started on imatinib at a daily dose of 100 mg after a median of 4 courses of pulse steroids and hydroxyurea (Table 1). All pts were required to be off therapy for at least 4 weeks prior to study enrollment; each had a long history of symptoms, which included dyspnea, frequent upper respiratory tract infections requiring antibiotic therapy, leukocytosis (white blood cell count [WBC] median, 23 × 10^9/L), and eosinophilia (median, 10.5 × 10^9/L).

Echocardiographic assessment before starting imatinib revealed endocardial thickening, which is a classic finding in HES,2 in only one patient (case 1). Basal measurements of serum concentrations of cTnT showed raised serum concentrations of cTnT in case 1 (cTnT > 0.02 ng/mL). Case 2 and the remaining 3 pts had basal serum concentrations of cTnT less than 0.02 ng/mL.

After 8 days of therapy with imatinib, case 1 developed progressive dyspnea and orthopnea; a new echocardiogram revealed severe generalized left ventricular hypokinesis and a left ventricular ejection fraction (LVEF) that decreased from 52% to 28%. The patient was started on high-dose steroids and 2 days later he experienced symptomatic improvement; a follow-up echocardiogram revealed an LVEF of 40%. Serial measurements of serum cTnT concentrations before starting imatinib and then every day for 15 days showed serum cTnT concentrations higher than 0.02 ng/mL persistently. The patient had a regular follow-up after 2 months and cTnT concentrations had remained higher than 0.02 ng/mL. In case 2, asymptomatic from the cardiac standpoint and with basal cTnT less than 0.02 ng/mL, an increase in the concentration of circulating cTnT was detected after 3 days of treatment with imatinib. Then, 4 days later the patient developed progressive dyspnea with cardiogenic shock and required intravenous pressor support; an echocardiogram revealed severe left ventricular hypokinesis with reduction of LVEF from 61% to 20%. The patient was started on high-dose steroids with rapid improvement of dyspnea; after 48 hours a
follow-up echocardiogram revealed that LVEF had increased to 35%, and serum cTnT concentrations decreased to less than 0.02 ng/mL after 15 days. The remaining 3 pts showed no echocardiographic and/or cTnT changes after treatment with imatinib and at the follow-up checks (Table 1).

In an idiopathic hypereosinophilic syndrome a major source of the morbidity and mortality is associated with cardiac involvement due to infiltrating eosinophils and based on an activation process involving surface molecules with release of eosinophilic cationic proteins that are known to be cytotoxic and to cause endothelial damage. Several reports have focused on the echocardiographic assessment of cardiovascular abnormalities associated with HES even if microscopic evidence of eosinophilic infiltration of the endomyocardium without echocardiographic evidence of abnormality occurs in at least a subset of patients with HES in percutaneous right ventricular biopsy samples. Cardiac Troponin T is a structural protein that attaches the troponin-tropomyosin complex to the thin filament of actin. Measurement of serum concentrations of cTnT in HES seems to indicate myocyte degeneration and may be helpful as a sensitive noninvasive marker of cardiac disorder. In our experience the rise of cTnT before starting imatinib and the evaluation of cTnT soon after imatinib have accurately predicted the development of acute left ventricular (LV) depression (cases 1 and 2).

The mechanism of myocyte degeneration in HES during therapy with imatinib is not fully understood. However, the time course of development of acute LV dysfunction after starting imatinib and the rapid response to corticosteroid therapy suggest that an inflammatory response to degranulation of infiltrating eosinophils is responsible for the acute cardiogenic shock. Thus, it is necessary to recognize this potentially life-threatening complication promptly so as to start corticosteroid therapy at once. A larger study is warranted to investigate the value of cTnT and serial echocardiograms in predicting cardiac dysfunction in pts with HES treated with imatinib.

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Response:

Imatinib treatment–induced cardiomyopathy in hypereosinophilic syndrome

Dr Pitini and colleagues describe 2 additional patients with imatinib-induced cardiomyopathy in the setting of hypereosinophilic syndrome (HES). Along with the index case,1 all 3 patients experienced severe left ventricular dysfunction (LVD) within 8 days of drug therapy. In the current correspondence, the authors demonstrate that both of their patients with LVD had an elevated serum troponin level either before or during imatinib therapy. Similarly, our patient also had an elevated pretreatment serum cTnT level (1.86 ng/mL) that increased to 5.88 ng/mL on the day of hospitalization for heart failure. These observations suggest that future studies of imatinib therapy in eosinophilic disorders should incorporate pre- and peritreatment measurements of serum troponin level as well as left ventricular ejection fraction in order to systematically study their correlation with the occurrence of drug-induced LVD. In the meantime, physicians who use imatinib for the treatment of HES should be fully aware of this peculiar as well as potentially fatal complication, especially in view of the fact that systemic corticosteroid therapy reversed the cardiac shock promptly in all 3 cases. Accordingly, one can consider the concurrent use of short-term corticosteroid therapy a few days before or during the first 2 weeks of imatinib therapy in HES. To that effect, we had successfully rechallenged our patient with imatinib therapy under corticosteroid cover and saw no ill effects. Nevertheless, the currently available information is not adequate to warrant making specific recommendations but strongly supports close monitoring of HES patients, in the first 2 weeks of imatinib therapy, for symptoms and signs of LVD.

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References


To the editor:

Epstein-Barr virus–associated B-cell non-Hodgkin lymphoma following treatment of hairy cell leukemia with cladribine

Epstein-Barr virus (EBV) is a tumorigenic herpes virus, which is associated with several human hematologic neoplasias such as Burkitt lymphoma, Hodgkin disease, and posttransplantation lymphoproliferative disease (PTLD). EBV-induced lymphoproliferative disease represents a broad spectrum, ranging from benign disorders to malignant non-Hodgkin lymphomas occurring mainly as complication of immuno-deficiency. However, its acute development after conventional chemotherapy as treatment for another malignancy is a rare finding.
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