Cardiotoxicity of imatinib mesylate: an extremely rare phenomenon or a major side effect?

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Imatinib mesylate (Gleevec/Glivec) is a small-molecule inhibitor, which blocks selectively the tyrosine kinase activity of c-abl, bcr-abl, platelet-derived growth factor receptor, c-fms and c-kit.¹ It is widely used for the treatment of Philadelphia chromosome-positive leukaemia and gastrointestinal stromal tumours.²⁻³ Imatinib might also become a novel therapeutic option for pulmonary arterial hypertension.⁴ Furthermore, imatinib is a potent anti-inflammatory and anti-fibrotic drug, and might be a promising candidate for the treatment of rheumatoid arthritis and systemic sclerosis.⁵⁻⁶

Kerkelä *et al*⁷ recently reported on 10 patients who developed congestive heart failure after taking imatinib mesylate. Histological evaluation of cardiac sections suggested toxic cardiomyopathy. The authors also presented experimental evidence for a causal role of the inhibition of c-abl in the pathogenesis of congestive heart failure. Further cases of cardiotoxicity from imatinib use have not been reported so far.

What are the practical consequences of this study? Is cardiotoxicity an extremely rare phenomenon or a major side effect of imatinib mesylate?

First and foremost, peripheral oedema and fluid retention, which occur in up to 60% of patients treated with imatinib, are not symptoms of cardiotoxicity. Kerkelä *et al* suggested that the cardiotoxic effects of imatinib are mediated via inhibition of c-abl signalling pathways. Therefore, one would also expect the development of peripheral oedema and fluid retention in patients treated with other c-abl kinase inhibitors. However, no such side effects have been reported with nilotinib, although nilotinib inhibits c-abl more potently.⁸

Furthermore, several patients reported to have had congestive heart failure while on imatinib had pre-existing cardiac disease or cardiovascular risk factors. Out of the 10 patients, 3 were previously diagnosed with coronary artery disease. Hypertension and diabetes were found in 7 and 4 patients, respectively. The frequency of other cardiovascular risk factors such as smoking and hyperlipidaemia has not been reported. Thus, imatinib might have precipitated pre-existing cardiac disease rather than inducing cardiotoxicity in the majority of the reported patients.

Finally, congestive heart failure has been reported in only 10 patients treated with imatinib so far. Looking at these 10 patients, one has to keep in mind that more than 100 000 patients have been treated with imatinib, including more than 10 000 patients in clinical trials. Development of congestive heart failure has not been reported in these patients, although cardiotoxicity was not a major outcome parameter in these trials. However, cardiotoxicity of imatinib might have been

overlooked in patients with oncological diseases, since these patients can present with alternative causes for cardiotoxicity.

In summary, imatinib and potentially also other abl-kinase inhibitors might induce congestive heart failure. This potential side effect warrants careful monitoring, which should be started immediately after initiation of the treatment, since congestive heart failure was detected within the first weeks of treatment in some patients. However, the incidence of cardiotoxicity seems to be very low and the cardiotoxic side effects might occur preferentially in patients with pre-existing cardiac disease. Thus, imatinib and related drugs are still promising drugs that might offer new therapeutic opportunities for the treatment of pulmonary hypertension, rheumatoid arthritis and systemic sclerosis.

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