Results of plasma N-terminal pro B-type natriuretic peptide and cardiac troponin monitoring in GIST patients do not support the existence of imatinib-induced cardiotoxicity

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Background: Recently, case reports of patients treated with imatinib (imatinib mesylate; Gleevec®; Glivec®, Novartis, Basel, Switzerland), a small molecule tyrosine kinase inhibitor, are applied successfully as standard therapy for the treatment of chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours (GIST) [1]. A recent publication of Kerkela et al. [2], however, without giving a patient denominator, suggested a risk of cardiotoxicity induced by imatinib, which was unexpected, given the previous toxicity data of large patient studies. Subsequent specific reports indicated a low incidence (if any) of New York Heart Association (NYHA) class III–VI heart failure due to imatinib, which was unexpected, given the previous toxicity data of large patient studies. Subsequent specific reports indicated a low incidence (if any) of New York Heart Association (NYHA) class III–VI heart failure due to imatinib, varying from 0.2% to 1.8% [3–5]. Although the clinical problem of imatinib-related cardiotoxicity may be limited, lower NYHA class, as well as subclinical cardiotoxicity, may be more frequently observed in patients treated with imatinib if paid attention to [6].

Natriuretic peptides are neurohormones which are increased in plasma in case of cardiac dysfunction. N-terminal pro B-type natriuretic peptide (NT-proBNP) is the prohormone of BNP and is secreted by cardiomyocytes in response to ventricular dilation or local wall stress, and can be used as a sensitive biochemical marker to detect left ventricular systolic dysfunction [7].

To evaluate whether imatinib induces (subclinical) cardiac toxicity, we prospectively evaluated cardiac function, including history, a physical examination, and determination of plasma NT-proBNP and serum cardiac troponin T (cTnT) concentrations in GIST patients treated with this agent.

patients and methods

patients and treatments

As part of surveillance programmes, plasma and serum from patients treated with imatinib for locally advanced and/or metastatic GIST were...
collected after informed consent before treatment and at 1 and 3 months thereafter. Imatinib (Novartis) was administered orally at 400–800 mg daily, continuously. Treatment was continued until disease progression or unacceptable toxicity.

cardiac evaluation
A cardiac evaluation, including a history and physical examination with special attention to signs and symptoms related to heart failure, was carried out before the start of imatinib treatment and 1 and 3 months after the start of treatment. If present, heart failure severity was classified according to the NYHA scale [8].

natriuretic peptides and cTnT concentrations
For the determination of plasma NT-proBNP and serum cTnT levels, peripheral blood samples were collected as serum or lithium-heparin plasma specimens using standard sampling tubes. Serum or plasma was separated and stored at −80°C until determination. NT-proBNP and cTnT levels were measured with an electrochemiluminescence immunoassay (Elecsys proBNP assay and Elecsys Troponin T assay, respectively; Roche Diagnostics, Mannheim, Germany). NT-proBNP has an upper limit of normal of 125 ng/l [9]. Age-dependent cut-off values are as follows: ≤50 years: 450 ng/l; 50–75 years: 900 ng/l; >75 years: 1800 ng/l [10]. cTnT values of ≥50 ng/l indicate myocardial injury.

statistics
Values are given in mean (± standard deviation) for normally distributed variables and median (range) for variables with a skewed distribution. Paired analysis was carried out with a Wilcoxon paired samples test. All P values are two-sided and P values <0.05 indicate statistical significance.

results
patients
Serum and plasma were obtained from 55 patients (34 male) with a mean age of 62 (±12) years. The mean follow-up duration was 9 (±3.7) months. Two patients had received prior chemotherapy; one had received four cycles of bleomycin, etoposide and cisplatin for a testicular germ-cell tumour, 18 years before imatinib, and the other 6 months of adjuvant capecitabine for colon carcinoma, 6 months before imatinib.

cardiac evaluation and cardiac marker measurements
Figure 1 represents individual plasma NT-proBNP values during imatinib treatment. Before the start of imatinib, two patients had chronic heart failure. One patient had NYHA class III symptoms on the basis of atrial fibrillation and mitral regurgitation, which remained stable during treatment. She had an elevated pretreatment NT-proBNP level, which increased from 2384 to 4014 ng/l after 3 months. The second patient had NYHA class IV symptoms at the start of imatinib therapy due to idiopathic dilated cardiomyopathy. The use of diuretics markedly improved his symptoms and lead to a decrease in plasma NT-proBNP from 19 229 before treatment to 294 ng/l after 3 months.

Only one of the patients with normal pretreatment NT-proBNP levels developed a plasma NT-proBNP level above the age-specific cut-off level (from pretreatment 437 to 1009 ng/l). This 58-year-old woman, with pre-existing asymptomatic mitral valve regurgitation, developed NYHA class II heart failure after 5 months. As she had had heart failure in the past, the relapse of symptoms was considered to be due to the mitral valve regurgitation. No other patient presented symptoms of cardiac failure during the study period.

Serum cTnT levels remained below the lower limit of normal for all patients during the follow-up period.

discussion
Imatinib is currently widely and successfully applied in the treatment of patients with chronic myelogenous leukaemia or GIST. The recent report by Kerkela et al. [2], indicating that the use of imatinib could induce cardiac dysfunction, alarmed many oncologists treating these patients. In the current study, we found that plasma NT-proBNP levels remained stable during the first 3 months of treatment. Only 1 of 55 patients developed symptomatic, drug-unrelated heart failure during imatinib treatment, coinciding with a marked increase in plasma NT-proBNP value. An increase
in serum cTnT was not observed at the various time points, as compared with pretreatment values.

The alarming data of Kerkela et al. [2], who did not mention the total number of patients at risk, have not been confirmed in subsequent reports with large patient numbers. For example, in the EORTC-ISG-AGITG phase III trial, the frequency of cardiomyopathy in 942 GIST patients treated with imatinib at a dose of either 400 or 800 mg daily was 0.2% [5], indicating that treatment with imatinib is not related to an increased risk of heart failure. Our data are in line with those, and may indicate that short-term imatinib treatment is not related to an increased rate of (subclinical) cardiotoxicity. In combination with the other studies reported that indicated that the few imatinib-related cardiac events can also occur after only a few days of treatment, indicating that if any, the drug rather than the cumulative dose may be responsible, our data confirm that standard cardiac monitoring does not appear required.

During the last years, the value of NT-proBNP has been studied in the oncological setting. For instance, plasma NT-proBNP measurement in anthracycline-treated breast cancer patients, proved to be a useful early marker for a decrease in left ventricular ejection fraction [11]. Interestingly, measurement of plasma BNP has recently been shown to be a practical and useable marker for the detection of imatinib-related cardiotoxicity [12].

Next to NT-proBNP, we also measured serum cTnT. In oncology, serum cTnT may be a useful marker for detecting subclinical cardiotoxicity induced by doxorubicin in adults [13, 14], although most data are currently derived from studies carried out in children. In our study, we measured for the first time cTnT prospectively in patients treated with imatinib and could not demonstrate any change in time.

A limitation of our study may be the fact that no objective measures of left ventricular function were included in the cardiac assessment. Another limitation of the current study may be our relatively small study population, considering the low reported incidence of cardiomyopathy during treatment of GIST patients with imatinib. Additionally, the follow-up duration was short.

In conclusion, plasma NT-proBNP and serum cTnT levels did not change during imatinib treatment, further indicating that treatment with imatinib is not related to an increased incidence of subclinical cardiotoxicity. Standard cardiac monitoring does not appear required with this agent.

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references