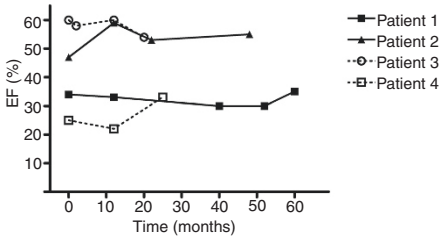

Figure 1 Ejection fraction (EF) values over time in four patients with cardiomyopathy or coronary artery disease.

after)? This information is important because cardiovascular disease is a common source of morbidity and its incidence in imatinib-treated patients should be compared to that expected in a population of similar age. In addition, as the two time points ('baseline' and 'imatinib') are discontinuous and not quantitative, the data should have been depicted, in our opinion, as a bar graph and not as curves.

At our center in Monza, Italy, a total of 103 chronic myeloid leukemia (CML) patients started treatment with imatinib between 1999 and 2005. This population of patients was composed of 43 women and 60 men, with a median age of 51 ± 5 (95% confidence interval) years. The median follow-up period was 48 months. One patient was lost to follow-up after 6 months of treatment. Thirty patients died, 27 because of CML progression (23 during the first year and 4 during years 2–4). Of the three deaths from non–CML-related causes, one was due to small-cell lung cancer and two were sudden deaths. In these two cases, one patient was an 86-year-old who died four months after starting imatinib, and who had a hematological but not cytogenetic response to imatinib treatment; the second was patient 4 of **Figure 1**, who died after 32 months of therapy while in complete cytogenetic remission. Patient follow-up consisted of a physical examination (including vital-sign determination) and routine blood tests every week during the first month, biweekly during the second and third months, and every three months thereafter. In general, electrocardiograms were performed annually and echocardiographic examinations were performed before starting imatinib treatment and at 8–12 months after treatment. No case of CHF developed in this group of patients, and we noted no significant drop in mean ejection fraction values among patients who completed at least 8–12 months of treatment (61 ± 4% versus 64 ± 3%, $P > 0.1$). In addition, four patients started imatinib treatment with known pre-existing cardiovascular morbidity; of these, three suffered from cardiomyopathy (patients 1, 2 and 4) and one (patient 3) from extensive coronary artery disease. In patients 1,3 and 4, the dose of imatinib was 400–600 mg/day. In patient 2, the dose was increased to 1 g/day at month 36 because of a cytogenetic relapse of CML. In none of these four patients was there a substantial drop in ejection fraction values over time (**Fig. 1**).

Although it remains possible that imatinib affects some function of cardiac myocytes, our data do not provide evidence for a clinically relevant and frequently occurring cardiotoxic effect of imatinib.

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1. Kerkelä, R *et al. Nat. Med.* **12**, 908–916 (2006).

To the editor:

We read with interest the article of Kerkelä *et al.*[1] discussing the potential cardiotoxicity of imatinib mesylate in animal models and detailing ten patients, nine from our institution, who developed congestive heart failure (CHF) on imatinib therapy. This report has generated significant concerns for patients and health care providers regarding the risks posed by imatinib therapy. To place the clinical experience reported in its broader context, we reviewed 1,276 patients with chronic myeloid leukemia (CML) who had been enrolled in clinical trials of imatinib from 28 July 1998 to 27 July 2006. The median follow-up time was 5 years. In all the imatinib protocols, standard research monitoring procedures were conducted before treatment and at regular intervals, as specified[2,3], including routine exams (such as clinical cardiac evaluations). Electrocardiograms, echocardiograms and chest radiograms were conducted routinely before treatment and as clinically indicated in follow-ups. Eligibility criteria excluded patients with cardiac problems (for example, patients in classes III and IV according to the New York Heart Association Class). After reviewing all reported adverse events, particularly those that could be considered as having a cardiac origin, we identified 22 patients (1.8%) as having symptoms that could be attributed to CHF. These 22 included the 9 patients from our institution reported by Kerkelä *et al.* Their median age was 70 years (range, 49–83 years). The diagnosis at the time of imatinib initiation was CML in chronic phase ($n = 11$), accelerated phase ($n = 4$) or blast phase ($n = 2$); myeloproliferative disorder ($n = 4$); or acute lymphoblastic leukemia ($n = 1$). Twelve patients had previously received interferon therapy and three had received anthracyclines. The median time from the start of imatinib therapy to a cardiac adverse event was 162 days (2–2,045 days). Eighteen patients had previous medical conditions predisposing them to cardiac disease: CHF ($n = 6$), diabetes ($n = 6$), hypertension ($n = 10$), coronary artery disease (CAD; $n = 8$), arrhythmia ($n = 3$) and cardiomyopathy ($n = 1$). Of the 22 patients, 15 underwent echocardiogram or multiple gated acquisition (MUGA) scans at the time of the CHF event: 9 of these 15 patients were documented as having a low ejection fraction, and 6 of these 9 had significant conditions predisposing them to cardiac disease (3 CAD, 2 CHF and 1 cardiomyopathy). Of the 22 patients with CHF symptoms, 11 continued imatinib therapy with dose adjustments and management for CHF symptoms without further complications. With the host of confounding factors involved in these patients, the occurrence of CHF in connection with imatinib use was reasonably unambiguous in only 7 of the 1,276 patients reviewed (0.5%). We conclude from our experience that imatinib therapy as a causal factor of CHF is rare. When seen, symptoms of CHF most frequently occur in elderly patients with pre-existing cardiac conditions and may often reflect predisposing cardiac compromise compounded by some element of fluid retention. Patients with a previous cardiac history should be monitored closely and treated aggressively with diuretics if they develop fluid retention.

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