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Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: Analyis of EORTC-ISG-AGITG study 62005

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ABSTRACT

Recent publications have suggested that imatinib (Glivec) may be cardiotoxic. We have therefore assessed the largest study on the agent performed in patients with gastrointestinal stromal tumours, randomising a daily dose of 400 mg versus 800 mg. 946 Patients were entered, 942 patients received at least one dose of imatinib. The median time on treatment was 24 months. A total of 24,574 exposure months could be analysed. We could not identify an excess of cardiac events in the study population. In 2 patients (0.2%) a possible cardiotoxic effect of imatinib could not fully be excluded.

The current analysis of a large randomised prospective study could not confirm previous suggestions of imatinib induced cardiac toxicity.

1. Introduction

During the last few years, the multitargeted tyrosine kinase inhibitor imatinib (Glivec™) has become the backbone of treatment for chronic myeloid leukaemia (CML) and for irresectable or metastatic gastrointestinal stromal tumors (GIST).[1–6] Despite the fact that both diseases are relatively rare,and in spite of the limitations of available treatments significant numbers of patients have already benefited from imatinib therapy. To date, there are relatively few large studies that have been published documenting imatinib side effects.[1,5,6] An unusual feature of imatinib therapy that is as yet unexplained is the fact that incidence and severity of side effects appear to be different in patients with either CML or GIST, despite the fact that they receive the same dose of the drug and are treated with the same (continuous dosing) treatment schedule.

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A recent study in CML patients reported 10 cases of severe cardiac toxicity (left ventricular failure).[7] Although the study did not report the denominator of patients exposed to imatinib, it also provided elegant experimental model evidence documenting the possible role of ABL in cardiac cells, in the induction of this possible side effect of imatinib. In another paper, 2 patients (one with CML, one with GIST, both with pre-existing cardiac risk factors) with developing cardiac failure were reported and brain natriuretic peptide was suggested as an early marker of cardiac toxicity.[8]

Since these two reports have also resulted in major concern in the GIST patient population treated with imatinib, and in view of the possible difference in toxicity profile between patients with CML and GIST, we decided to extensively explore the database of the large EORTC-ISG-AGITG[1] randomised study in 946 GIST patients.[5,9,10]

2. Patients and methods

This analysis was conducted in patients included in the randomised EORTC-ISG-AGITG phase III trial.[5] A total of 946 patients with advanced or metastatic GIST were randomised to be treated with imatinib at a dose of 400 mg once daily (standard dose arm) or 400 mg bid (high dose arm). In case of progressive disease in the standard dose arm, a cross-over to 400 mg bid was scheduled.

Eligibility criteria have extensively been outlined elsewhere[5] including a WHO performance score of 0–3, normal haematological and renal function, and AST and ALT being within 2.5 times the upper normal value (or 5 times in case of liver metastases). Patients with Class 3/4 cardiac problems as defined by the New York Heart Association Criteria (e.g, congestive heart failure, myocardial infarction within 2 months of study) or uncontrolled hypertension were excluded from the study.

Prior therapy for GIST was allowed and there was no upper age limit.

Toxicities were assessed weekly during the 2 first months of therapy, monthly up to 6 months, and 3 monthly thereafter, using the Common Toxicity Criteria (CTC), version 2.0. All Serious Adverse Events (SAEs), which included left ventricular failure, related or not to the study treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, had to be reported within 24 h.

Treatment was withheld until recovery in case of grade 2 non-haematological and grade 3 haematological toxicity; the dose was reduced in case of recurrence of those events, and in case of grade 3 non-haematological toxicity. Other eligibility criteria, evaluation criteria and efficacy results have been described elsewhere.[5]

Cardiovascular assessment was based upon the patients history and on physical examination (complete physical examination with pulse rate and blood pressure) that was performed weekly for the first 2 months of treatment, then monthly until the end of the 6th month of therapy, and subsequently every 3 months until treatment discontinuation. In addition, a chest X-ray was performed at the end of the 2nd, 4th and 6th months, and every 3 months thereafter.

3. Results

A total of 946 patients were randomised in the trial, four of them never started protocol therapy. The present analysis is therefore based on the 942 patients who received at least one dose of imatinib. The median follow up is 47 months, and the median exposure time to imatinib is 24 months. A total of 24,574 exposure months could be analysed. Median overall survival is 47 months. The reported side effects that we considered attributable to the cardiovascular system were analysed. Forty-six patients (4.9%) were reported to experience arrhythmia (1.4% grades 3 and 4) , 72 (7.6%) had an episode of hypotension (0.6% grades 3 and 4), edema was seen in 784 patients (83.2%), mainly periorbital (a reported side effect of imatinib) with 71 (7.5%) grades 3 and 4 (0.4%) grade 4. There were 7 patients for whom cardiac failure during Imatinib was reported, one of whom died of cardiac failure. In addition, there were three deaths from other cardiac events. These 10 cases (1%) are described in detail in Table 1.

Three patients died suddenly at home without any preceding symptoms. This makes a myocardial infarction more likely than cardiac failure.

Two patients were entered on study with a known cardiac insufficiency due to prior doxorubicin and one of them was reported to have had left ventricular failure (LVF) prior to study entry. Both had LVF while on imatinib but fully recovered despite ongoing drug exposure. Two patients, 91 and 83 years of age, respectively, were entered on study with known cardiac insufficiency and LVF due to cardiac disease prior to study entry. They also had pre-existing hypertension and atrial fibrillation, respectively, and were reported to develop LVF, while on imatinib. Both patients fully recovered despite ongoing drug exposure. If imatinib had been cardio toxic in those four patients, on top of pre-existing cardiac disease, one would have expected recurrent and increasingly more severe cardiac failure. Finally, a 71-year-old patient without reported pre-existing cardiac problems had LVF on day 141, while on imatinib but fully recovered despite continued exposure to imatinib. This again makes imatinib related cardiotoxicity in this patient less likely.

This leaves 2 patients (0.2% of all patients exposed to Imatinib in the study) in whom one cannot completely rule out a cardiomyopathic effect of imatinib. Of note, both patients were very old. The cumulative incidence is given in Fig. 1. Importantly, there does not seem to be any relation to dose.

4. Discussion

Given the recent reports of possible cardiomyopathy induced by imatinib,[7,8] we have carefully analysed the database of our phase III study in GIST patients. This accrued 946 patients followed for a median of 4 years, treated at a dose of either 400 or 800 mg daily. It is important to note that in the latter group patients were receiving twice the current standard dose recommended in GIST. Analysing all symptoms and toxicity scores that could possibly be attributable to cardiac problems,

[1] EORTC–European Organization for Research and Treatment of Cancer, ISG–Italian Sarcoma Group, AGITG–Australasian Gatro-Intestinal Trials Group.

Table 1 – Patients with reported cardiac failure and/or death due to cardiac event while on imatinib

Seqid	Age	Sex	PS (WHO)	Other relevant chronic disease	Daily imatinib dose (mg)	Narrative	Outcome of cardiac event
184	76	M	1	–	800	Died on day 1378 possibly due to LVF. Suspicion on LVF expressed based on orthostatic hypotension 2 months before, which was not treated	Died
395	38	M	0	Doxorubicin induced cardiomyopathy with prestudy LVEF 42%	800	LVF on day 179. Successfully treated. Continued imatinib without any further cardiac problem	Recovered
411	67	M	0	Doxorubicin induced cardiomyopathy; non insulin-dep.diab.	400	Known LVF prior to study entry. Recurrent LVF on day 87. Successfully treated. Continued imatinib without any further cardiac problem	Recovered
520	83	M	1	Hypertension, chronic aterial fibrilation	800	Developed LVF on day 21. Successfully treated. Continued imatinib without any further cardiac problem. Died of pneumonia on day 1378	Recovered
675	83	M	2	Mild angina, and asthma	400	Died on day 64 with multiple organ failure. PI did not suspect relationship with drug	Died
713	58	F	0	–	400	Sudden death on day 183, no cardiac signs reported before death	Died
799	71	F	1	–	800	LVF suspected on day 141 but no further information. Continued imatinib without any further cardiac problem	Recovered
892	53	M	1	–	800	Sudden death on day 469, no cardiac signs reported beforehand	Died
925	91	M	3	Left ventricular failure. Pacemaker	400	Leg oedema on day 63, treated successfully. Continued imatinib without any further cardiac problem reported	Recovered
933	70	M	1	–	800	Sudden death on day 523. Signs of myocardial infarction	Died

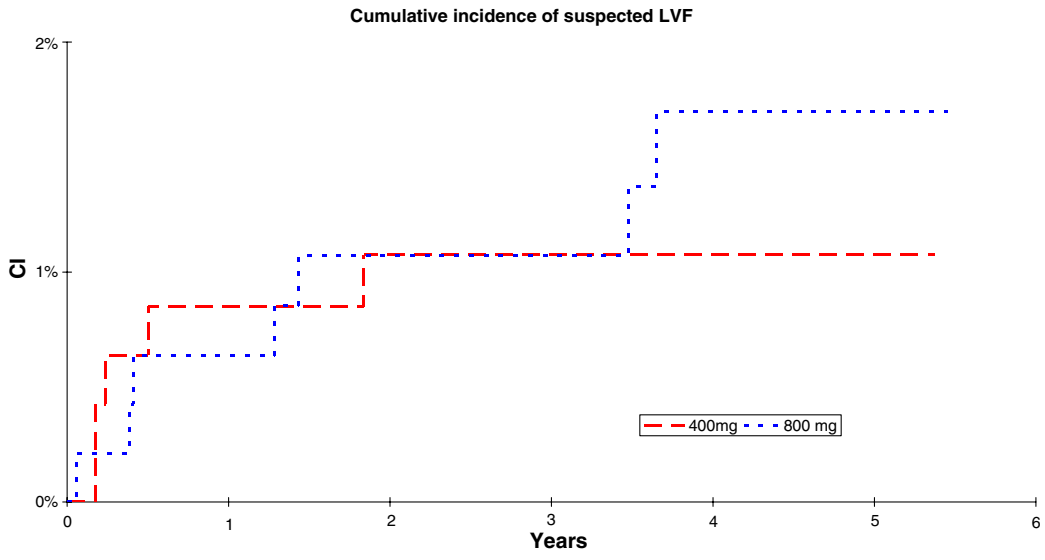

Fig. 1 – The cumulative incidence of LVF related to daily dose of imatinib.

we were unable to identify any clear cut pattern. Most reported cases related to acute events rather than possible cardiac failure. Taking all 'cardiac events' grades 3 and 4 (ventricular failure is a serious clinical problem which one would expect to be scored at least grade 3), the maximum incidence of cardiotoxicity would be 2.6% (25 events in 946 patients). But when analysing these cases in detail, it turned out that most of them were related to other events than cardiac failure.

Analysing our data in detail we were able to identify 10 cases (1.1% of the total study population) of either an SAE or reported death, where a closer look for a possible cardiomyopathic effect of imatinib seemed indicated. Three patients died suddenly at home without any preceding symptoms. Cardiac failure if lethal would lead to symptoms at least for a few hours prior to death, this makes a myocardial infarction in these patients more likely than cardiac failure. Importantly, all three patients were in the age range where myocardial infarctions do occur. Two very elderly patients (91 and 83 years of age, respectively) with known cardiac insufficiency and LVF due to cardiac disease, and with pre-existing cardiac co-morbidity, were entered on study and reported to develop ventricular failure while on imatinib, but both fully recovered despite ongoing drug exposure. If imatinib would have been cardio toxic in those patients, on top of a pre-existing cardiac disease, one would have expected further recurrent and increasingly more severe cardiac failure. Finally, a 71-year-old patient without reported pre-existing cardiac problems developed LVF while on imatinib, but fully recovered despite ongoing imatinib treatment and did not have any further LVF. This again makes imatinib related cardiotoxicity in this patient less likely.

In only 2 of the 10 patients (0.2%), we could not rule out the possibility that imatinib might have caused cardiac failure. In all other patients this was considered unlikely. Given the fact that some of the reported events occurred within or around 60 days from treatment start, percentages will not rise if we only take into account patients who were exposed for a longer period of time. Of note, the rate of cardiac deaths in this study is not higher than to be expected in an otherwise 'healthy' population of this age range.

Hence the rate of possible imatinib induced cardiomyopathy in this study is 0.2%. The incidence of overall cardiac toxicity from imatinib in GIST patients seems to be an extremely rare event. In patients treated with imatinib for metastatic or advanced GIST, we currently see no indication to perform regular assessment of cardiac function. On the other hand, in experimental settings such as adjuvant treatment, where cure is the aim, a somewhat more careful approach may be considered.

Whether there is a difference in cardiac susceptibility to imatinib between patients with chronic myeloid leukaemia and those with GIST remains unknown. The underlying mechanism for this possible difference remains unclear. Given the exposure time to imatinib in our study population, it is not very likely that difference in susceptibility, if any, can be explained by differences in drug exposure. The currently available data also do not allow a comparison of cardiac risk factors between the two populations.

In conclusion, the rate of cardiac failure in association with imatinib therapy as reported in this study is 0.2%. In a population with pre-existing cardiac disease, it may increase to 2%. Regular cardiac assessment in patients with metastatic GIST treated with imatinib does not seem indicated, but cardiac monitoring can be considered in imatinib adjuvant studies.

Conflict of interest statement

J.V., J.Y.B., and A.v.O have received honoraria from Novartis for consultancy. P.C. has received honoraria from Novartis for lectures, written contributions, and participation in advisory boards, has received travel reimbursement for meetings, and research or educational grants for his institution. D.K. has received honoraria for lectures from Novartis and a study grant for the Australasian Gastrointestinal Trials Group. P.R. has received a study grant and honoraria for lectures from Novartis. M.V.G. has received a study grant for EORTC from Novartis. I.J. has received honoraria for consultancy and participation in symposia from Novartis. A.L.C. and R.I. declare that they have no conflict of interest.

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