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# Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumors: a report of the EORTC Soft Tissue and Bone Sarcoma Group

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**Abstract**

In a phase I study conducted by the EORTC Soft Tissue and Bone Sarcoma Group, 40 patients with advanced soft tissue sarcomas, most of whom had gastrointestinal stromal tumors (GISTs), received imatinib at doses of 400 mg q.d., 300 mg b.i.d., 400 mg b.i.d., or 500 mg b.i.d. Dose-limiting toxicities, including severe nausea, vomiting, edema and rash, were seen at the highest dose level; the maximum tolerated dose was therefore 400 mg b.i.d. Imatinib was active in the group of 35 patients with GISTs, producing partial responses in 19 (54%) patients and stable disease in 13 patients (37%). Responding patients have now been followed for a minimum of 10 months. The most common side effects seen in patients continuing on therapy have been periorbital edema (40%), peripheral edema (37.5%), fatigue (30%), skin rash (30%) and nausea/vomiting (25%). Severe late myelosuppression has also been seen occasionally. Eighteen (51%) GIST patients continue to have partial responses and 11 (31%) continue with stable disease. Thus, 82% of patients with GISTs are still obtaining clinically important benefits with continued imatinib therapy. Some patients showed accelerated progressive disease shortly after starting imatinib. On the other hand, following drug withdrawal, 2 patients had reductions in tumor burden and remain alive without drug therapy. In summary, imatinib is generally well tolerated and has significant activity during long-term treatment of patients with advanced GISTs. 

*Keywords:* Imatinib; Gastrointestinal stromal tumor; GIST; Soft-tissue sarcoma; Maximum tolerated dose

## 1. Introduction

Imatinib (STI571) is a potent and selective inhibitor of several tyrosine kinases, including Bcr-Abl, platelet-derived growth factor receptor (PDGFR) and c-kit [1–3]. Bcr-Abl, a fusion product of the Philadelphia chromosome, appears critical in the development of chronic myeloid leukemia (CML) [4]. In clinical trials, CML patients failing first-line therapy achieved durable hematologic and cytogenetic responses when treated with imatinib [5,6]. PDGFR and c-kit are receptor tyrosine kinases that mediate the biochemical effects of platelet-derived growth factor (PDGF) and stem-cell factor (SCF), respectively. A 50% inhibition ($IC_{50}$) of these kinases is observed with approximately 100 nmol/l imatinib, which is simi-

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lar to the concentration needed to block Bcr-Abl [2,7,8]. Overexpression of PDGFR has been reported in virtually all subtypes of soft tissue sarcomas and moreover, c-kit expression is a prerequisite for a diagnosis of gastrointestinal stromal tumors (GISTs) [9]. Mutations in the c-kit proto-oncogene leading to constitutive activation of the c-kit tyrosine kinase have been described in many malignant human GISTs [10–12]. The expression of this kinase is believed to promote tumor growth or inhibit tumor apoptosis. Taken together, these data provide a rationale for evaluating imatinib in patients with soft tissue sarcomas.

By the summer of 2000, clinical experience with imatinib in CML was largely at daily doses of 400 to 600 mg, but little information was available on the dose-response relationship in patients with solid tumors. Accordingly, a phase I study was designed to identify the dose-limiting toxicity of imatinib in patients with advanced soft tissue sarcomas, including GISTs [3].

## 2. Study design

Three centers (Leuven, Belgium; London, U.K.; and Rotterdam, The Netherlands) of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group participated in this phase I study. Eligible patients had histological evidence of soft tissue sarcoma, and for a diagnosis of GISTs, positive c-kit expression on the basis of CD117 immunohistochemical staining was required. Measurable disease and evidence of progression within 6 weeks of starting treatment were also required. Other eligibility criteria included age $>15$ years; World Health Organization performance status (WHO PS) $<3$; adequate hematologic, renal and hepatic function; and no concomitant anticoagulant therapy with warfarin-coumarin derivatives. Previous chemotherapy was allowed, provided it had been discontinued at least 4 weeks earlier. Previous radiotherapy was allowed unless it had been delivered to a sole index lesion. All patients provided written informed consent according to local, national and ICH/EU-CGP guidelines.

Imatinib was administered in 100-mg capsules. Patients were instructed to take imatinib orally, preferably after meals. Eight patients were scheduled to be treated at each dose level. A maximum of four dose levels were scheduled, starting at 400 mg q.d. The subsequent dose levels were 300 mg b.i.d., 400 mg b.i.d. and 500 mg b.i.d. Treatment was to be discontinued with disease progression, unacceptable toxicity, or if a patient withdrew consent for further treatment. Otherwise, treatment was planned to continue for a minimum of 1 year in patients with complete or partial objective responses or stable disease. Patients were evaluated weekly during the first 8 weeks, then biweekly for the next 4 weeks, and then monthly thereafter. Patients remaining on treatment are now seen bimonthly [3].

Toxicity was assessed using the common toxicity criteria (CTC) of the US National Cancer Institute (version 2.0) [13]. The maximum tolerated dose (MTD) was achieved when two of six to eight patients at a given dose level had dose-limiting toxicity (DLT) within the first 8 weeks of treatment. DLTs were defined by one of the following five criteria: absolute neutrophil counts (ANC) $\leq 0.5 \times 10^9$/l lasting for at least 7 days; ANC $< 1 \times 10^9$/l with temperature above 38.5°C; grade 4 thrombocytopenia; or any grade 3–4 nonhematologic toxicity, except nausea and/or vomiting that could be controlled; or alopecia. The imatinib dose that would be recommended for further study would be the dose level immediately below the MTD.

The decision to escalate the dose to the next dose level was based on whether DLTs were seen within the first 4 weeks in the first four patients at a dose level. If DLTs were not observed, then four patients were enrolled at the next dose level and the four subsequent patients were given the previous dose level. This schedule was used for the first three dose levels, but at 500 mg b.i.d., one DLT was seen in the first four patients, and then additional DLTs were observed in the next four patients. In order to ensure that a safe dose could be recommended for general use, eight additional patients were enrolled subsequently at the 400 mg b.i.d. level.

## 3. Patient demographics

Forty patients were enrolled between August 3 and December 21, 2000, including 25 (62.5%) men and 15 (37.5%) women. Median age was 53 years (range: 29 to 69 years) and median WHO PS was 1 (range: 0 to 2). These patients were heavily pretreated; 24 (60%) patients had previous chemotherapy and four (10%) had previous radiotherapy. The majority (75%) had liver metastases. Histologically, 35 (90%) patients had GISTs, and the other five patients had c-kit-negative sarcomas, including three (7.5%) patients with leiomyosarcomas, one (2.5%) patient with an angiosarcoma and one (2.5%) patient with an unclassified sarcoma.

## 4. Toxicity

During the first 8 weeks of treatment, 18 (45%) patients had CTC grade 3 hematologic toxicity, but only one (2.5%) patient had a hematologic DLT. This patient developed neutropenia persisting for more than 1 week while receiving imatinib 400 mg b.i.d. After neutrophil counts recovered, this patient was successfully rechallenged at 300 mg b.i.d. and remains on treatment. Toxicity findings are now available after a minimum follow-up of 10 months. Two (5%) cases of grade 4 neutropenia have been seen — 1 patient in each of the two highest dosage groups. The potential of developing neutropenia during long-term

treatment underscores the need to evaluate blood counts at regular intervals, particularly if a patient develops fever. Grade 3 leukopenia, neutropenia and anemia were seen in four, five and five patients, respectively. Thrombocytopenia was not problematic, as only one patient had a grade 1 drop in platelet counts.

Nonhematologic DLTs were observed during the first 8 weeks of treatment in two patients at the 300 mg b.i.d. level (grade 3 edema and rash, respectively). The patient with severe edema stopped taking imatinib, was treated with diuretics and then successfully resumed imatinib treatment at the next lower dose level (400 mg q.d.). The patient with severe rash also stopped imatinib therapy, but later resumed treatment initially at 400 mg q.d. and then at 300 mg b.i.d., a dose that she continues to receive. Nonhematologic DLTs were not seen in the 400 mg b.i.d. cohort. However, five of the eight patients at the highest dose level developed nonhematologic DLTs, including one patient with uncontrollable nausea, one with uncontrollable vomiting, one with both uncontrollable nausea and vomiting, one with grade 3 rash and one with grade 3 dyspnea due to pleural and abdominal fluids. This latter patient stopped treatment but later resumed imatinib 400 mg b.i.d. Other side effects were mostly mild and manageable. On the basis of these toxicity findings, the MTD of imatinib is 400 mg b.i.d. Three patients are still on 500 mg b.i.d. and are doing well. On average, patients assigned to this dose level received a mean dose intensity of 89% (range: 35% to 100%) during the first 8 weeks.

In patients who remain on imatinib therapy, the most common side effects include periorbital edema (40%), peripheral edema occurring in the extremities or as temporary ascites or pleural fluid (37.5%), and fatigue (30%) (Fig. 1). Skin rash was seen in 30% of patients, but it mostly resolved after 6 to 8 weeks of continued therapy. Grade 2–3 nausea and/or vomiting was reported in 25% of patients, but it was generally well controlled by metoclopramide. Grade 2 anorexia and diarrhea were reported in 15% and 12.5% of patients, respectively. Finally, as noted previously, severe late myelosuppression was also seen occasionally.

## 5. Treatment responses

Objective responses to imatinib were evaluated every 8 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST) [14]. Imatinib was active in patients with GISTs, but not in those with c-kit-negative soft tissue sarcomas. Of the 35 patients with GISTs, 19 (54%) patients achieved confirmed partial responses (≥30% reduction in measurable disease) and 13 (37%) additional patients had stable disease (Table 1). Two (5%) patients had progressive disease and the last patient could not be evaluated [3].

As of September 2001, 18 (51%) GIST patients continued to have partial responses and 11 (31%) continued with stable disease, implying that 82% of GIST patients are continuing to obtain clinically important benefits after a minimum of 9 months of imatinib therapy (Table 1). Four GIST patients have died, including one patient who had progressive disease initially and the patient who could not be evaluated for response. Of the other two deaths, one patient relapsed after achieving a partial response and

Table 1
Responses to imatinib in patients with GISTs ($n = 35$)

| | Best response $n$ (%) | Current response [a] $n$ (%) |
|---|---|---|
| Partial response | 19 (54) | 18 (51) |
| Stable disease | 13 (37) | 11 (31) |
| Progressive disease | 2 (5) | 3 (8) |
| Could not be evaluated | 1 (2.8) | – |
| Alive; no treatment | – | 3 (8) |

[a] As of September 2001.

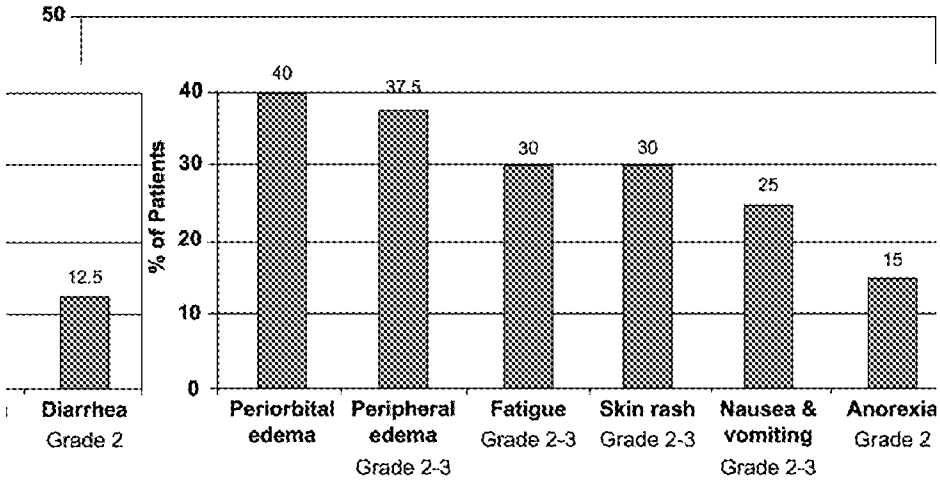


Fig. 1. Update of nonhematologic side effects after a minimum of 8 months of imatinib therapy.

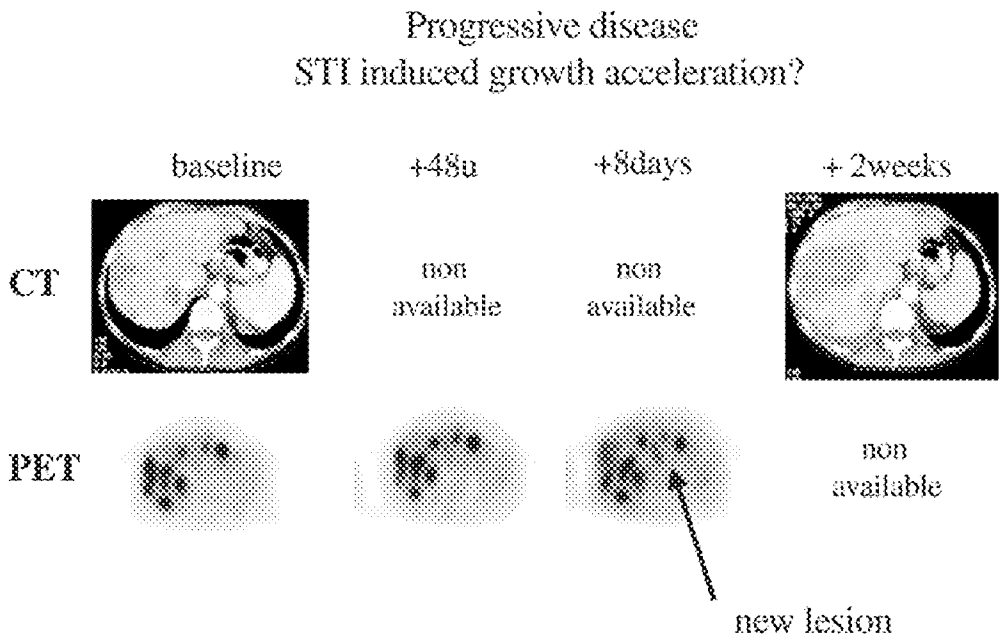


Fig. 2. Imatinib-induced growth acceleration? Disease burden after discontinuing therapy.

one patient progressed shortly after disease had stabilized. The remaining three patients are still alive but they are no longer receiving imatinib.

In selected GIST patients, $^{18}$fluorodeoxyglucose-positron emission tomography ($^{18}$FDG-PET) scans were performed on days 0, 8 and 28 of imatinib therapy. Overall, 14 patients showed uptake of $^{18}$FDG and were evaluable by PET. As recommended by the EORTC PET group, response was defined by ≥25% decreases in standardized uptake values of $^{18}$FDG, whereas progressive disease was defined by any of the following: >25% increase in standardized uptake values, ≥20% increase in volume, or the appearance of new lesions [15]. Eight patients had complete responses on day 8 that were confirmed on day 28, two patients had partial responses on day 8 and complete responses on day 28, one patient showed no change in $^{18}$FDG uptake on day 8 or 28, and three patients showed progressive disease either due to the presence of new lesions or enhanced $^{18}$FDG uptake. Responses by $^{18}$FDG-PET correlated with clinical improvement and objective responses seen by computed tomography (CT) after 8 weeks of therapy (Table 2).

Table 2
Correlation between PET-scan evaluation on days 8 and 28 and RECIST criteria after 8 weeks of therapy

| | CR day 8 CR day 28 | PR day 8 CR day 28 | NC day 8 NC day 28 | PD day 8 |
|---|---|---|---|---|
| Total patients | 8 | 2 | 1 | 3 |
| Partial response | 4 | 1 | | |
| Marginal response | 3 | 1 | | |
| No change | 1 | | 1 | |
| Progressive disease | | | | 3 |

CR = complete response; PR = partial response; NC = no change; PD = progressive disease.

Some patients appeared to show gross acceleration of disease shortly after onset of imatinib (Fig. 2). One patient who had been previously treated with classical cytotoxic chemotherapy had gross acceleration of disease that was evident on day 21 by CT and PET; she died on day 23. In a second patient, PET revealed a new lesion on day 8 that had not been present in previous scans at baseline or day 2, and it also showed greater $^{18}$FDG intensity in some other lesions. Pleural fluid and edema were also present, and imatinib was discontinued. Notably, a CT performed 2 months later showed that one tumor had disappeared, another had declined and a third was stable. Her condition remained stable in another CT taken at 5 months after stopping therapy. Similarly, a third patient with large abdominal disease discontinued imatinib after PET and CT showed progressive disease. After stopping treatment, pleural fluid resolved and $^{18}$FDG uptake declined and, 6 months later, the tumor burden was decreased. The contribution of imatinib to the reduction of disease in these latter two patients is unclear. It is plausible that imatinib killed a large number of tumor cells, which resulted in substantial edema but, once the edema was cleared, these patients appeared to have partial responses without continuing imatinib.

## 6. Conclusion

On the basis of this phase I study, imatinib 400 mg b.i.d. is the recommended dose for patients with GISTs. After

8 weeks of treatment, the safety and tolerability of this dose are acceptable, although it remains to be determined whether it is superior to lower doses, notably 400 mg q.d. This question is being addressed in two ongoing phase III trials, in which patients are being randomly assigned to imatinib 400 mg q.d. or 400 mg b.i.d [16]. Importantly, the results of this phase I study should be contrasted with those of other phase II studies in this disease. Normally, patients in these studies all die within 12 months, but with imatinib, 80% of patients remain on drug and continue to obtain clinically important benefits (either partial responses or stable disease) after a minimum of 8 months. Only three patients with GISTs had progressive disease on imatinib therapy.

This phase I study included five patients who did not have GISTs. One patient had stable disease and the other four had progressive disease. Accrual in a phase II EORTC study of imatinib in patients with non-GIST soft tissue sarcomas was completed in April 2001. Preliminary findings support the observations seen in the present study (Verweij, personal communication).

At the present time, two patients who progressed after receiving imatinib 400 mg q.d. for 16 and 20 weeks, respectively, are being treated with imatinib 400 mg b.i.d. Notably, one patient has achieved a partial response after previously having stable disease as the best response to once-daily treatment. This patient continues to have a partial response after 12 months of receiving the higher dose. The other patient who was progressive on the lower dose became stable once the imatinib dose was escalated. These observations provide further evidence supporting 400 mg b.i.d. as the recommended dose of imatinib.

In conclusion, imatinib represents a major advance in the treatment of GISTs. The successful treatment of these solid tumors with a selective tyrosine kinase inhibitor offers the promise that other anticancer agents directed against specific molecular abnormalities will be developed in the future. In selecting future cancer targets, it will be important to study malignancies in which only one or two genes are involved initially in the disease process. As lessons are learned, it may ultimately be possible to apply these agents to more complicated malignancies, such as lung, breast and colon cancer, where many different genes appear to have etiologic significance and, accordingly, multiple molecularly targeted drugs will likely be necessary.

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