Imatinib for the treatment of patients with unresectable or metastatic malignant KIT-positive gastrointestinal stromal tumours : an open-label Belgian trial

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Abstract

Background : **Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract. They are defined immunohistologically as KIT positive tumours. The only effective treatment for malignant GIST was surgery until 2000. Imatinib mesylate (STI571, Glivec®) has shown substantial anticancer activity in patients with metastatic or unresectable GIST.**

Patients and methods : **57 patients who were diagnosed with unresectable or metastatic malignant GIST were entered into this study. The patients were given 400 mg Glivec orally once daily. The dose could be increased to 600 mg orally once daily and then to 400 mg twice daily if tumour progression was noticed. Daily treatment was interrupted or dose was decreased only in the case of limiting toxicities. We evaluated the tumour response and the safety of the drug.**

Results : **85% of GIST patients showed a partial response or stable disease after 8 weeks of treatment with imatinib. The main side effects were nausea, vomiting, anorexia, skin rash, periorbital oedema and diarrhea.**

Conclusion : **This study confirms that imatinib is an active agent against malignant GIST with manageable toxicities.** (Acta gastro-enterol. belg., **2006**, 69, **367-371**).

Introduction

Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumours of the gastrointestinal tract (1). They are believed to originate from (precursors of) interstitial cells of Cajal, the gastrointestinal pacemaker cells, and are characterised by the expression of the tyrosine kinase KIT (CD117) (2). KIT-activating mutations are detected in more than 80% of sporadic GIST (3). These mutations result in gain-of-function with activation of the receptor without binding of the physiological ligand (stem cell factor). It is believed that the constitutively activated KIT receptor is the underlying pathogenic event in GIST tumorigenesis (4).

GIST are known to be very resistant to conventional chemotherapy and show no response to radiation therapy (5). The development of imatinib mesylate (Glivec®, Novartis, Basel Switzerland) has revolutionized the treatment of GIST. Imatinib selectively inhibits specific tyrosine kinases, including KIT, ABL, BCR-ABL and platelet-derived growth factor receptor (PDGFR) (6). Imatinib was first used in patients with Philadelphia - chromosome positive chronic myeloid leukaemia (7). In GIST, imatinib controlled tumour growth in up to 85% of advanced GIST in phase I, II and III trials (8-11). The toxicities of imatinib including oedema, rash, nausea, diarrhea, abdominal pain and fatigue are usually manageable.

We conducted an open-label multi-centre Belgian trial to evaluate the tumour response in GIST patients treated with imatinib and to assess its safety.

Patients and methods

Patient selection

Patients $\geq$ 18 years of age, with histologically documented diagnosis of malignant, unresectable and/or metastatic GIST were selected. Immunohistochemical documentation of c-kit (CD117) expression was assessed (preferably on a tumour sample taken within 6 weeks of study entry). At least one measurable site of disease, as defined by RECIST Criteria (12), had to be present or by other response assessment criteria, as appropriate.

The performance status was quoted as 0, 1, 2 or 3 on the ECOG performance scale. The end organ function had to be adequate, defined as the following : total bilirubin $< 1.5 \times$ upper limit of normal (ULN), SGOT (AST) and SGPT (ALT) $< 2.5 \times$ UNL (or $< 5 \times$ ULN if hepatic metastases were present), serum creatinin $< 1.5 \times$ ULN, absolute neutrophil count (ANC) $> 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L. Female patients of childbearing potential had to have a negative pregnancy test within 7 days before initiation of study drug dosing. Post-menopausal women had to be amenorrheic for at least 12 months to be considered of non-childbearing

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Table 1. — **ECOG performance status**

Grade	ECOG
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light housework, office work.
2	Ambulatory and capable of complete self-care but unable to carry out more sustained work activities and are in bed less than 50% of time during the day.
3	Restrained to only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled, cannot carry on any self-care, and are totally confined to bed or chair.

potential. Male and female patients of reproductive potential agreed to employ an effective contraceptive method throughout the study and for up to 3 months following discontinuation of imatinib. Written informed consent was obtained for all patients. Patients with impaired cardiac function (NYHA III / IV), severe and/or uncontrolled medical disease, known brain metastases, known chronic liver disease, known HIV infection, recent chemotherapy or surgery (< 4 weeks), radiotherapy to ≥ 25% of the bone marrow or non-compliant patients were excluded.

As evaluation of the clinical status, the Eastern Cooperative Oncology Group (ECOG) performance status scale was chosen for this study (Table 1).

Study design

The presented study was an open-label multi-centre Belgian trial designed to evaluate the activity of imatinib for inducing objective responses in GIST and to assess its safety.

The patients received Glivec® 400 mg orally once daily for up to 12 months. The dose could be increased to 600 mg orally once daily and then to 400 mg twice daily if patients were progressing. Daily treatment was interrupted only in the case of limiting toxicities (grade 3 or 4).

Side effects and serious adverse events, laboratory parameters including hematology, chemistry, vital signs, physical examinations, and all concomitant therapies were recorded.

Patient evaluation

Tumour responses were defined by the RECIST response criteria. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions and recorded and measured at baseline. Target lesions were selected based on the longest diameter (LD) and suitability for accurate repetitive measurements, as judged clinically or by imaging techniques. A sum of the LD for all target lesions was calculated and reported as the baseline sum LD. The baseline sum LD was used as reference to assess the objective tumour response.

Complete Response (CR) was defined as a disappearance of all target lesions. Partial Response (PR) was defined as at least a 30% decrease in the sum of LD of target lesions taking as a reference the baseline sum LD. Progression (PD) was defined as at least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of at least one new lesion. Finally stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Statistical analysis

Descriptive summary statistics were calculated such as mean, median, standard deviation (SD), standard error (SE), minimum-maximum and Shapiro-Wilk test for continuous variables, and frequencies and percentages of patients or reports for categorical variables.

Results

Patient characteristics

Fifty seven patients with malignant GISTs were enrolled into the study between April 2002 and January 2003. In all patients, GIST was diagnosed immunohistochemically by being KIT positive. Furthermore, in 43 patients out of 57 (75.4%) KIT staining was confirmed by the department of pathology in the University Hospital Gasthuisberg. The demographic data are presented in Table 2. Median age was 65 years, range 29-91 years. There were 34 men and 23 women included in the study. The majority of primary GIST sites were the stomach and small intestine including the duodenum. The major site of tumour metastasis was the liver. Median duration of treatment in this study was 208 days (range, 12-391 days). All patients were assessed for response to imatinib treatment in terms of efficacy and toxicity.

All patients were ambulatory. 81% was able to carry out some work and more than half of these were fully active. At inclusion the majority of the patients (81%) were ambulatory and able to carry out at least work of light or sedentary nature (ECOG performance status 0-

Table 2. — **Patient characteristics (n = 57)**

Characteristics	n (%)
Age, years	
Mean	61
Median	65
Range	29-91
Gender	
Male	34 (60)
Female	23 (40)
ECOG performance status	
Grade 0	25(44)
Grade 1	21(37)
Grade 2	8(14)
Primary site	
Stomach	17 (30)
Duodenum	4 (7)
Small intestine	14 (24)
Rectum	4 (7)
Esophagus	2 (4)
Prostate	1 (2)
Unknown	15 (26)
Site of tumor metastasis	
Liver	34 (60)
Peritoneum	19 (33)
Lymph nodes	14 (25)
Small intestine	7 (12)
Retroperitoneal	7 (12)
Lung	5 (9)
Spleen	3 (5)
Pancreas	3 (5)
Bone	1 (2)
Adrenal gland	1(2)

Table 3. — **Response to treatment with imatinib in GIST patients (n = 55). All responses were subject to peer review and responses were classified according to the RECIST criteria**

Response after 8 weeks of treatment	n (%)
Complete response	0
Partial response	21 (38)
Stable disease	26 (47)
Progressive disease	8 (15)
Overall objective response	47 (85)

1). Over time, the proportion of fully active patients (grade 0) among those who remained in remission tended to increase from 44% at the start to 56% at week 24, whilst the number of patients in grades 1 or 2 tended to decrease until week 24, either reflecting an improvement of their performance towards normality, or a natural elimination of the worst cases, the total number of patients still in trial being 39 at that time, out of 54 at the start of performance evaluation. At week 56, 80% of the remaining patients in remission (n = 9) were still in stage 0 or 1, half of them fully performant.

Response to treatment

Data on the anti-tumour response to imatinib are shown in Table 3. 85% of GIST patients achieved an objective response after 8 weeks of treatment with imatinib, with 38% of patients showing PR (n = 21) and 47% of patients showing SD (n = 26). 77% of patients still showed PR (33%, n = 3) or SD (44%, n = 4) after 56 weeks of treatment (not shown). It is noteworthy that the decreasing number of patients over time is not primarily due to death or loss of therapeutic control, but due to the end of the study (study was closed in July 2003). PD was observed in 15% (n = 8) of the patients after 8 weeks of treatment, 7% (n = 3) at week 24, and 22% (n = 2) at week 56.

Table 4. — **Adverse events**

Toxicity	% of patients
Skin rash	58
Diarrhea	54
Asthenia	49
Nausea	40
Periorbital oedema	39
Infections	37
Oedema	33
Anorexia	26
Gastrointestinal pain	23
Vomiting	19
Eye disorders	14
Muscle cramps	14
Fever	11
Dyspnea	11
Anemia	11

Adverse events

The mean weight remained stable during the trial, no statistically significant changes being detected. The most common toxic effects seen during the treatment were nausea, vomiting and anorexia, affecting 85% of the treated population (Table 4). Nausea was considered mild (grade 1) in 87% of the reports and in 72% of patients the nausea was transient. In 93% of patients, the vomiting was mild (grade 1) and transient. None of these side-effects were severe (more than grade 2). These adverse events were also reported in some instances at inclusion. Skin disorders were reported in 70% of the patients, mostly as rash (28%), itching (15.8%) and dry skin (14%). The rash was considered as mild (grade 1) to moderate (grade 2) in 16 reports (88.9%) and linked to therapy in most of the cases (94%). It was present during the whole observation period in 55.6% of the cases. For itching and dry skin, all complaints were classified as mild (grade 1) to moderate (grade 2), and 60% were noted as transient. A possible link to therapy was suggested in 80% of the reports. Pain was the third most common adverse event, but did not appear to be limited to one specific region, although 7 patients (12%) complained of abdominal pain and cramps. In 15 cases (26%) the gastro-intestinal pain was reported as mild (grade 1), 5 (9%) moderate (grade 2) and 3 (5%) severe (grade 3). In 61% of these reports, the pain was transient, and linked to therapy in 2 cases (9%). Again, in some occasions, these were already reported at entry.

About 50% of the patients complained of diarrhea (54.4%), mostly mild (grade 1) (83%), and in 66% of patients, the diarrhea was transient. Asthenia was also recorded in nearly half of the patients, mild (grade 1) in

70% and transient in 55% of the records. Periorbital edema was also reported (38,8%), mainly "puffy eyes" (31.6% of the population studied), mostly mild, but remaining throughout the study in half of the cases.

Four patients died during the study. One patient, 85 years old, anorectic, with a GIST originating from the stomach and with pleural and retroperitoneal metastasis, previously treated by partial gastrectomy, died due to respiratory failure after 24 days of treatment. A link with imatinib was not suspected by the investigator. A 77 years old diabetic patient, with primary lesion in the small intestine and with lymph node, liver and colon invasion at entry, died after 12 days, presumably due to an intestinal infarction. An 82 years old patient with a gastric GIST and liver, peritoneal and splenic metastasis died due to the underlying disease after 7 months of treatment. Finally, an anorectic patient, aged 47 years, with a primary oesophageal GIST and lymph node invasion at entry, died due to disease progression after 5 months of treatment.

Discussion

Gastrointestinal stromal tumours (GIST) are mesenchymal tumours of the gastrointestinal tract known to be very resistant to cytotoxic chemotherapy. Before the introduction of imatinib, surgery was the only effective treatment available (5), however despite the attempt of resection of local recurrences, the prognosis of patients with malignant GIST remained poor. The development of imatinib mesylate (Glivec®) has dramatically changed the treatment of GIST. This small molecule is highly effective in blocking the tyrosine kinase activity of the stem cell factor receptor c-KIT. In GIST, a gain of function mutation often occurs in *KIT*, resulting in ligand-independent activation of its tyrosine kinase function (4). Multi-center clinical trials have proved that imatinib is highly effective for the treatment of inoperable and/or metastatic GIST and remains so far the only effective systemic treatment (9,11).

We conducted an open-label multi-centre Belgian trial to further assess the anti-tumour response in GIST patients treated with imatinib. Our study confirms that imatinib mesylate is an active anticancer agent for malignant GIST, and that toxicities are manageable. Forty seven of fifty five patients with malignant GISTs had an objective response (85%) ; twenty one of these forty seven patients exhibited a confirmed partial response (38%) and the other twenty six showed stable disease (47%). The rate of clinical benefit was 85%, and these responses occurred within 2 months. This high response rate is similar to that previously reported (Table 5) (8-10). There was no relationship between response and patient characteristics.

The side effects due to imatinib were mild and the dose had to be reduced due to intolerable side effects only in a small subset of patients (n = 5). The most common side effects were nausea, vomiting, anorexia and skin rash. Most symptoms, however, were transient. No major toxicity was observed.

The development of imatinib mesylate heralds the era of targeted cancer therapy. Since the use of imatinib for the treatment of GISTs, patient outcomes have improved dramatically. The spectacular success of imatinib in GIST patients demonstrates how molecular targeting can fulfil the promise of low toxicity and high response rates. The reason that GIST is effectively treated with imatinib is the fact that these tumour cells contain a dominant genetic change involving the targeted kinase KIT that is integral to the biology of GIST. Finding new targets in other sarcomas and understanding how to use the targeting drugs in sarcoma are urgent challenges, in particular because this group of tumours responds poorly to conventional cytotoxic chemotherapy.

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Table 5. — **GIST response to imatinib, previously reported (RECIST criteria)**

	van Oosterom *et al.* (2001)	Demetri *et al.* (2002)	Verweij *et al.* (2004)
Median follow-up (months)	9	9	25
Complete response :	0		4%
Partial response	54%	54%	67%
Stable disease	37%	28%	19%
Progressive disease	9%	14%	11%
Overall objective response	91%	82%	90%
Could not be evaluated	0%	4%	0%

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