

Treatment of Advanced Gastrointestinal Stromal Tumours with Imatinib: A Single Institution Experience*

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ABSTRACT

Background. Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the digestive tract. They express KIT, a growth factor receptor tyrosine kinase encoded by the protooncogene *c-kit*. Advanced unresectable GIST is a fatal disease that resists conventional chemotherapy. Imatinib is the first synthetic inhibitor of a signal transduction pathway that has been proven effective for GISTs. This study aims to report the experience of the Department of Medical Oncology at the National Cancer Centre, Singapore (NCCS) on the treatment of advanced GIST with the novel tyrosine kinase inhibitor Imatinib.

Methods. All patients with advanced GIST treated with Imatinib were identified from the NCC database. Demographic data, disease status, sites of involvement, treatment dose, treatment duration, response rates and toxicities were collected and analysed by descriptive statistics.

Results. A total of 15 patients with GIST were treated with Imatinib between September 2001 to July 2003 with a median duration of treatment of 11 months and a median follow-up of 14 months. Common sites of involvement included the liver (67%), stomach (40%), and omentum (40%). Imatinib was given at a dose range of 200 to 800 mg daily (mean daily dose of 433 mg). Among 14 evaluable patients, 10 (71%) had partial response while 4 (29%) had progression. Grade 3 and 4 haematologic toxicities were rare consisting of anaemia and thrombocytopenia. Adverse events were commonly grades 1 or 2 oedema, myalgia and fatigue.

Conclusion. The encouraging response rate of 71% and tolerable toxicity profile of Imatinib make it a promising treatment for advanced GISTs.

Keywords: Gleevec, Glivec, sarcoma, STI571

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the digestive tract.¹ These tumours are thought to originate from the same precursor cells as the interstitial cells of Cajal, which are considered to be the pacemaker cells for the autonomous movement of the gastrointestinal tract.^{2,3} They occur predominantly in middle-aged and older people. Approximately 70% of GISTs develop in the stomach, 20% in the small intestine, and less than 10% in the oesophagus, colon, and rectum.⁴ In a series

reported by Plaat *et al*, GISTs metastasise in 59%, with an overall survival of 31 months.⁵ In a study by DeMatteo *et al*, involving 200 patients with GIST, the median survival of patients with complete resection of the primary disease was 66 months compared with 22 months for those with incomplete resection or whose tumour was unresectable. Recurrence of GIST after complete surgical resection is usual. With a median follow-up of 24 months, 40% of patients who had complete resection of the primary tumour had recurred. Recurrences was predominantly intrabdominal.⁶

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GISTs are generally resistant to conventional intravenous (IV) chemotherapeutic agents as well as radiotherapy.⁵ Prior to the year 2000, there was no effective chemotherapy regimen for advanced or metastatic disease.

Most malignant cells in GISTs express KIT, a growth factor receptor tyrosine kinase encoded by the protooncogene *c-kit*. Gain of function mutations in *c-kit*, particularly in exon 11, are observed in both sporadic and hereditary cases, and the *c-kit* protooncogene has been postulated to play an important role in tumorigenesis.^{7,8} Various series suggested the presence of *c-kit* mutations in 50 to 92% of GISTs.⁹⁻¹¹

Imatinib (formerly STI-571, tradename Glivec) is the first synthetic inhibitor of a signal transduction pathway that has been proven effective for GISTs.¹²⁻¹⁴

To date, there have been no local reports on the response rate of Imatinib on advanced GISTs in the Singapore population. The aim of this study was to report the experience of the Department of Medical Oncology of National Cancer Centre, Singapore (NCCS) in the treatment of advanced GISTs with the novel tyrosine kinase inhibitor Imatinib.

METHODS

All patients with advanced GISTs treated with Imatinib from September 2001 to July 2003 were identified from the NCC database. Demographic data, disease status, sites of involvement, treatment dose, treatment duration, response rates and toxicities were collected and analysed by descriptive statistics.

Response was defined by the standard World Health Organization Criteria. Complete response was defined as disappearance of all lesions. Partial response (PR) required at least 50% reduction in the sum of the product of all bidimensionally measurable tumour size. Progressive disease (PD) was defined as the sum of the product of all bidimensionally measurable lesions by >25% or the development of new lesions. Stable disease was defined as when neither PD nor PR criteria were met. Toxicities were defined using the National Cancer Institute Common Toxicity Criteria, version 2.0.¹⁵

RESULTS

A total of 15 patients with advanced GISTs were treated with Imatinib between September 2001 to July 2003 in our institution. The patient characteristics are outlined in Table 1. All patients had overexpression

Table 1. Patient demographics (n=15).

Sex	
Male	5
Female	10
Patient age (years)	
Median:	50
Range:	37–85
Disease status	
Newly diagnosed	7
Recurrent disease	8
Prior treatments	
Surgery	10
Chemotherapy	2
Follow-up duration (months)	
Median:	14
Range:	1–22
Time on treatment (Months)	
Median:	11
Range:	0.2–22
Imatinib dose received (mg/day)	
Mean:	433
Range:	200–800

of *c-kit* confirmed by immunohistochemistry. Imatinib dose ranged from 200 to 800mg/day, with a mean dose of 433mg/day taken in two orally-administered doses.

All patients had radiologically measurable disease. The liver was the most common site of involvement (67%), followed by the stomach (40%), and omentum (40%) (Fig. 1).

One patient was not evaluable due to the short period of Imatinib intake — he discontinued Imatinib after 11 days because of angioedema and rashes. Among the remaining 14 evaluable patients, 10 (71%) had partial response while 4 (29%) had progressive disease while taking Imatinib. One of the 10 patients who had partial response developed progressive disease after 22 months of treatment (Fig. 2).

Figure 3 shows the dramatic response of a 45-year-old Chinese man with advanced GIST involving the omentum before and after 19 months on Imatinib.

Toxicity

There were relatively less severe toxicities as compared to mild toxicities (Tables 2 and 3). Common haematological toxicities included 13% Grade 3 or 4 anaemia and 7% Grade 3 or 4 thrombocytopenia. There was no Grade 3 or 4 neutropenia. The most common mild haematological toxicities (Grade 1 or 2) included anaemia (87%) and neutropenia (53%). The more common non-haematologic toxicities included oedema, pain, and fatigue which were mostly not severe

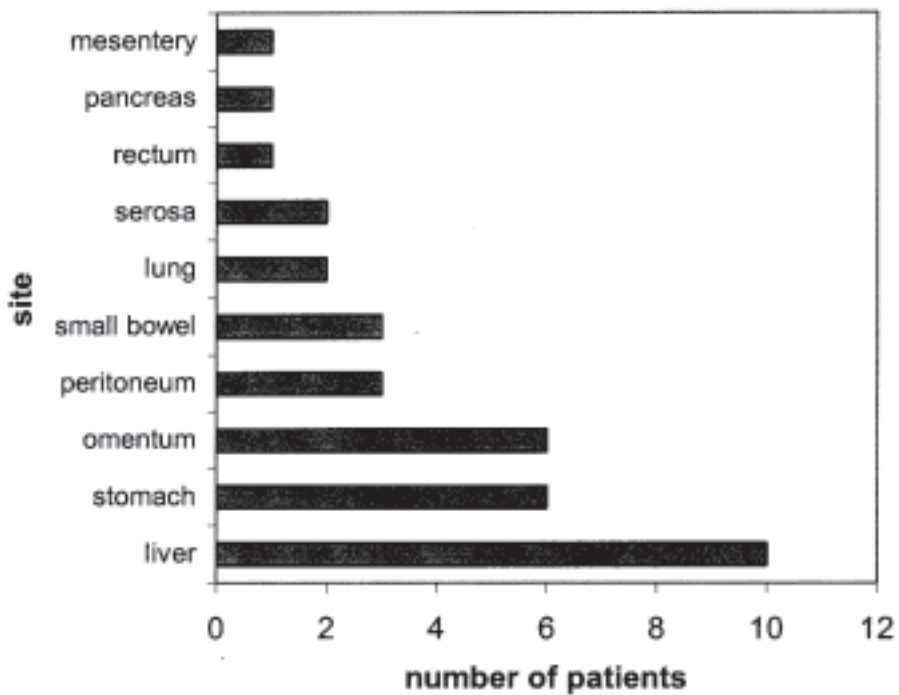


Fig. 1. Site involvement among patients with advanced GIST (n=15).

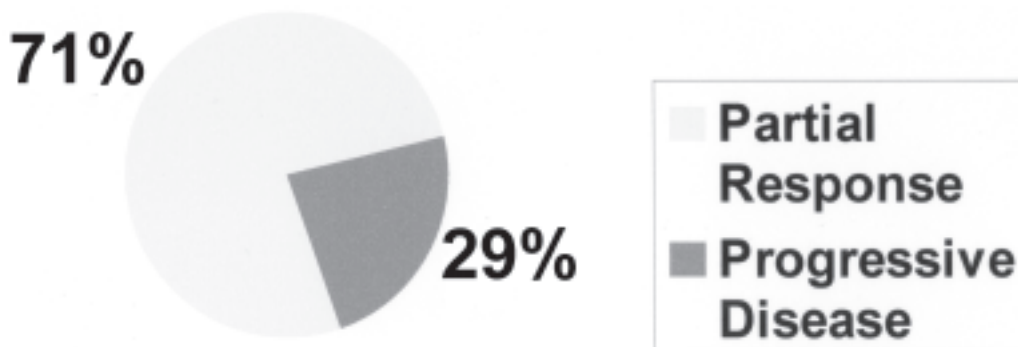
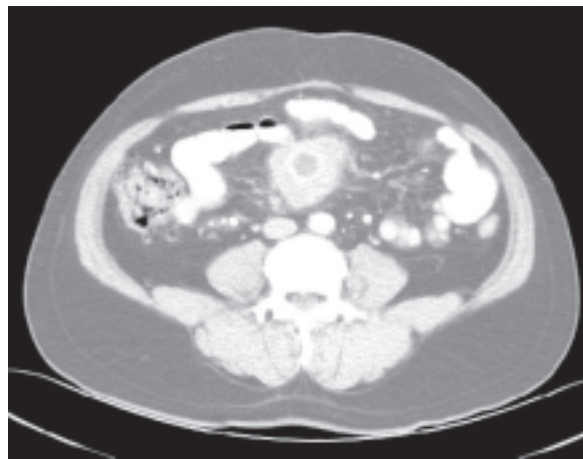
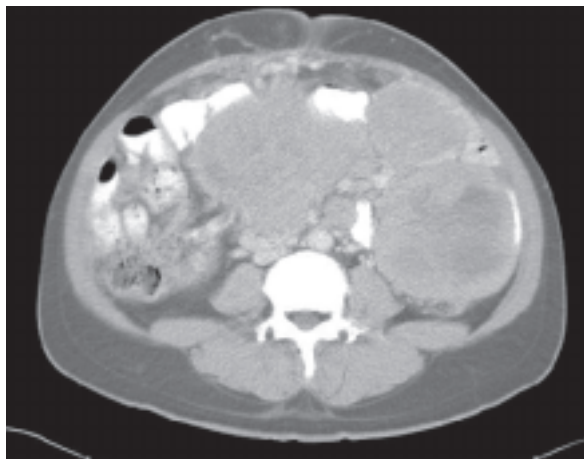


Fig. 2. Response rate of Imatinib among evaluable patients with advanced GIST (n=14).



Figs 3a and 3b. A 45-year-old Chinese male with lower abdominal GIST located at the omentum showing dramatic response before and after 19 months of Imatinib.

Table 2. Non-haematologic toxicities (n=15).

Adverse Events	Grade 1 or 2 (%)	Grade 3 or 4 (%)
Oedema	47	7
Pain	47	7
Fatigue	40	0
Rash	33	7
Myalgia	33	0
Nausea	27	0
Diarrhoea	27	0
Vomiting	20	13
Abdominal distention	20	0
Arthralgia	20	0
Pruritus	20	0
Bleeding	13	7
Constipation	13	0
Weight gain	13	0

(Grade 1 or 2). Grade 3 or 4 vomiting occurred in 13% of patients while 7% of patients developed oedema, pain, bleeding and rashes, respectively. There were no treatment-related deaths in our cohort of patients.

There was a total of 3 deaths which resulted from disease progression. The median duration of survival had not been reached at the time of writing.

DISCUSSION

Research in molecular biology has revealed that protein tyrosine kinases play a fundamental role in the transduction of biochemical signals involved in the regulation of cell proliferation, growth and function.¹³ Deregulated activity of these enzymes has been observed in various malignancies.¹³ Therefore, tyrosine kinase inhibitors are important in the development of new treatments for selected malignancies.

Imatinib is a small molecule that is a highly selective inhibitor of the protein tyrosine kinase family comprising Abl (the chimeric Bcr-Abl fusion protein found in chronic myeloid leukaemia), the platelet derived growth factor (PDGF) receptor alpha and beta, and the product of the c-kit proto-oncogene (KIT).

GISTs are characterised by uncontrolled constitutive activation of KIT.^{9,16,17} Imatinib was approved by the Food and Drug Administration in May 2001 for the treatment of chronic myeloid leukaemia refractory to interferon therapy and in February 2002 for the treatment of GISTs.

Although some studies of GISTs had shown a male predominance while others showed equal gender distribution, our study showed a female predilection

Table 3. Haematologic toxicities and biochemical abnormalities (n=15).

Laboratory Abnormalities	Grade 1 or 2 (%)	Grade 3 or 4 (%)
Anaemia	87	13
Thrombocytopenia	13	7
Neutropenia	53	0
Elevated alkaline phosphatase	27	0
Elevated AST	33	0
Elevated ALT	27	0
Elevated bilirubin	20	7
Elevated creatinine	13	0

(67%).¹⁸⁻²¹ It should be noted that this did not reflect the actual gender distribution of GIST patients treated in NCC because the study was limited to only patients with advanced GISTs and who were treated with Imatinib.

Ten of the 15 patients in our study had undergone surgery, while 2 had IV chemotherapy prior to treatment with Imatinib. Neither of the 2 patients who received IV chemotherapy exhibited an objective response — one patient received single agent cyclophosphamide while the other received oxaliplatin and 5 fluorouracil. All 15 patients had unresectable advanced GISTs at the start of Imatinib treatment.

GISTs usually show a high-level primary resistance to conventional chemotherapy, many with as low as 5% response rate with Dacarbazine-Mitomycin-Doxorubicin-Cisplatin combination regimen.²² Because of the recurrent nature of GISTs, advanced disease is usually unresectable and invariably fatal.

Of the 14 evaluable patients, 10 (71%) had partial response while 4 (29%) had progressive disease. Initially symptomatic patients who had responded had marked clinical improvement. This demonstrated the clinical benefit and significant antitumour response of patients with c-kit positive advanced GISTs.

Our study concurs with previous studies on Imatinib for advanced GISTs. In a phase I study by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group of 35 evaluable patients with GIST, 54% had partial response while 37% had stable disease.²³ In a phase II study of 147 patients receiving either 400 or 600 mg of Imatinib daily, 54% had partial response while 28% had stable disease.²⁴

A recent Korean study evaluated the efficacy and safety of Imatinib among 33 Korean patients with metastatic or unresectable GISTs.²⁵ Of the 31 evaluable patients,

48.4% had partial response while 32.3% had stable disease.²⁵

Our study showed a relatively higher response rate as compared to other studies. A stable disease response was not observed probably because of the small sample size of this retrospective study as well as patient selection.

Heinrich *et al* have investigated the relationship between mutations of isoforms of KIT or PDGFRA tyrosine kinases and response to Imatinib among 127 advanced GIST patients.²⁶ Their results showed that patients whose tumour expressed an exon 11 mutant KIT isoform had a longer time to treatment failure than those patients whose tumour expressed either an exon 9 KIT mutation or had no detectable kinase mutation. In multivariate analysis, the presence of an exon 11 KIT mutation was the strongest predictor of clinical response, decreased risk of treatment failure and improved overall survival.²⁶

It is possible that the patient population of our study may have had a favourable genomic tumour mutation, thus resulting in a higher response rate. It would be interesting to investigate if mutations of KIT or PDGFRA were present among the patient population of our study. However, this is not possible at this point in time.

The patients in our study received different doses of Imatinib because the ideal dose had not yet been determined during the start of their treatment. Recently, 2 phase III trials compared 2 different daily oral doses of Imatinib: 400mg and 800mg/day.^{27,28} Interim analyses showed no significant differences between these 2 levels of doses of Imatinib in terms of efficacy. However, the EORTC trial demonstrated improved progression free survival in the 800mg group.²⁷

Three out of 4 of our patients who had progressive disease progressed while they were on the 800mg dosage. The fourth patient progressed rapidly 6 days after starting on 400mg of Imatinib and died before the dose of imatinib could be escalated.

Toxicities in our study were mostly mild to moderate (Grade 1 to 2) and tolerable. Grades 3 and 4 toxicities consisted of anaemia in 2 patients (13%), vomiting in 2 (13%), oedema in 1 (7%), pain in 1 (7%), rash in 1 (7%), bleeding in 1 (7%), thrombocytopenia in 1 (7%), and elevated bilirubin in 1 (7%). These toxicities resolved within a few days to weeks after cessation of treatment, and patients could continue at a lower dose. These toxicities are similar to those reported in other studies with Imatinib.²³⁻²⁵

The short median follow-up duration of 14 months in our study made it inadequate and premature to assess the significance of the time to treatment progression of the few patients whose disease had progressed.

The duration of Imatinib as well as the role of Imatinib in the adjuvant setting are yet to be established and there are many on-going trials addressing these issues.²⁹

CONCLUSION

The encouraging response rate of 71%, convenience of oral dosing and tolerable toxicity profile of Imatinib in our experience make it a relatively safe and effective choice for treatment for patients with advanced GISTs.

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