ADIS DRUG PROFILE

Drugs 2003; 63 (5): 513-522
0012-6667/03/0005-0513/$33.00/0

Imatinib Mesylate

In the Treatment of Gastrointestinal Stromal Tumours

Katherine F. Croom and *Caroline M. Perry*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Imatinib mesylate (imatinib) is an orally administered competitive inhibitor of the tyrosine kinases associated with the KIT protein (stem cell factor receptor), ABL protein and platelet-derived growth factor receptors. The KIT tyrosine kinase is abnormally expressed in gastrointestinal stromal tumour (GIST), a rare neoplasm for which there has been no effective systemic therapy.

▲ In a randomised, nonblind, multicentre study that evaluated imatinib 400 or 600mg once daily in 147 patients with advanced GIST, confirmed partial responses were achieved in 54% of patients overall (median duration of follow-up was 288 days). Stable disease was experienced by 28% of patients and the estimated 1-year survival rate was 88%.

▲ Similar response rates were reported in a smaller, dose-escalation study, in which objective tumour response was a secondary endpoint.

▲ Although nearly all patients with GIST treated with imatinib experienced adverse events, most events were mild or moderate in nature. Severe or serious adverse events occurred in 21% of patients in the larger study, and included gastrointestinal or tumour haemorrhage.

Features and properties of imatinib mesylate (imatinib, STI571, CGP 57148B, Glivec®/Gleevec®[1])	
New indication	
Treatment of unresectable and/or metastatic CD117-positive gastrointestinal stromal tumour (GIST)	
Mechanism of action	
Inhibition of KIT tyrosine kinase	Blocks adenosine triphosphate binding, preventing substrate phosphorylation and subsequent signal transduction
Dosage and administration	
Recommended dose	400 or 600mg (US) 400mg (Europe)
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic properties (400mg once daily in patients with GIST)	
Peak plasma concentration	2.9 mg/L
Time to peak plasma concentration	2–4 h
Area under the curve at steady state	61 ± 25 mg • h/L
Metabolised by cytochrome P450 enzymes	
Elimination half-life	18–20 h
Adverse events	
Most frequent	Oedema (74%); gastrointestinal events, e.g. nausea, diarrhoea
Severe/serious adverse events	Neutropenia/leucopenia; tumour or gastrointestinal haemorrhage

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

The control of cellular processes, such as cell growth, division and death, involves signal transduction,[1] which commonly involves the transfer of phosphate from adenosine triphosphate (ATP) to tyrosine residues on substrate proteins, by tyrosine kinase enzymes.[1-3]

Activation of oncogenes coding for kinase proteins can lead to the production of kinases that are continually active in the absence of a normal stimulus,[3] leading to increased cell proliferation and/or decreased apoptosis. A major focus of cancer research in recent years has been to identify oncogenic molecules and the signal transduction pathways in which they are involved, in order to develop specifically targeted drugs.[1,3]

One such drug is imatinib mesylate (imatinib, Glivic®/Gleevec®), an orally administered 2-phenylaminopyrimidine derivative that is a competitive inhibitor of the tyrosine kinases associated with platelet-derived growth factor (PDGF) receptors, the Abelson (ABL) protein and the KIT protein (also known as stem cell factor [SCF] receptor).[4-6] Imatinib was initially evaluated for the treatment of chronic myeloid leukaemia (CML) [reviewed previously in *Drugs*[4]].

More recently, imatinib has been approved for the treatment of patients with advanced gastrointestinal stromal tumour (GIST), in which KIT, a tyrosine kinase receptor, is abnormally expressed. GISTs are soft tissue gastrointestinal sarcomas probably arising from mesenchymal cells.[7,8] They are rare neoplasms, with between 5000 and 10 000 new cases being diagnosed each year in the US.[9] GISTs occur throughout the gastrointestinal tract but the stomach and small intestine are the most common sites.[8] Symptoms depend on the site and size of the tumour, and may include abdominal pain, gastrointestinal bleeding or signs of obstruction; small tumours may be asymptomatic.[8] The diagnosis of GIST is made by immunohistochemical staining for CD117, a cell surface antigen on the extracellular domain of KIT, in conjunction with pathological examination of tissue with light microscopy.[8,10]

All GISTs may have some degree of malignant potential.[10] They are unresponsive to standard chemotherapy and to radiotherapy, and the mainstay of treatment in the past has been surgery. However, recurrence rates are high, and there has been no effective systemic treatment for unresectable GIST or metastatic disease.[9] For patients in whom complete resection is not possible, or in patients with metastatic or recurrent disease, the median duration of survival is 9–12 months,[11,12] and 10–19 months, respectively.[11,12]

Gain-of-function mutations of the *KIT* proto-oncogene occur in up to 90% of GISTs,[13,14] allowing constitutive activation of tyrosine kinase (i.e. auto-phosphorylation of tyrosine residues independent of ligand-receptor binding), leading to aberrant cell division and tumour growth.[7]

Imatinib selectively inhibits the tyrosine kinase activity associated with KIT, which forms the basis of the rationale for evaluating its effects in GIST. Subsequent to initial evidence of the clinical efficacy of imatinib in a single patient with progressive, metastatic, CD117-positive GIST,[15] formal studies of imatinib in this new indication were initiated. This article summarises the pharmacology, efficacy and tolerability profile of imatinib in the treatment of patients with advanced GIST.

1. Pharmacodynamic Profile

This section provides an overview of the pharmacodynamic data discussed in the previous article on imatinib in CML,[4] together with a summary of pharmacodynamic effects relevant to its use in GIST.

- Imatinib is a competitive inhibitor of ATP binding to the tyrosine kinase domain of receptors such as KIT. This prevents the transfer of phosphate from ATP to the substrate and therefore inhibits signal transduction. Imatinib inhibits the kinase activity associated with both *KIT* mutations (leading to constitutive activation of KIT receptors),[16] and also with wild type *KIT*.[17-19]
- Imatinib reduced tyrosine phosphorylation in a cell line (GIST882) established from a patient with

GIST, with a gain-of-function mutation of *KIT* causing SCF-independent activation. Complete inhibition was seen at a concentration of 1 μmol/L (the concentration at which 50% of activity was inhibited [IC_{50}] was not reported).[19] Imatinib also inhibited KIT tyrosine kinase activity in SCF-dependent cell lines (including myeloid leukaemia and small cell lung cancer [SCLC] cells), at an IC_{50} of 0.1 μmol/L in cell-based assays[5,16,20] and 0.2 μmol/L using an *in vitro* kinase assay,[20] and led to complete inhibition at a concentration of 1 μmol/L.[16]

- The inhibitory activity of imatinib against KIT is consistent with its effects against the tyrosine kinases associated with BCR-ABL, v-ABL, TEL-ABL and PDGF receptors, for which inhibition was seen at an IC_{50} of 0.1–0.35 μmol/L in cell-based assays, and an IC_{50} of 0.025–0.038 μmol/L for *in vitro* substrate phosphorylation.[5,6,21,22]
- Constitutively active KIT signalling in the GIST882 and GIST780 cell lines was inhibited by incubation with imatinib 0.1–10 μmol/L for 4–7 days and 1 μmol/L for 2 days, respectively, resulting in decreased cell proliferation and a dose-dependent increase in early apoptosis. Focus formation was decreased by at least 20-fold at concentrations of ≥0.1 μmol/L.[19] The growth and viability of a mast cell leukaemia cell line with constitutively active KIT and also SCF-dependent cell lines (SCLC and myeloid leukaemia cells) were also inhibited by imatinib 1 μmol/L.[16,20] These effects are comparable to the activity of imatinib against CML cell lines expressing BCR-ABL, in which inhibition of proliferation was seen at a concentration of 1 μmol/L.[6]
- In animal models, imatinib inhibited the growth of KIT-expressing colorectal tumours,[23] as well as BCR-ABL-expressing tumours,[6,24] and several different PDGF-mediated tumours.[25-28]
- Limited data are available on resistance to imatinib in patients with GIST, although one clinical trial reported primary resistance in 5% of treated patients, and the onset of resistance after several months of treatment in others (see section 3).[29] The molecular mechanisms causing resistance in GIST remain to be elucidated.[29]

2. Pharmacokinetic Profile

The majority of pharmacokinetic data for imatinib have been derived from studies in healthy volunteers and patients with CML (reviewed in *Drugs*[4]). The pharmacokinetics of oral imatinib were evaluated in patients with GIST receiving 400 or 600mg once daily; 19 patients had full pharmacokinetic analyses performed on days 1 and 28 (at steady state), and 54 patients had limited samples taken for population pharmacokinetic analyses.[29,30] The profile in patients with GIST is similar to that in patients with CML; an overview of the pharmacokinetic characteristics of imatinib is provided in this section.

Absorption and Distribution

- Imatinib was absorbed rapidly after oral administration to patients with GIST, patients with CML and healthy volunteers,[17,31] with maximum plasma concentrations being reached after 2 to 4 hours.[31] Mean absolute bioavailability was 98%,[31] and food had no clinically relevant effect on the absorption or bioavailability of imatinib in patients with CML.[32] During administration of imatinib 400mg once daily for 28 days, the mean maximum plasma concentration at steady state was 2.9 mg/L in patients with GIST[17] and 2.3 mg/L in patients with CML.[33]
- In patients with GIST, the mean area under the plasma concentration-time curve (AUC) at steady state was 1.2 times higher in patients receiving imatinib 600mg daily for 4 weeks than in those receiving 400mg (75 ± 31 vs 61 ± 25 mg • h/L).[29] The mean AUC increased proportionally over the 25–1000mg dose range in patients with CML, after both single and multiple doses.[30,33] There was 1.5- to 2.5-fold accumulation (based on AUC) at steady state, after once daily administration for 1 month.[17,30]
- No specific data are available on the effect of gastrointestinal surgery on the absorption of imatinib; however, therapeutic plasma concentra-

tions were achieved with daily doses of 400mg and 600mg in patients with GIST, most of whom had had prior resections.[29]

- On the basis of *in vitro* testing, at clinically relevant concentrations imatinib was approximately 95% protein bound, mostly to albumin and α_1-acid-glycoprotein.[31] The volume of distribution in patients with CML was approximately 435L;[30] there was an association between increasing age and increased volume of distribution, but this was not clinically significant.[34]

Metabolism and Excretion

- Imatinib is metabolised in the liver, predominantly by the cytochrome P450 isoform CYP3A4; other cytochrome P450 enzymes such as CYP1A2, CYP2D6, CYP2C9 and CYP2C19 have a limited role. The major metabolite is the *N*-demethylated piperazine derivative, which has similar *in vitro* activity to the parent compound; the plasma AUC for this metabolite is 15–16% of the AUC for imatinib.[31,34] Specific pharmacokinetic data on patients with hepatic impairment are not available.[34]
- Coadministered drugs that are inducers of CYP3A4 (e.g. phenytoin) may increase imatinib metabolism resulting in decreased plasma concentrations.[31,33] Conversely, CYP3A4 inhibitors (e.g. ketoconazole and erythromycin) may increase plasma concentrations of imatinib.[31] Metabolism of other substrates of CYP3A4 (e.g. simvastatin) and also of substrates of CYP2C9, CYP2D6 and CYP3A4/5 may be inhibited by concomitant administration of imatinib.[31]
- The plasma elimination half-life of imatinib was 18–20, 13–16 and 18 hours in patients with GIST,[17,29] patients with CML[33] and healthy volunteers,[31] respectively. The half-life of the major active metabolite was approximately 40 hours in healthy volunteers.[31]
- No significant effect of bodyweight on clearance was seen in patients with GIST;[35] however, in patients with CML, increased bodyweight was associated with increased clearance, although adjustment of the initial dose was not warranted.[31,34] There was a statistically significant association between decreased albumin or increased white blood cell count and reduced clearance in patients with GIST; however, these changes were not sufficient to necessitate dose adjustments.[34]
- Elimination of imatinib is mainly in the faeces, with 81% of a ^{14}C-labelled dose administered to healthy volunteers being recovered in the faeces within 7 days, and 13% in the urine. Most of the dose was accounted for by metabolites, with only 25% being excreted as unchanged drug.[31]

3. Therapeutic Trials

The efficacy of imatinib in patients with advanced GIST has been investigated in a large, randomised, nonblind, multicentre study.[29] Additional data are available from a smaller, non-randomised dose-escalation study, which started recruiting at a similar time to the larger study, and was aimed at establishing the maximum tolerated dose of imatinib (see section 4); efficacy was assessed as a secondary endpoint.[36,37] At the time of reporting (as full papers) patients had been followed up for a minimum of 9 months and both studies remained ongoing. Preliminary results are also available for an unpublished study in which 51 patients with soft tissue sarcoma, including 27 patients with advanced unresectable or metastatic GIST, were treated with 800mg imatinib per day; details of the design and methodology are not available.[38]

There are two published reports of the dose-escalation study; the earlier one assessed response rates in 40 patients, 36 of whom had GIST whereas the later paper reported responses in 35 patients with GIST;[36,37] the remaining patients had non-GIST, soft tissue sarcomas. Results from the more recent paper are presented in this review. Originally the efficacy trial was designed as a small, proof-of-concept study in 36 patients, but because of the response rate seen,[39] the sample size was increased to 200 patients.[29] The results of an interim analysis led to recruitment being terminated at 147 patients.[29]

The patient characteristics and dosages used in the two published trials were as follows. Patients had

unresectable and/or metastatic, CD117-positive GIST (and at least one previously untreated, measurable tumour)[29] or advanced soft tissue sarcomas that had progressed within the previous 6 weeks (including 35 patients with CD117-positive GISTs and 5 with non-GIST soft tissue sarcomas).[36] More than 50% of patients in both studies had received prior chemotherapy,[29,36] 10–15% had been treated with radiotherapy[29,36] and almost all of the patients in the efficacy study had undergone surgery.[29]

Imatinib 400mg (n = 73) or 600mg (n = 74) was administered orally once daily in the randomised efficacy trial.[29] In the non-randomised dose-ranging trial oral doses of imatinib were 400mg once daily (n = 8), or 300mg (n = 8), 400mg (n = 16) or 500mg all twice daily (n = 8).[36] These treatments were continued until progression of disease,[29,37] unacceptable toxicity or the refusal of treatment by the patient (and for a minimum of 1 year in patients showing an objective reponse).[37] In the efficacy study, patients receiving 400mg who showed disease progression had their dosage escalated to 600mg.

In both studies effectiveness was assessed in terms of objective tumour response rate, using the South Western Oncology Group (SWOG) criteria[40] in the efficacy study (and based on computed tomography or magnetic resonance imaging), and the Response Evaluation Criteria in Solid Tumours (RECIST)[41] in the dose-escalation study (using computed tomography).[36,37] Tumour responses were classified as follows:

- complete response – disappearance of all disease;[29,36]
- partial response – ≥50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions[29] or ≥30% decrease in the sum of the longest diameter of target lesions,[36] and no progression of disease and no new lesions;
- stable disease – did not qualify as a complete response, partial response or progression;[29,36]
- disease progression – an increase of either ≥50% or 10 cm^2 (whichever was smaller) in the sum of the products of all measurable lesions, or worsening of evaluable disease, or reappearance of any lesion, or appearance of a new lesion, or failure to return for evaluation because of disease progression (SWOG criteria);[29] or ≥20% increase in the sum of the longest diameters of target lesions over smallest sum observed, or unequivocal progression of non-measurable disease, or appearance of new lesions, or death due to disease without prior documentation of progression (RECIST criteria).[36]

Secondary endpoints in the efficacy study included time to treatment failure (defined as disease progression, death or discontinuation of treatment, unless their condition no longer required treatment), and overall survival. The study also evaluated the performance status of patients during treatment and the pharmacokinetic profile of imatinib (see section 2).[29]

Response Rates

- In both clinical trials, more than 80% of patients benefited from treatment with imatinib in terms of tumour response (partial response or disease stabilisation) at dosages of between 400mg once daily and 500mg twice daily. Just over half of the patients in both studies achieved confirmed partial responses.[29,36]
- In the large efficacy study, at the cut-off timepoint for the report (15 October 2001), the median duration of follow-up was 288 days, and all patients had been followed up for at least 9 months. Tumour response was assessed at 1, 3 and 6 months and then 6-monthly or when medically indicated; response rates were based on the intention-to-treat population.
- There were no statistically significant differences in the rate or duration of response between the 400 and 600mg once daily dosages.[29] Confirmed partial responses were achieved in 79 patients (53.7% [95% CI 45.3–62.0]), with a reduction in tumour size of between 50 and 96% (figure 1). A further 41 patients had stable disease (27.9% [95% CI 20.8–35.9]). There were no complete responses, and disease progression occurred in 20

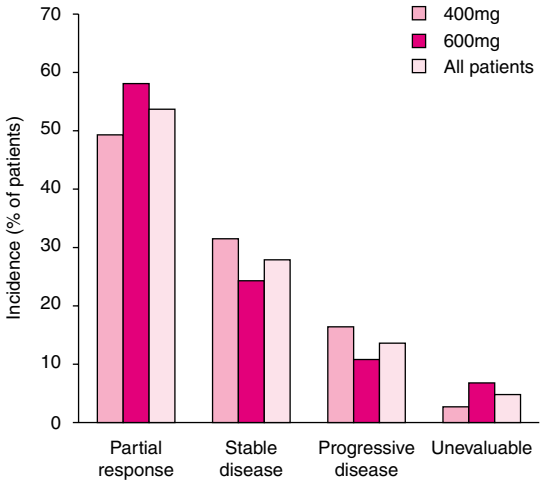

Fig. 1. Objective tumour response rates in patients with gastrointestinal stromal tumour treated with imatinib mesylate. Results from a randomised, nonblind, multicentre study in which patients were randomised to receive 400mg (n = 73) or 600mg (n = 74) once daily; tumour response rates were assessed using South Western Oncology Group criteria. Best response achieved is shown. No patient showed a complete response in either group.[29]

patients (13.6%), 12 of whom initially received 400mg imatinib. Primary resistance to imatinib was seen in 5% of patients during the first 2 months of treatment, and responses could not be assessed in a further 5% of patients.[29]

- The tumour response rates for the 35 patients with GIST in the dose-escalation study were consistent with the results for the efficacy study. All patients had been followed up for a minimum of 9 months, with evaluations of objective response being performed every 8 weeks. Nineteen patients (54%) achieved confirmed partial responses, and 13 others (37%) had stable disease. Two patients (5%) had early progression of disease within 3 weeks of commencing treatment, and the response could not be evaluated in one patient. Again, there were no complete responses. Tumour response rates for individual dose groups were not reported.[36]
- The median time to an objective response in the efficacy study was 13 weeks.[29] The median time to treatment failure and median duration of response had not been reached at the time of reporting (at which point the median duration of follow-up after the onset of response was 24 weeks), but some responses had persisted for more than 46 weeks (number of patients not stated).[29] In the dose-escalation study, after a minimum follow-up of 9 months, 82% of patients continued to show either a partial response (51%) or stable disease (31%).[36]
- In both studies, some patients who had disease progression were then given a higher dosage of imatinib and showed an improved response at the new dosage. Nine of the patients in the efficacy study were escalated from 400mg once daily to 600mg once daily; one of these patients then had a partial response and two patients had stable disease.[29] Two patients in the dose-escalation study who had disease progression after 4 months treatment with 400mg once daily, had their dosage increased to 400mg twice daily, and one subsequently showed a minor response.[37]
- In the third study, in which patients received 800mg daily, the overall objective response rate (not further defined) in patients with GIST was 71%, with a median time to response of 4 months; at 12 months 73% of patients were progression free.[38]

Overall Survival

- At the time of reporting, the median duration of survival in the efficacy study could not be assessed. Fourteen patients had died, nine from the 400mg group and five from the 600mg group; ten of these deaths were due to progressive disease and four were due to causes unrelated to study drug.[29,42] The estimated 1-year survival rate for all patients was 88%.[29] After a minimum follow-up of 9 months in the dose-escalation study, four patients had died, three of them from disease progression; the fourth patient was one who could not be evaluated for response.[36]

Performance Status

- The functional status of patients with GIST improved during treatment with imatinib, based on

assessments made during the efficacy study. A baseline performance status of 3 or less, using the Eastern Oncology Group (ECOG) criteria,[43] was required for entry into the trial. At 4 months into the study, the number of patients with normal performance status (as indicated by an ECOG score of zero) had increased from 42% at baseline to 64%. Over the same period the number of patients with an ECOG score of 2 or 3 (indicating moderate to substantial functional disability) decreased from 19% to 5%.[29]

4. Tolerability

Adverse events were assessed using the US National Cancer Institute common toxicity criteria (NCI CTC) in both the efficacy and the dose-escalation studies. In the latter study, adverse events were reported for all 40 patients, including the five patients with non-GIST soft-tissue sarcoma, and the focus of the reporting was on dose-limiting toxicity within the first 8 weeks of treatment.[36]

- The adverse events reported in the dose-escalation study were broadly similar to those documented in the larger study. In both trials the most common adverse event was oedema, which was documented in 74.1% of patients during the efficacy study and 75.0% of patients in the first 8 weeks of the dose-escalation study. This was predominantly superficial (facial and leg oedema), with periorbital oedema occurring in 47.6% and 30.0% of patients in the efficacy and dose-escalation studies, respectively.[29,37]
- Gastrointestinal adverse events were also common, with nausea, vomiting and diarrhoea occurring in 52.4%, 12.9% and 44.9%, respectively, in the efficacy study, and 42.5%, 27.5% and 35.0%, respectively, during the first 8 weeks of the dose-escalation trial.[29,37]
- Skin rash and fatigue were also reported frequently. Rash or dermatitis was recorded for 55.0% of patients in the first 8 weeks of the dose-escalation study, but tended to resolve after that time.[36] The incidence of skin rash in the efficacy study (30.6%) is similar to that reported for patients who remained on treatment after a minimum of 10 months follow-up in the dose-escalation trial (30.0%). Fatigue and myalgia were reported by 34.7% and 39.5% of patients, respectively, in the efficacy study, and fatigue by 30.0% of patients in the dose-escalation study after 10 months.[29,36]
- Overall, adverse events were mostly mild to moderate in severity at dosages up to 400mg twice daily. Severe adverse events reported in both studies included neutropenia and gastrointestinal or intratumoural haemorrhage.[29,36,37]
- Almost all of the 147 patients in the multicentre efficacy study (98.0%) experienced some mild or moderate adverse events (NCI CTC grade 1 or 2) that were potentially related to treatment with imatinib (figure 2); 21.1% of patients experienced severe and/or serious adverse events (grade 3 or 4).[29] Although the incidence of some adverse events was higher in the 600mg group than the 400mg group, there was no significant difference in the severity.[29]
- Grade 3 or 4 haematological adverse events occurred in 12 patients (8.2%) in the efficacy study and 19 patients (47.5%) during the first 8 weeks of the dose-escalation study (for which doses were not stated). These events included grade 3 or 4 neutropenia or leucopenia in 9 patients (6.2%) in the efficacy trial,[29] and 12 patients in the dose-escalation study (one patient during the first 8 weeks, and 11 patients during long-term follow-up).[36]
- Grade 3 or 4 gastrointestinal events occurring during the efficacy study included diarrhoea (2.0%), nausea (1.4%), vomiting and abdominal pain (both 0.7%). There were 3 reports (7.5%) of grade 3 nausea and/or vomiting in the dose-escalation study (all during the first 8 weeks, in patients receiving 500mg twice daily).[29,36] Grade 3 or 4 tumour haemorrhage or gastrointestinal haemorrhage was seen in 8 patients (5.4%) in the efficacy study, generally those with bulky tumours.[29] Tumour haemorrhage also occurred in three patients (7.5%) in the first 8 weeks of the dose-escalation study, however the severity of the events and the dosages at which they occurred were not stated.[37]
- Grade 3 or 4 dermatitis or rash was documented in 4 patients (2.7%) in the efficacy study, and 1

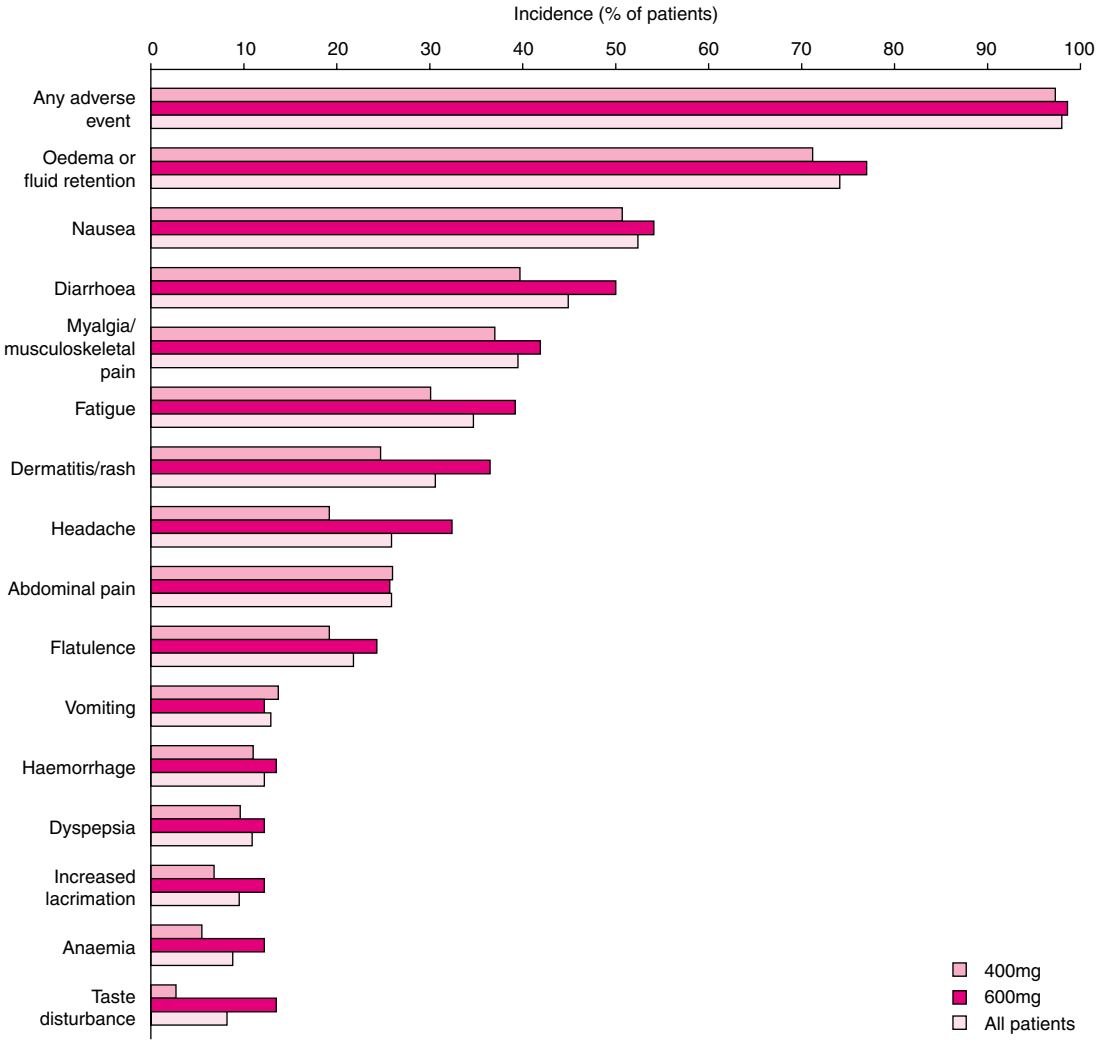

Fig. 2. Adverse events with imatinib mesylate in the treatment of patients with gastrointestinal stromal tumour. Data from a multicentre, randomised study: adverse events of any grade, with suspected relationship to imatinib, with an incidence ≥10% at either dose, for patients receiving 400mg once daily (n = 73), 600mg once daily (n = 74) and for all patients combined (n = 147).[29]

patient in the first 8 weeks of the dose-escalation study (receiving 300mg twice daily).[29,36,37] Although oedema was the most common adverse event overall, it reached grade 3 or 4 severity in only 2 patients (1.4%) in the efficacy study.[29] During the first 8 weeks of the dose-escalation study, one patient receiving 500mg twice daily developed grade 3 dyspnoea due to accumulation of pleural and abdominal fluids.[36]

- In the dose-escalation trial, dose-limiting toxicity was defined as grade 3 or 4 nonhaematological toxicity (except for controllable nausea and/or vomiting, and alopecia), grade 4 neutropenia (absolute neutrophil count $\leq 0.5 \times 10^9$/L) for 7 days,

febrile neutropenia or grade 4 thrombocytopenia.[37] During the first 8 weeks, adverse events which met these criteria occurred in two patients receiving 300mg twice daily (grade 3 oedema and grade 3 rash), one patient receiving 400mg twice daily (grade 4 neutropenia) and five patients receiving 500mg twice daily (grade 3 nausea and/or vomiting in three patients, grade 3 oedema and grade 3 dyspnoea in one patient each). The maximum tolerated dosage was 400mg twice daily.[36]

- A case report of two patients with GIST and documented liver metastases causing impaired hepatic function (as indicated by markedly elevated liver enzymes and/or bilirubin levels), stated that no unexpected or serious adverse events were observed during 4 months of treatment with imatinib at 400–600mg daily.[44]

5. Dosage and Administration

In the US, the recommended dosage of imatinib for adult patients with unresectable and/or metastatic malignant GIST is 400mg or 600mg once daily. The recommended dosage in the European prescribing information is 400mg once daily. The capsules are administered orally, with a meal and a glass of water.[31,34]

If a severe, non-haematological adverse reaction develops, treatment should be withheld until it has resolved. In the event of hepatotoxicity, a subsequent dose reduction may also be required. Interruption of treatment and dose reduction are also necessary in the case of severe neutropenia or thrombocytopenia.[31,34]

6. Imatinib Mesylate: Current Status

Imatinib has been approved in the US and in Europe for the treatment of adult patients with CD117-positive, unresectable and/or metastatic malignant GIST.[29,31,34]

Imatinib has shown efficacy in terms of tumour regression and disease stabilisation in patients with advanced GIST, and is generally well tolerated. The assessment of effectiveness is based on objective tumour response rates in noncomparator studies, and long-term data on the effects of imatinib on the natural history of the disease are not yet available. Two large-scale studies comparing daily doses of 400mg and 800mg imatinib, which are ongoing, should provide additional efficacy and tolerability data, and help to determine the optimal dose in patients with GIST.[17] Trials of adjuvant therapy with imatinib are also ongoing.[45]

References

1. Griffin J. The biology of signal transduction inhibition: basic science to novel therapies. Semin Oncol 2001 Oct; 28 (5 Suppl 17): 3-8
2. Druker BJ, Lydon NB. Lessons learned from the development of an Abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J Clin Invest 2000; 105 (1): 3-7
3. Kolibaba KS, Druker BJ. Protein tyrosine kinases and cancer. Biochim Biophys Acta 1997; 1333: F217-48
4. Lyseng-Williamson K, Jarvis B. Imatinib. Drugs 2001; 61 (12): 1765-74; discussion 1775-6
5. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor ST1571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000; 295 (1): 139-45
6. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996 May; 2: 561-6
7. Savage DG, Antman KH. Imatinib mesylate-a new oral targeted therapy. N Engl J Med 2002 Feb 28; 346 (9): 683-93
8. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. Hum Pathol 1999; 30 (10): 1213-20
9. Blanke CD, Eisenberg BL, Heinrich MC. Gastrointestinal stromal tumors. Curr Treat Options Oncol 2001 Dec; 2 (6): 485-91
10. Berman J, O'Leary TJ. Gastrointestinal stromal tumor workshop. Hum Pathol 2001 Jun; 32 (6): 578-82
11. DeMatteo RP, Lewis J, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231 (1): 51-8
12. McGrath PC, Neifeld JP, Lawrence Jr. W, et al. Gastrointestinal Sarcomas: analysis of prognostic factors. Ann Surg 1987; 206: 706-10
13. Singer S, Rubin BP, Lux ML, et al. Prognostic value of KIT mutation type, mitotic activity and histologic subtype in gastrointestinal stromal tumors. J Clin Oncol 2002; 20 (18): 3898-905
14. Heinrich MC, Corless CL, Blanke C, et al. KIT mutational status predicts clinical response to STI571 in patients with metastatic gastrointestinal stromal tumors [abstract]. 38th Annual Meeting of the American Society of Clinical Oncology 2002 May 1; 21: 2 (plus oral presentation)
15. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001 Apr 5; 344 (14): 1052-6
16. Heinrich MC, Griffith DJ, Druker BJ, et al. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000; 96 (3): 925-32
17. Glivec® GIST clinical monograph. Basel, Switzerland: Novartis Pharma AG, 2002

18. Schindler T, Bornmann W, Pellicena P, et al. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. Science 2000; 289: 1938-42
19. Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. Oncogene 2001 Aug 16; 20 (36): 5054-8
20. Krystall GW, Honsawek S, Litz J, et al. The selective tyrosine kinase inhibitor STI571 inhibits small cell lung cancer growth. Clin Cancer Res 2000 Aug; 6: 3319-26
21. Buchdunger E, Zimmermann J, Mett H, et al. Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminoprimidine derivative. Cancer Res 1996; 56: 100-4
22. Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. Blood 1997 Dec 15; 90: 4947-52
23. Attoub S, Rivat C, Rodrigues S, et al. The c-kit tyrosine kinase inhibitor STI571 for colorectal cancer therapy. Cancer Res 2002 Sep 1; 62 (17): 4879-83
24. le Coutre P, Mologni L, Cleris L, et al. In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. J Natl Cancer Inst 1999 Jan 20; 91 (2): 163-8
25. Shimizu A, O'Brien KP, Sjöblom T, et al. The dermatofibrosarcoma protuberans-associated collagen type I α 1/platelet-derived growth factor (PDGF) β-chain fusion gene generates a transforming protein that is processed to functional PDGF-BB. Cancer Res 1999; 59: 3719-23
26. Sjöblom T, Shimizu A, O'Brien KP, et al. Growth inhibition of dermatofibrosarcoma protuberans tumors by the platelet-derived growth factor receptor antagonist ST1571 through induction of apoptosis. Cancer Res 2001; 61: 5778-83
27. Kilic T, Alberta JA, Zdunek PR, et al. Intracranial inhibition of platelet-derived growth factor-mediated glioblastoma cell growth by an orally active inhibitor of the 2-phenylaminopyrimidine class. Cancer Res 2000; 60: 5143-50
28. Uehara H, Kim SJ, Karashima T, et al. Blockade of PDGF-R signaling by STI571 inhibits angiogenesis and growth of human prostate cancer cells in the bone of nude mice [abstract]. 92nd Ann Meet Am Assoc Cancer Res 2001 Mar; 42: 407
29. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002 Aug 15; 347 (7): 472-80
30. Committee for Proprietary Medicinal Products. European public assessment report on Glivec (Revision 1): scientific discussion. London, UK: European Agency for the Evaluation of Medicinal Products, 2002; CPMP/2418/01
31. Gleevec™ (imatinib mesylate) capsules prescribing information. USA: Novartis, 2002
32. Reckmann AH, Fischer T, Peng B, et al. Effect of food on STI571 Glivec pharmacokinetics and bioavailability [abstract]. 37th Annual Meeting of the American Society of Clinical Oncology 2001 May 12; 20 (Part 1): 307
33. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001; 344 (14): 1031-7
34. Summary of product characteristics: Glivec 100mg capsules. Horsham, United Kingdom: Novartis Europharm Limited, 2002
35. Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 2002 Oct; 8 (10): 3034-8
36. van Oosterom AT, Judson IR, Verweij J, et al. Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumours: a report of the EORTC soft tissue and bone sarcoma group. Eur J Cancer 2002; 38 Suppl. 5: S83-7
37. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 2001 Oct 27; 358 (9291): 1421-3
38. Novartis Oncology. Glivec® First successful systemic treatment for GIST. 2002; Symposium highlights. (Data on file)
39. Blanke CD, von Mehren M, Joensuu H, et al. Evaluation of the safety and efficacy of an oral molecularly-targeted therapy, STI571, in patients with unresectable or metastatic gastrointestinal stromal tumors expressing C-KIT [abstract]. 37th Annual Meeting of the American Society of Clinical Oncology 2001 May 1; 20: 1 (plus oral presentation)
40. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 1992; 10: 239-53
41. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92 (3): 205-16
42. von Mehren M, Blanke C, Joensuu H, et al. High incidence of durable responses induced by imatinib mesylate (Gleevec™) in patients with unresectable and metastatic gastrointestinal stromal tumors (GISTs) [abstract]. Proc Am Soc Clin Oncol 2001; 20: 1A
43. Oken MM, Creech RH, Douglass CT, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-55
44. Bauer S, Hagen V, Pielken HJ, et al. Imatinib mesylate therapy in patients with gastrointestinal stromal tumors and impaired liver function. Anticancer Drugs 2002 Sep; 13 (8): 847-9
45. National Cancer Institute. Clinical Trials [online]. Available from URL: http://cancer.gov/clinical_trials [Accessed 2003 Jan 15]

Correspondence: *Katherine F. Croom*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz