Minireview

Imatinib and gastrointestinal stromal tumors: Where do we go from here?

Ugo De Giorgi[1] and Jaap Verweij[2]

[1]Department of Oncology, Istituto Toscano Tumori, San Giuseppe Hospital, Empoli (Florence), Italy and [2]Department of Medical Oncology, Erasmus University Medical Center, Daniel den Hoed, Rotterdam, the Netherlands

Abstract

Imatinib has tremendously changed the treatment of gastrointestinal stromal tumors (GIST). Research is currently focusing on its optimal use and the mechanisms of resistance that may emerge. A multidisciplinary approach including medical oncologists, surgeons, radiologists, and pathologists is crucial for the optimal management of these patients. Moreover, imatinib treatment in GIST represents an extraordinary model to expand our knowledge on the molecular mechanisms that are basic to the effects of molecularly targeted therapies. This review summarizes the existing knowledge of the imatinib treatment in GIST and describes directions for further development. [Mol Cancer Ther 2005;4(3):495–501]

Introduction

Gastrointestinal stromal tumors (GIST) are the most common abdominal mesenchymal neoplasms, occurring in 10 to 20 cases per million at a median age of 60 years with similar male/female incidence (1, 2). The primary tumor site is located in the gastrointestinal tract in nearly 95% of cases: stomach (50–60%), small bowel (20–30%), large bowel (10%), esophagus (5%), and in mesentery, omentum, and retroperitoneum in <10% of cases (3). Despite radical surgical resection, 40% to 80% of GISTs recur intraabdominally with local relapse, peritoneal seeding, or liver metastases (4). Regional lymph node and extra-abdominal metastases are rare (4). After radical resection, the 5-year overall survival is nearly 50%, whereas for unresectable or metastatic GISTs, in the pre-imatinib era, the median survival was estimated at 9 to 20 months (4, 5).

GIST cells share many phenotypic features with interstitial cells of Cajal, which are the pacemaker cells of the gut and are considered to originate from the same lineage (5, 6). In nearly 90% to 95% of cases, GISTs characteristically express KIT protein, a transmembrane receptor for stem cell factor with the intracytoplasmic portion functioning as a tyrosine kinase (7). GISTs are characterized by gain-of-function mutations in the KIT proto-oncogene, most commonly involving the exon 11, but in other cases involving exon 9, 13, or 17 (8). In GISTs without KIT mutations, the gain-of-function mutations in the platelet-derived growth factor receptor α (PDGFRα) seem to be an alternative oncogenetic mechanism (9, 10).

Imatinib (imatinib mesylate, commercially available as Gleevec or Glivec, Novartis, Basel, Switzerland), formerly known as STI-571, is an inhibitor of certain tyrosine kinases including the KIT protein, the BCR-ABL fusion protein present in Philadelphia chromosome–positive chronic myeloid leukemia, and the PDGFRs expressed in some sarcomas, gliomas, Philadelphia chromosome–negative chronic myeloid leukemias, and GISTs lacking KIT mutations (9–12). Preclinical models of human GIST cells showed that the inhibition of mutant KIT in GIST by imatinib led to growth arrest and eventually apoptosis (13). These insights coupled with the necessity of effective therapies for patients with unresectable or metastatic GIST, led to a rapid clinical development. After the encouraging results in the first reported patient, three initial phase I/II studies and two following phase III randomized trials showed very impressive results with imatinib treatment in patients with metastatic or unresectable GIST, leading to a rapid approval by the Food and Drug Administration in February 2002 (14–21). The current focus of research is on the refinement of imatinib treatment and on the elucidation of mechanisms of drug resistance.

Current Imatinib Treatment in GIST

All clinical studies with imatinib in advanced GIST showed high overall response rate and suggested improved quality of life, whereas the phase III studies suggested an increased progression-free and overall survivals (15–20). These studies are summarized in Table 1. To date, imatinib 400 mg/d is the recommended starting dose for metastatic GIST (21). Indeed, the final results of the phase II randomized study (imatinib 400 versus 600 mg/d) and the results of both the National Cancer Institute-Intergroup S0033 and the European-Australian phase III randomized trials (comparing imatinib 400 versus 800 mg/d) did not show differences neither in terms of response induction nor in terms of overall survival (17, 19, 20). However, the European-Australian phase III randomized trial has

Table 1.   Early results of the clinical studies with imatinib treatment in metastatic GIST patients

Study group (Ref.)	Study design	Imatinib dose (mg)	Total patients	Overall PR + SD (%)	2-y Progression-free survival	Follow-up period (mo)
EORTC (16)	Phase I	400–1,000	35	51 + 31	NA	Minimum: 9
US-Finland (17)	Phase II randomized	400 versus 600	147	54 + 28	NA	Minimum: 9
EORTC (18)	Phase II	400	27	71* + 18	NA	Minimum: 12
NCI (19) (Intergroup S0033)	Phase III randomized	400 versus 800	746	48* + 26	50% versus 53% ($P > 0.05$)	Median: 25
EORTC, ISG, AGITG (20)	Phase III randomized	400 versus 800	946	51* + 33	50% versus 56% ($P = 0.026$)	Median: 25

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; NCI, National Cancer Institute; ISG, Italian Sarcoma Group; AGITG, Australasian Gastro-Intestinal Trials Group; PR, partial response; SD, stable disease; NA, not available.
*Including 3% to 5% of patients achieving complete remission.

recently reported a statistically significant advantage in progression-free survival for the higher dose of imatinib (20). The progression-free survival curves were similar in the National Cancer Institute trial, albeit not statistically significant (19), probably due to its smaller patient population and possible differences in KIT mutation site. Thus, particularly in the metastatic setting, the starting dose may require reconsideration.

Recently, the 1-year results of a French phase III study of continuous versus intermittent imatinib treatment have shown rapid and frequent progression at 3 months in patients discontinuing imatinib (22). The continuous imatinib administration is therefore confirmed as standard approach.

The French study provided also some guidance that imatinib should not be discontinued after resection of residual disease, even in patients with successful microscopically radical removal of residual disease (22), because history has taught us that there is never microscopic radicality in such circumstances (17). Thus, imatinib treatment should not be stopped, even in patients with either complete remission or partial remission with radical resection of residual disease.

In both phase III randomized trials, the crossover from imatinib 400 to 800 mg/d in patients with progressive disease induced further disease remission or stabilization in 33% to 38% of patients (19, 20). Therefore, this option should be considered as first option for patients with progressive disease at the 400 mg/d dose. In patients with limited disease, when surgery is feasible, the resection of progressive lesions should be considered and imatinib should not be discontinued after surgery (23). Radiofrequency ablation and hepatic artery embolization are alternative options for the control of clonal evolution of unresectable liver lesions refractory to imatinib (4, 24). Finally, progressive patients could be offered enrollment into ongoing clinical trials with new molecularly targeted therapies.

Imatinib treatment was generally safe and well tolerated, although 99% of patients presented some mild to moderate side effects (20). Toxic death occurred in 0.5% to 2%, mainly due to bleeding or hepatic toxicity (19, 20). About 20% of patients experienced usually reversible grade 3 to 4 nonhematologic or hematologic toxicities, most of which were manageable. Less than 2% of patients were taken off treatment due to side effects (17–20). The most common side effects included with decreasing frequency are anemia, periorbital edema, nausea, diarrhea, fatigue, neutropenia, and skin rash. Periorbital edema and skin rash frequently seemed to be self-limiting despite continued treatment (20). No major differences were seen in the severity of adverse events between the 400 and 600 mg dose groups in the U.S. phase II randomized study, although overall incidence of diarrhea, muscle cramps, headache and periorbital edema was somewhat higher in the 600 mg group (17). Instead, an increased incidence of severe (grades 3–4) adverse events was noted in patients who started imatinib at 800 mg/d in the two phase III randomized studies, whereas a higher incidence of treatment-related deaths in the high-dose arm was reported in the National Cancer Institute trial only (19, 20). Dose interruptions or treatment discontinuations were mainly attributable to nonhematologic side effects (20). For patients with grade 3 to 4 anemia and/or neutropenia, the use of hematopoietic growth factors (erythropoietin and granulocyte colony-stimulating factor) could be considered (25, 26).

In the European-Australian trial, the daily dose of imatinib had to be reduced to ≤ 300 mg in 16% of patients allocated 400 mg/d dose (20). Progression-free survival in patients treated with imatinib 300 mg did not differ from the one in patients treated at higher doses, but patients with dose reduction to 200 mg presented a worse progression-free survival compared with higher doses (20). This observation could be affected by selection bias. However, extensive efforts, including the best supportive measures, should be made to avoid reducing imatinib dose below 300 mg.

Pharmacologic Issues

Imatinib is primarily metabolized in the liver by CYP3A4. Other isoforms such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19 are involved to a much lesser extent (27, 28).

Substances inhibiting CYP3A4, such as ketaconazole, may decrease metabolism and increase imatinib plasma concentrations (29). Instead, inducers of CYP3A4, such as St. John's Wort and rifampicin, may increase metabolism and decrease imatinib concentrations, significantly reducing exposure to imatinib (30–32). Imatinib increases plasma concentration of other CYP3A4 substrates. The coadministration of imatinib with simvastatin (CYP3A4 substrate) increases the exposure to simvastatin significantly by 2- to 3-fold (33). Caution is therefore required when giving imatinib with CYP3A4 substrates with a narrow therapeutic window. Imatinib is also a weak inducer of CYP2C9 and CYP2D6 (27). Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard eparin as long as adequate studies to better define this pharmacokinetic interaction have not been done (27). The potential interaction with substrates of CYP2D6 (e.g., fluoxetine) needs further studies.

For patients with varying degrees of liver and renal dysfunction, the preliminary data of a phase I study were not conclusive and specific recommendations for imatinib dosing in these patients were not given (34, 35). Care should therefore be taken for the time being.

After 3 to 12 months of treatment with imatinib, a decrease in the exposure of >40% was documented in GIST patients (36), due to a decrease in drug clearance. These data could explain the observation that the toxic effects during imatinib therapy tended to decrease after the first 2 months of treatment (18, 20, 36). Inflammatory response and an increase in plasma levels of α1-acid glycoprotein may affect imatinib metabolism and clearance (37, 38).

An interesting hypothesis involves a possible role for liver tumor regression inducing liver regeneration with resulting restoration of enzymatic activity. This could explain the increase of the imatinib clearance in patients with liver metastases responsive to imatinib treatment. A clinical study has recently started to assess this issue.

Role of KIT and PDGFRα Mutational Status

The gain-of-function mutations of KIT and PDGFRα play a key role in GIST pathogenesis (39). These mutations are an early event, as evidenced by KIT mutations found in incidental GISTs ≤1 cm in size and germ line KIT mutations in familial GIST syndromes (40, 41). A series of characteristic cytogenic abnormalities represent secondary events associated with increased malignant potential and disease progression (42). Mutations in the KIT gene occur with decreasing frequency in exons 11, 9, 13, and 17 (43–47). Mutations in the *PDGFRα* gene involve either exon 18 or 12 (43, 44, 46). No untreated GIST has an activating mutation in more than one KIT exon, and all PDGFR-mutant GISTs are found in tumors lacking a KIT mutation (9, 43, 44). A subset of GISTs is wild type for both KIT and PDGFR (43, 44). The type of mutations provides relevant prognostic information. Table 2 summarizes the correlation among presence of activating mutations, response to imatinib and progression-free survival. Patients with tumors expressing exon 11 mutations in KIT have a statistically significantly better progression-free survival compared with patients with tumors harboring exon 9 mutations in KIT or patients with no evidence of mutations (43, 44).

Table 2. Correlation of activating mutations with response to imatinib and progression-free survival in GIST patients

Tyrosine kinase* (exon)	Product	Mutation types	Frequency in GISTs (%)	Primary location	Partial response (%)	Median PFS
KIT (43, 44)						
Exon 11	Portion of the cytoplasmatic juxtamembrane domain	Deletion/insertion of codons 557 and 559 and point mutations: codons 557, 559, 560, and 576	66–71	Mainly stomach	83.5	23 mo
Exon 9	Region located in the extracellular domain	AY501-502 duplication/insertion or FAF506-508 duplication/insertion	10–18	Small bowel in 90-95% of cases	47.8	7 mo
Exon 13	First part of the split tyrosine kinase domain	Point mutation K642E	1–4	Not defined	100[†]	NA
Exon 17	Phosphotransferase domain (TK II domain)	Point mutations N822H, N822K, D816V	1–4	Not defined	50[†]	NA
PDGFRα (10, 43, 44)						
Exon 12	Juxtamembrane domain	Point mutation V561D	1–2	Only stomach	66.7[†]	NA
Exon 18	TK II domain	Point mutation D842V	2–6	Only stomach	0[†]	NA
Wild type (43, 44, 48)	—	—	1–12	Stomach or omentum/mesentery	0[†]	3 mo

Abbreviations: PFS, progression-free survival; NA, not available.
*Numbers in parentheses are reference citations.
[†]This data should be considered with caution because of the small number of reported cases.

GISTs that show little or no immunohistochemical staining for KIT may still harbor a KIT exon 11 mutation or PDGFRα mutations and still respond to imatinib treatment (48, 49). Therefore, kinase genotyping may be even more important than immunohistochemistry, and patients with immunohistochemically KIT-negative GISTs should not, a priori, be denied imatinib therapy.

Mechanisms of Imatinib Resistance

Various mechanisms are responsible for imatinib resistance in GISTs. A preliminary study in patients with early imatinib resistance and late resistance (progression after initial response or disease stabilization) suggested four mechanisms of biological imatinib resistance: (a) acquisition of a new KIT or PDGFRα point mutation, coexpressed with the pre-imatinib mutations in the same genes, and resultant strong phosphorylation of KIT or PDGFRα; (b) KIT genomic amplification with overexpression of the KIT oncoprotein, without new point mutation; (c) activation of an alternate receptor tyrosine kinase protein, accompanied by loss of KIT oncoprotein expression; and (d) KIT or PDGFRα activation outside the juxtamembrane hotspot region, in the absence of a secondary genomic mutation. All mechanisms of resistance were involved in patients with late imatinib resistance, whereas the latter mechanism was also involved in patients with early resistance (50). All GISTs at progression showed activation of essential downstream pathways dependent on KIT or PDGFRα stimulation in untreated tumors.

Other possible mechanisms of resistance could involve the active cellular transport of imatinib. Active transport processes mediate both influx and efflux of imatinib. Differential expression of hOCT1 (influx transporter) and MDR1 or BCRP (efflux transporters) may be a critical determinant of intracellular drug levels and hence resistance to imatinib (51, 52).

A recent report about a reduction in the exposure to imatinib over time in GIST patients coupled with the observation that toxic effects decrease after the first 2 months of imatinib therapy has suggested a possible pharmacokinetic mechanism of resistance (36). It is unknown how narrow the therapeutic dose range of imatinib is in GIST patients. Results of the largest phase III randomized trial (comparing imatinib 400 versus 800 mg/d) have recently documented a statistically significant advantage in progression-free survival for the higher dose of imatinib (20). Moreover, dose reduction to 200 mg presented a worse progression-free survival compared with higher doses (20). Finally, the crossover from imatinib 400 to 800 mg in patients with progressive disease induced further disease remission or stabilization in a subgroup of patients (19, 20). Pharmacokinetic studies to further elucidate these issues are ongoing.

Residual Disease

Whereas imatinib induces high overall response rates, most responses are partial and rarely the drug induces pathologic complete remissions (17, 23). This has stimulated an ongoing debate on what to do when seemingly resectable residual lesions are achieved during imatinib treatment. Obviously, to yield valuable recommendations, optimal collaboration among medical oncologist, radiologist, and surgeon is crucial, also to determine the optimal timing of surgery.

Currently, few data exist on the histologic changes in GISTs during imatinib treatment. Biopsies done during imatinib treatment showed a hypocellular myxohyaline stroma with small numbers of scattered atypical nuclei and, frequently, prominent stromal hemorrhage, whereas tumor necrosis was rarely observed. In addition, relevant numbers of residual KIT-positive vital tumor cells were found, even in patients with a very good response to treatment. These residual tumor cells often showed pyknotic nuclei and reduced cytoplasmatic volume (17) and a different extent of myxoid degeneration and apoptotic figures (53).

An important issue to solve is to assess the functional features of residual disease. Loss of KIT expression has been observed in some advanced GISTs that have become imatinib resistant (48). We do know that KIT overexpression is an early event in the pathogenesis of GIST, but we do not know if the tumor stem cells also present this feature. Recently, researchers have shown that KIT expression is characteristic of the committed hematopoietic progenitor cells but was totally absent in the hematopoietic stem cells *in vitro* (54). The incapability of imatinib to produce complete responses, may thus be due to the presence of cells that are truly not expressing KIT and thus insensitive to imatinib.

Imaging Issues

The radiological findings of GISTs have been recently described in the literature. GISTs seem typically large, well-circumscribed, heterogeneous tumors that rarely obstruct viscera, despite their large size and with propensity to metastasize to the liver and peritoneum (55). During imatinib treatment, tumor response is commonly monitored with anatomic methods such as computed tomography (CT) or magnetic resonance and functional imaging such as ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET).

In GIST patients, response to imatinib treatment as assessed by FDG-PET could occur rapidly, although actual tumor regression can be slow. The median time to CT/magnetic resonance response was 3 to 4 months (17–20). The use of FDG-PET provided greater information about the extent of disease and intratumoral metabolic activity than CT (17–20). Notably, FDG-PET showed evidence of a response to imatinib therapy before any measurable changes were seen on CT. In some cases, FDG-PET detected treatment responses as early as 24 hours after starting imatinib (17). Standard anatomic tumor response criteria, such as response evaluation criteria in solid tumors and WHO and Southwest Oncology Group criteria, may be inappropriate to monitor the effect of imatinib treatment

(20, 56). Cystic changes of responding lesions with parallel increase in lesion size can lead to underassessment of imatinib activity (16). After initial response to imatinib, the typical "nodule within mass" is a unique pattern of disease progression observed in GISTs without changes in tumor size (57). Moreover, patients with stable disease as best response to imatinib assessed by standard anatomic imaging achieve comparable overall survival to patients with partial remission (19). Taken together, these data suggest that for GIST disease-specific response criteria need to be developed.

Due to the results of PET scan imaging in the monitoring of GIST response to imatinib, other novel technologies such as new PET scanning, CT/PET scanning, dynamic contrast-enhanced magnetic resonance, contrast-enhanced and Doppler ultrasonography, and use of radionuclides, have gained attention, to monitor tumor both changes during imatinib treatment in GIST and response to novel agents (58–60). Among these, angiosonography has recently showed early changes in tumor vascularization before any change in tumor size in GIST patients receiving imatinib (61).

Future Directions

The role of imatinib in metastatic GIST is now relatively well defined. But what about further uses?

As many as 40% to 80% of radically resected primary GISTs will recur or metastasize (4), suggesting that microscopic disease and/or micrometastases frequently remains after surgery. Although adequate surgery is crucial for optimal survival of these patients, adjuvant and/or neoadjuvant use of imatinib may in theory further improve the results. We need to await the results of these trials, but in theory, they could modify the approach to GIST in patients with earlier stages of disease.

The molecular classification of GISTs based on KIT and PDGFRα mutational status may provide more exact prognostic estimates and with the possibility of an individually tailored imatinib treatment (44–49), certainly if confirmed in larger series. Such screening can be used in the design and interpretation of new clinical trials in GISTs with imatinib and/or other new molecularly targeted therapies. These techniques could also help to better understand the mechanisms of resistance.

The gene expression patterns in GIST has been recently characterized using DNA microarrays (62). The gene *FLJ10261*, encoding for the DOG1 protein, is specifically expressed in GISTs. DOG1, a protein of unknown function, strongly expressed on the cell surface of 98% of GISTs, whereas it is rarely expressed in other soft tissue sarcomas (63). Reactivity for DOG1 may aid in the diagnosis of GISTs, including PDGFR mutants that fail to express KIT antigen and lead to appropriate treatment with imatinib. In addition, the protein kinase C theta, a novel protein kinase C isotype involved in T-cell activation, is highly and specifically expressed in GIST and easily detected by immunohisto-chemistry, and it could be a sensitive and specific marker for the diagnosis of this malignancy (64).

Longitudinal studies of GIST patients treated with imatinib revealed a therapy-induced increase in IFN-γ production by natural killer cells, correlating with an enhanced antitumor response (65). These data point to a novel mode of antitumor action for imatinib needing further investigation.

The availability of an i.v. formulation of imatinib may be useful in case of swallowing problems (66), and targeted radionuclide delivery could be another tool (67). Because imatinib cellular uptake is a temperature-dependent active process (50, 51), abdominal or locoregional external hyperthermia could be investigated to increase the intra-cellular imatinib levels particularly in patients with only peritoneal spread.

New molecularly targeted therapies are in develop-ment for GIST patients refractory to imatinib. All GISTs at progression showed activation of essential down-stream pathways, including the AKT/mammalian target of rapamycin pathway, that are dependent on KIT or PDGFRα oncogenic stimulation in untreated tumors (50). SU11248 is a multitargeted kinase inhibitor of KIT, FLT3, PDGFR, and vascular endothelial growth factor receptor. SU11248 induced clinical benefit (defined by partial response or stable disease during >6 months) in 65% of patients with GIST refractory or intolerant to imatinib (68). A phase III randomized trial comparing SU11248 versus placebo is currently ongoing in these patients. RAD001 (everolimus), a rapamycin analogue inhibitor of the protein kinase mammalian target of rapamycin, is currently investigated in combination with imatinib in patients with GIST refractory to imatinib. Preliminary results showed that the combination was safe and well tolerated, but a tumor flare of FDG uptake (PET) after short interruption of imatinib and then reduced FDG uptake with the imatinib-RAD001 combination, suggesting a residual activity in some clones. Accordingly, the study design was modified to avoid interruption of imatinib (69). Other new drugs currently evaluated in imatinib refrac-tory patients are Oblimersen, an antisense oligonucleotide to the bcl-2 mRNA; Bevacizumab, a neutralizing antibody to vascular endothelial growth factor; CCI 779, a rapamy-cin analogue inhibitor of the protein kinase mammalian target of rapamycin; PTK787/ZK222584, AMG 706, BAY 43-9006, and many other multi-tyrosine kinase inhibitors; and PKC 412, an inhibitor of protein kinase C and vascular endothelial growth factor–dependent angiogenesis (70).

Imatinib can be considered the prototype tyrosine kinase inhibitor and has certainly revolutionized the treatment of GIST. This has paved the way for other molecularly targeted treatments, and will totally change our approach in the treatment of cancer.

References

1. De Matteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol 2002;33:466 – 77.

2. Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001;438:1 – 12.

3. Fletcher CDM, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459 – 65.

4. De Matteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence pattern and prognostic factors for survival. Ann Surg 2000;231:51 – 8.

5. Graadt van Roggen JF, van Velthuysen ML, Hogendoorn PC. The histopathological differential diagnosis of gastrointestinal stromal tumours. J Clin Pathol 2001;54:96 – 102.

6. Kindblom L-G, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152:1259 – 69.

7. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001;61:8118 – 21.

8. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-KIT in human gastrointestinal stromal tumors. Science 1998;279:577 – 80.

9. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708 – 10.

10. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor α gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660 – 7.

11. 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;2:561 – 6.

12. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000;96:925 – 32.

13. Tuveson DA, Willis NA, Jacks T, et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. Oncogene 2001;20:5054 – 8.

14. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with metastatic gastrointestinal stromal tumour. N Engl J Med 2001;344:1052 – 6.

15. 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;358:1421 – 3.

16. van Oosterom AT, Judson IR, Verweij J, et al. Update of a 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. Eur J Cancer 2002;38 Suppl 5:S83 – 7.

17. 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;347:472 – 80.

18. Verweij J, van Oosterom A, Blay J-Y, et al. Imatinib mesylate (STI-571 Glivec, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. Eur J Cancer 2003;39:2006 – 11.

19. Rankin C, Von Mehren M, Blanke C, et al. Phase III dose-randomized study of imatinib mesylate (STI571) for GIST: Intergroup S0033 early results. Proc Am Soc Clin Oncol 2004;23:815. (abstr 9005).

20. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127 – 34.

21. 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;8:3034 – 8.

22. Blay J-Y, Berthaud P, Perol D, et al. Continuous vs intermittent imatinib treatment in advanced GIST after one year: a prospective randomized phase III trial of the French Sarcoma Group. Proc Am Soc Clin Oncol 2004;23:815. (abstr 9006).

23. Scaife CL, Hunt KK, Patel SR, et al. Is there a role for surgery in patients with ''unresectable'' cKIT$^+$ gastrointestinal stromal tumors treated with imatinib mesylate? Am J Surg 2003;186:665 – 9.

24. Dileo P, Randhawa R, Vansonnenberg E, et al. Safety and efficacy of percutaneous radio-frequency ablation in patients with metastatic gastro-intestinal stromal tumor with clonal evolution of lesions refractory to imatinib mesylate. Proc Am Soc Clin Oncol 2004;23:9024.

25. Duffaud F, Lecesne A, Ray-Coquard I, et al. Erythropoietin for anemia treatment of patients with GIST receiving imatinib. Proc Am Soc Clin Oncol 2004;23:825. (abstr 9046).

26. Heim D, Ebnöther M, Meyer-Monard S, et al. G-CSF for imatinib-induced neutropenia. Leukemia 2003;17:805 – 7.

27. Novartis Pharmaceutical Corporation. Gleevec (imatinib mesylate) prescribing information. Novartis Pharmaceuticals Corporation, NJ, USA, 2004. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf. Accessed February 2005.

28. de Jong FA, Verweij J. Role of imatinib mesylate (Gleevec/Glivec) in gastrointestinal stromal tumors. Expert Rev Anticancer Ther 2003;3:757 – 66.

29. Dutreix C, Peng B, Mehring G, et al. Pharmacokinetic interaction between ketoconazole and imatinib mesylate (Glivec) in healthy subjects. Cancer Chemother Pharmacol 2004;54:290 – 4.

30. Smith PF, Bullock JM, Booker BM, Haas CE, Berenson CS, Jusko WJ. Induction of imatinib metabolism by hypericum perforatum. Blood 2004;104:1229 – 30.

31. Bolton AE, Peng B, Hubert M, et al. Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects. Cancer Chemother Pharmacol 2004;53:102 – 6.

32. Fryem RF, Fitzgeraldm SM, Lagattutam TF, Hruskam MW, Egorin MJ. Effect of St John's wort on imatinib mesylate pharmacokinetics. Clin Pharmacol Ther 2004;76:323 – 9.

33. O'Brien SG, Meinhardt P, Bond E, et al. Effects of imatinib mesylate (STI571, Glivec) on the pharmacokinetics of simvastatin, a cytochrome *P*450 3A4 substrate, in patients with chronic myeloid leukaemia. Br J Cancer 2003;89:1855 – 9.

34. Ramanathan RK, Remick SC, Mulkerin D, et al. P-5331: a phase I pharmacokinetic study of STI571 in patients with advanced malignancies and varying degrees of liver dysfunction. Proc Am Soc Clin Oncol 2003;22:126. (abstr 502).

35. Remick SC, Ramanathan RK, Mulkerin D, et al. P-5340: a phase I pharmacokinetic study of STI571 in patients with advanced malignancies and varying degrees of renal dysfunction. Proc Am Soc Clin Oncol 2003;22:126. (abstr 503).

36. Judson IR, Donato Di Paola E, Verweij J, et al. Population pharmacokinetics (PK) analysis and PK-pharmacodynamic (PD) correlations in phase I/II trial of imatinib in gastrointestinal stromal tumours (GIST) conducted by the European Organisation for Research and Treatment Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol Epub 2004 Dec 9.

37. Delbaldo C, Chatelut E, Rè M, et al. Inflammatory response affects the pharmacokinetics and pharmacodynamics of imatinib and CGP 74588 in patients with advanced gastro-intestinal-sarcoma (GIST). Proc Am Soc Clin Oncol 2004;23:144. (abstr 2070).

38. Slaviero KA, Clarke SJ, Rivory LP. Inflammatory response: an unrecognised source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy. Lancet Oncol 2003;4:224 – 32.

39. Duensing A, Medeiros F, McConarty B, et al. Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). Oncogene 2004;23:3999 – 4006.

40. Corless CL, McGreevey L, Haley A, Town A, Heinrich MC. KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. Am J Pathol 2002;160:1567 – 72.

41. Nishida T, Hirota S, Taniguchi M, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 1998;19:323 – 4.

42. Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. Hum Pathol 2002;33:484 – 95.

43. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342 – 9.

44. Corless LC, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004;22:3813 – 25.

45. Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2004;40:689 – 95.

46. Antonescu CR, Viale A, Sarran L, et al. Gene expression in gastrointestinal stromal tumors is distinguished by KIT genotype and anatomic site. Clin Cancer Res 2004;15:3282 – 90.

47. Frolov A, Chahwan S, Ochs M, et al. Response markers and the molecular mechanisms of action of Gleevec in gastrointestinal stromal tumors. Mol Cancer Ther 2003;2:699 – 709.

48. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol 2004;28:889 – 94.

49. Bauer S, Corless CL, Heinrich MC, et al. Response to imatinib mesylate of a gastrointestinal stromal tumor with very low expression of KIT. Cancer Chemother Pharmacol 2003;51:261 – 5.

50. Fletcher JA, Corless CL, Dimitrijevic S, et al. Mechanisms of resistance to imatinib mesylate in advanced gastrointestinal tumor. Proc Am Soc Clin Oncol 2003;22:815. (abstr 3275).

51. Thomas J, Wang L, Clark RE, Pirmohamed M. Active transport of imatinib into and out of cells: implications for drug resistance. Blood 2004;104:3739 – 45.

52. Burger H, Van Tol H, Boersma AW, et al. Imatinib mesylate (STI571) is a substrate for the breast cancer resistance protein (BCRP)/ABCG2 drug pump. Blood 2004;104:2940 – 2.

53. Hohenberger P, Bauer S, Schneider U, et al. Tumor resection following imatinib pretreatment in GI stromal tumors. Proc Am Soc Clin Oncol 2003;21:3288a.

54. Bartolovic K, Balabanov S, Hartmann U, et al. Inhibitory effect of imatinib on normal progenitor cells *in vitro*. Blood 2004;103:523 – 9.

55. Burkill GJ, Badran M, Al-Muderis O, et al. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. Radiology 2003;226:527 – 32.

56. Casali PG, Fumagalli E, Messina A, et al. Tumor response to imatinib mesylate in advanced GIST. Proc Am Soc Clin Oncol 2004;23:821. (abstr 9028).

57. Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with gastrointestinal stromal tumor (GIST): molecular and radiological evaluation of new lesions. Proc Am Soc Clin Oncol 2004;23:197. (abstr 3010).

58. Knopp MV, von Tengg-Kobligk H, Choyke PL. Functional magnetic resonance imaging in oncology for diagnosis and therapy monitoring. Mol Cancer Ther 2003;2:419 – 26.

59. Blasberg RG. Molecular imaging and cancer. Mol Cancer Ther 2003;2:335 – 43.

60. Lassau N, Lamuraglia M, Leclère J, et al. Doppler-ultrasonography with perfusion software and contrast medium injection as an early evaluation tool of gastro intestinal stromal tumor (GIST) treated by imatinib: results of a prospective study. Proc Am Soc Clin Oncol 2004;23:826. (abstr 9048).

61. De Giorgi U, Aliberti C, Benea G, Conti M, Marangolo M. Effect of angio-sonography with a second generation contrast agent to assess tumor response to imatinib treatment in patients with advanced gastro-intestinal stromal tumor (GIST). Proc Am Soc Clin Oncol 2004;23:366. (abstr 4216).

62. Subramanian S, West RB, Corless CL, et al. Gastrointestinal stromal tumors (GISTs) with KIT and PDGFRA mutations have distinct gene expression profiles. Oncogene 2004;23:7780 – 90.

63. West RB, Corless CL, Chen X, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am J Pathol 2004;165:107 – 13.

64. Blay P, Astudillo A, Buesa JM, et al. Protein kinase C theta is highly expressed in gastrointestinal stromal tumors but not in other mesenchymal neoplasias. Clin Cancer Res 2004;10:4089 – 95.

65. Borg C, Terme M, Taieb J, et al. Novel mode of action of c-kit tyrosine kinase inhibitors leading to NK cell-dependent antitumor effects. J Clin Invest 2004;114:379 – 88.

66. Peng B, Dutreix C, Mehring G, et al. Absolute bioavailability of imatinib orally versus intravenous infusion. J Clin Pharmacol 2004;44:158 – 62.

67. Jong M, Kwekkeboom D, Valkema R, Krenning EP. Radiolabelled peptides for tumour therapy: current status and future directions. Eur J Nucl Med Mol Imaging 2003;30:463 – 9.

68. Demetri GD, Desai J, Fletcher JA, et al. SU11248, a multi-targeted tyrosine kinase inhibitor, can overcome imatinib (IM) resistance caused by diverse genomic mechanisms in patients (pts) with metastatic gastrointestinal stromal tumor (GIST). Proc Am Soc Clin Oncol 2004;23:195. (abstr 3001).

69. Van Oosterom AT, Dumez H, Desai J, et al. Combination signal transduction inhibition: A phase I/II trial of the oral mTOR-inhibitor everolimus (RAD001) and imatinib mesylate in patients with gastrointestinal stromal tumor (GIST) refractory to IM. Proc Am Soc Clin Oncol 2004;23:195. (abstr 3002).

70. National Cancer Institute Clinical Trials. [cited 2005 Feb]. Available from: http://cancer.gov/search/ResultsClinicalTrials.aspx?protocol-searchid = 1428474.

Molecular Cancer Therapeutics

Imatinib and gastrointestinal stromal tumors: Where do we go from here?

Ugo De Giorgi and Jaap Verweij

Mol Cancer Ther 2005;4:495-501.

Updated version	Access the most recent version of this article at: http://mct.aacrjournals.org/content/4/3/495

Cited articles	This article cites 59 articles, 16 of which you can access for free at: http://mct.aacrjournals.org/content/4/3/495.full#ref-list-1
Citing articles	This article has been cited by 4 HighWire-hosted articles. Access the articles at: http://mct.aacrjournals.org/content/4/3/495.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://mct.aacrjournals.org/content/4/3/495. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.