Minireview

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

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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 mesentry, omentum, and retroperitoneum in <10% of cases (3). Despite radical surgical resection, 40% to 80% of GISTs recur intra-abdominally 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 oncogenic 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 survival (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

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

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.

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

<table>
<thead>
<tr>
<th>Tyrosine kinase* (exon)</th>
<th>Product</th>
<th>Mutation types</th>
<th>Frequency in GISTs (%)</th>
<th>Primary location</th>
<th>Partial response (%)</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT (43, 44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 11</td>
<td>Portion of the cytoplasmatic juxtamembrane domain</td>
<td>Deletion/insertion of codons 557 and 559 and point mutations: codons 557, 559, 560, and 576</td>
<td>66–71</td>
<td>Mainly stomach</td>
<td>83.5</td>
<td>23 mo</td>
</tr>
<tr>
<td>Exon 9</td>
<td>Region located in the extracellular domain</td>
<td>AY501-502 duplication/insertion or FA506-508 duplication/insertion</td>
<td>10–18</td>
<td>Small bowel in 90–95% of cases</td>
<td>47.8</td>
<td>7 mo</td>
</tr>
<tr>
<td>Exon 13</td>
<td>First part of the split tyrosine kinase domain (TK II domain)</td>
<td>Point mutation K642E</td>
<td>1–4</td>
<td>Not defined</td>
<td>100†</td>
<td>NA</td>
</tr>
<tr>
<td>Exon 17</td>
<td>Phosphotransferase domain</td>
<td>Point mutations N822H, N822K, D816V</td>
<td>1–4</td>
<td>Not defined</td>
<td>50†</td>
<td>NA</td>
</tr>
<tr>
<td>PDGFRα (10, 43, 44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 12</td>
<td>Juxtamembrane domain</td>
<td>Point mutation V561D</td>
<td>1–2</td>
<td>Only stomach</td>
<td>66.7†</td>
<td>NA</td>
</tr>
<tr>
<td>Exon 18</td>
<td>TK II domain</td>
<td>Point mutation D842V</td>
<td>2–6</td>
<td>Only stomach</td>
<td>0†</td>
<td>NA</td>
</tr>
<tr>
<td>Wild type (43, 44, 48)</td>
<td>—</td>
<td>—</td>
<td>1–12</td>
<td>Stomach or omentum/mesentry</td>
<td>0†</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

**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 of 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 18F-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 immunohistochemistry, 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 intracellular imatinib levels particularly in patients with only peritoneal spread.

New molecularly targeted therapies are in development for GIST patients refractory to imatinib. All GISTs at progression showed activation of essential downstream 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 multitypered 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 refractory patients are Oblimersen, an antisense oligonucleotide to the bcl-2 mRNA; Bevacizumab, a neutralizing antibody to vascular endothelial growth factor; CCI 779, a rapamycin 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.

Acknowledgments

We thank Floris A. de Jong for his critical review of the article and for his valuable comments.
References

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