Clonal Evolution of Resistance to Imatinib in Patients with Metastatic Gastrointestinal Stromal Tumors

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Abstract Purpose: Resistance to imatinib mesylate is emerging as a clinical challenge in patients with metastatic gastrointestinal stromal tumors (GIST). Novel patterns of progression have been noted in a number of these patients. The objective of this study was to correlate molecular and radiologic patterns of imatinib-refractory disease with existing conventional criteria for disease progression. Experimental Design: Patients with metastatic GIST treated with imatinib were followed with serial computed tomography/magnetic resonance imaging and [18F]fluoro-2-deoxy-D-glucose positron emission tomography. Where feasible, biopsies were done to document disease progression. Results: A total of 89 patients were followed for a median of 43 months. Forty-eight patients developed progressive disease. A unique “resistant clonal nodule” pattern (defined as a new enhancing nodular focus enclosed within a preexisting tumor mass) was seen in 23 of 48 patients and was thought to represent emergence of clones resistant to imatinib. Nodules were demonstrable a median of 5 months (range, 0–13 months) before objective progression defined by tumor size criteria and were the first sign of progression in 18 of 23 patients. Median survival among patients whose first progression was nodular was 35.1 months, compared with 44.6 months for patients whose first progression met Southwest Oncology Group criteria (P = 0.31). Comparative tumor biopsies were done in 10 patients at baseline and from progressing nodules. Genotypic analyses of KIT and PDGFRα kinases were done, revealing new activating kinase mutations in 80% (8 of 10) of these patients. Conclusion: The resistant clonal nodule is a unique pattern of disease progression seen in patients with GISTs after an initial response to imatinib and reflects the emergence of imatinib-resistant clones. Conventional tumor measurements (Southwest Oncology Group/Response Evaluation Criteria in Solid Tumors) do not detect this subtle finding. A new enhancing nodule growing within a preexisting tumor mass should be classified as a new lesion and be regarded, at least, as partial progression of GIST.

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors that arise throughout the entire length of the gastrointestinal tract. Almost all GISTs express the stem cell factor receptor tyrosine kinase KIT (1–3). Activating mutations in the gene encoding KIT, present in at least 90% of GISTs, are the most frequent molecular mechanism underlying GIST oncogenesis (4–10). Most GISTs have KIT gene mutations in exon 11 or exon 9, encoding the intracellular and extracellular juxtamembrane portions of KIT that regulate kinase activity. Approximately one third of GISTs lacking KIT mutations instead have activating mutations in the gene encoding platelet-derived growth factor receptor-α (PDGFRα; refs. 11–14). The molecular elucidation of the pathogenesis of GIST has therefore provided the rationale for molecularly targeted therapy for this disease.

Imatinib (Glivec, Gleevec; Novartis Pharma AG), a selective inhibitor of KIT and PDGFR, as well as certain other tyrosine kinases, is indicated as first-line therapy for metastatic and unresectable malignant GIST (15–20). Clinical evidence supporting the indication of imatinib for GIST was obtained from phase 1, 2, and 3 studies of patients with advanced GIST, in which partial responses were obtained in the majority of patients (21–24).

Responses to imatinib in GIST patients depend on the presence, and genomic location, of KIT oncogenic mutations...
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(22, 25). Patients with exon 11 KIT mutations had a partial response rate of 84% compared with a 0% partial response rate among patients without KIT mutations. Similar results were obtained in the European Organization for Research and Treatment of Cancer study group (26). These clinical observations are consistent with laboratory studies showing that a specific KIT exon 11 point mutation (V560G) is associated with increased susceptibility to imatinib inhibition of kinase activity compared with wild-type KIT (27).

Translation of imatinib response to survival benefit has been shown in long-term follow-up studies. The survival rate among GIST patients treated with imatinib is estimated to be 84% at 83 weeks, with disease progression after a median of 84 weeks and with median overall survival of nearly 5 years (22). Data from a phase 3 trial comparing 400 and 800 mg/d imatinib doses indicated progression-free survival at 24 months of 48% and 56%, respectively, among 946 patients with GISTs. These studies show that imatinib prolongs survival of GIST patients when compared with historical controls such as the European Organization for Research and Treatment of Cancer database, with 2-year survival of 69% versus 17%, respectively (24). These studies also reveal, however, that in some patients disease progression develops over time despite continued imatinib therapy.

We, as well as other groups, have previously reported on imaging changes seen in patients with progressing GISTs (28–30). In this study, we have sought to further explore the radiologic patterns of GIST progression and to identify and characterize early indications of relapse during imatinib therapy to supplement Southwest Oncology Group (SWOG)/Response Evaluation Criteria in Solid Tumors criteria for disease progression. A second objective was to investigate the underlying molecular mechanisms of imatinib refractoriness or resistance in GIST.

Materials and Methods

Patients

This study included 89 patients with metastatic GISTs treated with imatinib at doses of 400 to 800 mg/d. All patients included in this evaluation were enrolled in clinical trials investigating the efficacy of imatinib in metastatic or unresectable GIST, approved by the Institutional Review Board for the Dana-Farber/Harvard Cancer Center. Written informed consent was obtained from each patient, both for the clinical trial in which they were participating in and for the analysis of tumor-associated genetic alterations. At the time of this analysis, patients have been followed for a median of 43 months.

Radiographic evaluation

Computed tomography scans. All patients underwent contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis (5- or 7-mm-thick slices, 100 mL i.v., contrast-Oxilan 300). Patients were restaged at ~6-week intervals for the first 3 months, and then trimonthly. Magnetic resonance imaging. Magnetic resonance imaging (MRI) scans of the liver were done in selected cases, either for patients in whom contrast-enhanced CT scans were contraindicated or when planning percutaneous interventional procedures, such as radiofrequency or cryoablation. In the latter patients, MRI scans were reviewed qualitatively for interval changes in FDG uptake in all measurable lesions.

Results

Patients

Eighty-nine GIST patients treated with imatinib 400 to 800 mg/d were followed for an average of 43 months. The
present analysis is limited to 48 patients who experienced disease progression (as defined by conventional SWOG criteria) during treatment with imatinib. This group (Table 1) was composed of 27 men and 21 women with a median age of 48 years (range, 18-84 years).

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>48</td>
</tr>
<tr>
<td>Male</td>
<td>27 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Median age (range), y</td>
<td>48 (18-84)</td>
</tr>
<tr>
<td><strong>Best response to imatinib</strong></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial</td>
<td>38 (79)</td>
</tr>
<tr>
<td>Minor</td>
<td>10 (21)</td>
</tr>
<tr>
<td><strong>Anatomic location of GIST at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal only</td>
<td>47 (98)</td>
</tr>
<tr>
<td>Intra- and extrahepatic</td>
<td>33 (69)</td>
</tr>
<tr>
<td>Intrahepatic only</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Extrahepatic only</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Abdominal and thoracic</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Mode of disease progression</strong></td>
<td></td>
</tr>
<tr>
<td>New site of disease</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Progression of preexisting lesion</td>
<td>30 (63)</td>
</tr>
<tr>
<td>Mixed pattern of progression</td>
<td>7 (15)</td>
</tr>
</tbody>
</table>

### Response to imatinib

All 48 patients included in this analysis had initial responses to imatinib, with 79% (38 of 48) having a partial response and 21% (10 of 48) a minor response. Among patients experiencing progression during imatinib therapy, nearly all (98%, 47 of 48) had disease restricted to the abdomen at the beginning of treatment; 69% (33 of 48) had intrahepatic and extrahepatic disease, 17% (8 of 48) had only intrahepatic disease, and 15% (7 of 48) had only extrahepatic disease. A single patient had disease that also extended to the chest (Table 1).

### Disease progression

Patterns of disease progression are summarized in Table 1. Twenty-three percent (11 of 48) of patients had a new site of disease in the abdomen; 62% (30 of 48) had progression of a preexisting lesion [enlargement of a tumor mass in a preexisting site(s) of disease]; and 15% (7 of 48) had both new sites of disease and enlarging lesions.

#### Resistant nodules.

Overall, 48% (23 of 48) of patients with GIST disease progression developed a resistant nodule (Fig. 1). These nodules consisted of new enhancing foci enclosed within a preexisting tumor mass that was nonenhancing or hypoenhancing, and were easily missed if images were not carefully evaluated. Multiple small nodules developed in some patients over a period of months (Fig. 2). In most patients (78%, 18 of 23), the nodule arose from the edge of the mass.

![Fig. 1. A 62-year-old man with metastatic GIST. Imatinib was initiated at 600 mg/d. A, CT scan at baseline, before imatinib (all CT scans are contrast enhanced unless stated otherwise). B, CT scan after 9 mo of imatinib at the time of maximal overall response to imatinib. Note that tumor masses have not only decreased in size but also show decreased attenuation and have a more homogenous appearance. C, CT scan after 12 mo of imatinib. Note the initial appearance of a resistant clonal nodule (RCN; arrow). D, CT scan after 18 mo of imatinib. Note the growth of resistant clonal nodule but without any appreciable change in the external dimensions of the original mass (arrow).](/attachment/)
In 22% (5 of 23), nodules were located within the tumor mass itself.

These nodules became apparent on CT scans before detection of progressive disease defined on the basis of increased size of the original tumor mass(es). The median time between the observation of nodules and disease progression defined by conventional criteria was 5 months (range, 0-13 months). The resistant nodule proved to be the first indication of disease progression in 78% (18 of 23) of the patients in which they were detected.

The appearance of a resistant nodule seemed to be independent of imatinib starting dose, with doses ranging from 400 to 800 mg/d \( (P = 0.98; \text{Table 2}) \). The imatinib dose was increased in 9 of the 23 patients with a resistant nodule, but this dose escalation had no effect on the appearance or size of the nodules. In only 2 of 23 (9%) patients, a resistant nodule filled and then expanded the mass in which it was enclosed, thus resulting in the patient being classified as having progressive disease as defined by conventional tumor response criteria (Fig. 3).

Overall survival was measured from the date of registration to the date of death. Patients alive at last follow-up were censored on that date. Among patients with nodular progression, 20 of 23 have died, whereas 18 of 23 with standard progression have died. Median survival among patients whose first progression was nodular was 35.1 months, compared with 44.6 months for patients whose first progression met SWOG criteria. Using the log-rank test, this difference was not statistically significant \( (P = 0.31; \text{Fig. 4}) \).

**Mutation analysis of resistant nodules.** Ten of the patients with resistant nodules had CT-guided biopsies of tumors at baseline and of the intratumoral nodules at the time of progression. Analysis of KIT and PDGFRA revealed new mutations in 80% (8 of 10) of these patients (Table 3), with the majority being in KIT exon 17. No change from the baseline nucleic acid coding sequence was noted in 20% (2 of 10). In all cases, the biopsy specimens contained the original gain-of-function KIT mutation that was present in preimatinib specimens obtained from the same patient.

<table>
<thead>
<tr>
<th>Imatinib starting dose (mg/d)</th>
<th>Total no. patients ( (N = 48) )</th>
<th>No. patients developing nodules ( (n = 23) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>600</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>800</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Fig. 2.** A 42-year-old man with metastatic GIST. Imatinib was initiated at 400 mg/d. Patient developed multiple resistant clonal nodules. A, CT scan at time of maximal overall response to imatinib (6 mo). Note the classic features of response to imatinib including homogenous nonenhancing tumor masses. B, CT scan after 9 mo of imatinib. Note the early appearance of multiple resistant clonal nodules, but without any change in external dimensions of tumor masses or any change in their characteristics. C, CT scan after 15 mo of imatinib. Note the growth of multiple resistant clonal nodules. D, FDG-PET scan after 15 mo of imatinib. Note the appearance of multiple resistant clonal nodules.
Discussion

Overall, ~50% of GIST patients treated with imatinib are progression-free at 2 years, implying that 50% were initially refractory or eventually progressed (22, 24). These findings, combined with the observations that complete responses to imatinib are rare, suggest that resistance to imatinib is emerging as a clinical challenge. Current radiologic criteria (SWOG/WHO/Response Evaluation Criteria in Solid Tumors) used to assess response to imatinib have been criticized for not adequately reflecting the biological changes occurring within that tumor (28, 30).

Disease progression in GIST patients treated with imatinib is currently an unmet clinical need, with a lack of information correlating the radiological changes to the molecular mechanisms of resistance to imatinib in GIST. Conventional tumor response criteria are based on size measurements made in one or two dimensions of the tumor mass visualized on axial CT images (31, 35). According to conventional criteria, tumor masses that are stable in size indicate no disease progression (36).

Fig. 3. A 56-year-old woman with metastatic GIST. Imatinib was initiated at 400 mg/d. A, CT scan at baseline, before imatinib. B, CT scan after 6 mo of imatinib at the time of maximal overall response to imatinib. C, CT scan after 23 mo of imatinib. Note initial appearance of resistant clonal nodule (arrow). D, CT scan after 32 mo of imatinib. Note the significant growth of resistant clonal nodule that has now caused the surrounding mass to grow, thus leading to a change in the external tumor measurements (arrow). E, FDG-PET scan after 32 mo of imatinib. Note the nodular component of resistant clonal nodule and increased mass effect resulting in right-sided hydronephrosis (arrow).
In our study, ~50% of patients with metastatic GIST who initially responded to imatinib displayed a unique CT imaging pattern of disease recurrence referred to as a resistant nodule. Molecular analyses of these nodules reveal that they represent clones of disease arising as a consequence of resistance to imatinib and unequivocally indicate disease progression. These “resistant clonal nodules” were observed before the development of progressive disease defined by tumor size criteria, and provided the earliest indication of disease progression (i.e., clonal resistance to imatinib) in 18 of 23 patients in which they were observed. The development of nodules did seem to affect survival, with a shorter overall survival (35.1 versus 44.6 months) in those developing nodules as a first sign of disease progression. However, this was not statistically significant ($P = 0.31$) in our series (Fig. 4). These findings support the argument that size-based criteria alone, using external tumor measurements, are not sufficient to detect the type of progression exemplified by resistant clonal nodules unless expansion of the nodules results in a substantial increase in the size of the surrounding mass. It is not clear from our study whether a patient’s overall survival will be affected by developing a resistant clonal nodule as a first sign of resistance to imatinib. A larger study will need to be done to adequately answer this question.

To our knowledge, this pattern of tumor recurrence or progression has not been observed in other cancers. The appearance of resistant clonal nodules as sensitive markers of disease progression in GIST patients on imatinib therapy raises the question about whether this pattern is unique to GIST or instead reflects the manner in which resistance develops in any solid tumor that is growth arrested with a tyrosine kinase inhibitor. Further study will help determine whether the resistant clonal nodule is specific for GIST or more generally associated with molecularly targeted therapies for solid tumors.

The physical association of resistant clonal nodules to the original tumor is consistent with the hypothesis that the cells within the resistant clonal nodule arose as a subpopulation of the original tumor. This suggests a process of clonal evolution from the original tumor milieu, as opposed to a spontaneously arising neoplasm.

A number of molecular mechanisms leading to refractoriness or resistance to imatinib have been proposed (25, 37–39). The predominant mechanism in GIST, target resistance due to mutation, consists of a new activating point mutation occurring in KIT or PDGFRA that confers imatinib resistance. An alternate mechanism, target modulation, entails activation of an alternate receptor tyrosine kinase converging on the same downstream signaling molecules as with KIT or PDGFRA activation. This is most likely to occur in tumors that are “wild-type” (i.e., where no mutations are detectable in KIT or PDGFR). A third potential mechanism, target resistance by overexpression and genomic amplification, is seen in chronic myeloid leukemia but is not thought to be important in GIST.

The underlying molecular mechanism for GIST resistance to imatinib observed in our study seems to be a second activating mutation in association with the original KIT mutation. New KIT mutations were present in the biopsy specimens from 80% (8 of 10) of these patients. Our hypothesis is that these secondary mutations reactivate KIT kinase activity, in some

### Table 3. Mutation analysis for KIT and PDGFRA

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Baseline mutation</th>
<th>Nodule mutation</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exon 11 V560D</td>
<td>Exon 11V560D + exon 17 point mutation D816H</td>
<td>New mutation</td>
</tr>
<tr>
<td>2</td>
<td>Exon 11 deletion WKKV557-560F</td>
<td>Exon 11 deletion WKKV557-560F and exon 17 point mutation Y823D</td>
<td>New mutation</td>
</tr>
<tr>
<td>3</td>
<td>Exon 11 mutation deletion WKKV557-560C</td>
<td>Exon 11 mutation deletion WKKV557-560C and exon 17 point mutation Y823D</td>
<td>New mutation</td>
</tr>
<tr>
<td>4</td>
<td>Exon 11 deletion WKKV557-561</td>
<td>Exon 11 deletion WKKV557-561 and exon 17 point mutation N822K</td>
<td>New mutation</td>
</tr>
<tr>
<td>5</td>
<td>Exon 11 deletion YEYQ553-555</td>
<td>Exon 11 deletion YEYQ553-555 and exon 13 point mutation V654A</td>
<td>New mutation</td>
</tr>
<tr>
<td>6</td>
<td>Exon 11 point mutation V560G</td>
<td>Exon 11 point mutation V560G and exon 13 point mutation V654A</td>
<td>New mutation</td>
</tr>
<tr>
<td>7</td>
<td>Exon 13 K642E</td>
<td>Exon 13 point mutation K642E and exon 17 point mutation D816H</td>
<td>New mutation</td>
</tr>
<tr>
<td>8</td>
<td>Exon 13 K642E and exon 17 point mutation N822H</td>
<td>Exon 13 point mutation K642E and exon 17 point mutations C809G and N822H</td>
<td>New mutation</td>
</tr>
<tr>
<td>9</td>
<td>Exon 11 homozygous deletion KSV58-559</td>
<td>Exon 11 homozygous deletion KSV58-559</td>
<td>No change</td>
</tr>
<tr>
<td>10</td>
<td>Exon 11 mutation deletion PMY551-554</td>
<td>Exon 11 mutation deletion PMY551-554</td>
<td>No change</td>
</tr>
</tbody>
</table>
instances, by conferring imatinib insensitivity to the KIT kinase. Evidence supporting this hypothesis is derived from in vitro studies evaluating the ability of imatinib to inhibit recombinant human KIT or KIT derived from GISTs (25, 27). Mutants of exon 17 (D816V), which encodes the second catalytic domain of KIT, were found to code for mutant KIT molecules completely insensitive to imatinib. Two of our patients exhibited a mutation at this same site, although the point mutation encoded a different amino acid substitution (D816H) in the resistant clonal nodule. In our series, secondary point mutations in exon 17 (C809G, D816H, N822H, N822K, and Y823D) were seen in five of eight patients, whereas two of eight patients had secondary mutations in KIT exon 13 (V654A). Other groups have also reported that secondary activating mutations in KIT are the most common mechanism underlying the development of acquired resistance to imatinib (38, 40–43).

Four patients in the study by Debiec-Rychter et al. (40) exhibited distinct secondary mutations in exon 17 (D816G, D820Y, D820E, and N822K); four patients had the same secondary mutation in exon 11 (V654A) and one patient harbored a T670I mutation in the ATP binding region of KIT. Similarly, in the study by Antonescu et al. (38), secondary activating mutations were found in six of seven patients in exon 17, between amino acids 820 and 823. A single case report of late resistance to imatinib in GIST revealed an exon 11 mutation as well as a second mutation in the second kinase domain of exon 17 (Y823D; ref. 43). A second case report describes a KIT exon 14 mutation in addition to an exon 11 mutation detected in an isolated progressing peritoneal mass removed from a patient with advanced GIST on imatinib therapy (42). Further characterization revealed that this point mutation (T670I) prevents imatinib binding. Chen et al. (41) found secondary mutations in exon 13 (missense mutation resulting in a V654A substitution) in five of six patients who developed rapidly progressive GIST after an initial response to imatinib. More recently, Waldermann et al. examined material removed from patients having metastasectomy for multifocal acquired resistance and found each nodule to contain a single new mutation (i.e., a new clone) in addition to the original activating mutation. Different tumors removed contained different mutations, although these were always in the tyrosine kinase domains (i.e., exons 13, 14, and 17; ref. 44). Of note, all of these patients developed new sites of disease.

In addition to KIT mutations, Debiec-Rychter et al. (40) also found an example of an imatinib-resistant patient with a primary KIT mutation as well as a secondary mutation in the gene encoding PDGFRα (D842V). This suggests that this GIST lesion is now driven by imatinib-resistant PDGFR signaling. Whereas we included PDGFRα genes in our analysis, no secondary mutations were detected. Our patient series, as well as other reports, indicate that there are imatinib-resistant patients without detectable secondary mutations with the implication that other mechanisms of imatinib resistance are operating (40, 45).

Together, these results suggest that in many cases of GIST resistance to imatinib, mutant clones with new mutations yielding KIT kinase molecules insensitive to imatinib evolve and account for resistant clonal nodules. Recently, structural bases have been elucidated for KIT autoinhibition and for imatinib-mediated kinase inhibition (46). Perhaps, this crystal structure model combined with further in vitro analyses will provide insight into the molecular and structural basis for other KIT mutations associated with imatinib resistance.

Disease progression with chemotherapeutic agents is usually met with cessation of treatment to limit patient exposure to therapeutically ineffectual cytotoxic agents. Patients on imatinib therapy with limited GIST progression, shown as nodules within an otherwise responding tumor mass, are best viewed as presenting with two distinct tumors requiring separate treatment approaches. Continued imatinib therapy is essential to maintain suppression of the part of the tumor that remains sensitive to imatinib. Although dose escalation was not beneficial in this study, it is conceivable depending on the mechanism of imatinib resistance that dose escalation may be beneficial in certain cases of limited progression in GIST.

On the other hand, local resistant clones that compose the nodules and do not respond to imatinib dose escalation may be managed with an alternative approach incorporating continuation of systemic kinase inhibition with imatinib combined with a local treatment such as tumor ablation or surgery. The combination of imatinib and radiofrequency ablation has been used in five patients with resistant clonal nodules by our group. Overall disease control was achieved for an additional 4 to 12 months in this small patient subgroup (47). Although not been reported for this specific indication, other methods of local control commonly used in refractory GIST, such as selective hepatic arterial embolization or chemo-embolization, could also be considered as an alternate to radiofrequency ablation, depending on local expertise. Trials designed to evaluate whether surgical resection of tumor masses responding to imatinib is beneficial as an intervention before the development of resistance are under way. The effect of second-generation kinase inhibitors on clonally resistant nodules also warrants close examination. In summary, the resistant clonal nodule may be an important early clinical marker of acquired resistance to imatinib in patients with previously responding GISTs and warrants close scrutiny.

Acknowledgments

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References

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