

Resistance to Tyrosine Kinase Inhibitors in Gastrointestinal Stromal Tumors

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Abstract Gastrointestinal stromal tumors (GIST) are the most common type of sarcoma in the gastrointestinal tract. Surgery is the primary treatment modality, but many patients suffer disease recurrence or metastasis. Fortunately, the management of advanced GIST has been revolutionized by the use of small molecule kinase inhibitors that target the underlying pathogenetic mutant kinases found in the vast majority of cases. Approximately 85% of GISTs have oncogenic mutations in KIT, allowing for constitutive kinase activation that is responsible for cellular proliferation and survival. About 5 to 7% of GISTs have activating mutations of the homologous platelet-derived growth factor receptor alpha (PDGFRA) kinase. The progression-free and overall survival of patients with advanced disease is greatly improved by treatment with the kinase inhibitors imatinib and sunitinib. However, the emergence of drug-resistant tumor clones limits the long-term benefit of these drugs in most patients. Resistance to these kinase inhibitors is associated with distinctive clinical and molecular features, with the development of secondary mutations of the oncogenic kinase being the most common mechanism. We review the molecular basis of GIST response and/or resistance to TKIs, and discuss strategies to prevent and/or overcome drug resistance. These concepts are directly relevant to the development of targeted molecular therapy for other solid tumors. (Clin Cancer Res 2009;15(24):7510–8)

The implementation of tyrosine kinase inhibitor (TKI) therapy has revolutionized the treatment of gastrointestinal stromal tumors (GIST). Currently, imatinib is approved for first-line therapy and sunitinib is approved for imatinib-resistant GIST. Unfortunately, similar to the experience using TKIs to treat other cancers, the emergence of drug-resistant GIST is becoming a problem for many patients, and there is a clear need for more agents and other approaches to the treatment of advanced GIST (1–5). Here, we review current knowledge on the response of GISTs to TKI therapy and the mechanisms by which resistance develops. Alternative targets and therapeutic options for patients with imatinib + sunitinib-resistant GIST are discussed.

GIST: Overview and Molecular Biology

GISTs are mesenchymal tumors of the gastrointestinal tract characterized by their expression and thus positive staining

for KIT (CD 117) in approximately 95% of cases (6–9). Although KIT serves as a phenotypic marker for most GISTs, their underlying biology shows marked heterogeneity.

KIT is a 145-kD transmembrane tyrosine kinase that serves as the receptor for stem cell factor (Fig. 1). The binding of stem cell factor to KIT results in receptor homodimerization and resultant activation of tyrosine kinase activity and downstream intracellular signal transduction pathways, most notably the RAS-RAF-MAPK and PI3K-AKT-mTOR pathways (10–12). Approximately 85% of GISTs have oncogenic mutations in KIT, allowing constitutive kinase activation. The most commonly mutated region of KIT is exon 11, which encodes the juxtamembrane domain. Auto-inhibited KIT is stabilized by this domain, which inserts into the kinase-active site and disrupts formation of the activated structure (Figs. 1 and 2; ref. 13). In-frame deletions, insertions, or point mutations of this region disrupt this auto-inhibitory motif and allow ligand-independent receptor activation. Exon 11 mutations are found in approximately 70% of tumors (14–16). KIT mutations in the extracellular domain (exon 9) are most commonly associated with GISTs of the small bowel and occur in approximately 10 to 15% of cases. Less frequently, primary mutations in the kinase I domain (exon 13) or activation loop (exon 17) are found (Fig. 1; refs. 14–16).

Approximately 5 to 7% of GISTs harbor oncogenic mutations in the juxtamembrane domain (exon 12) or activation loop (exon 18) of platelet-derived growth factor receptor alpha (PDGFRA), a receptor tyrosine kinase that is highly homologous to KIT. PDGFRA mutations are mutually exclusive with KIT mutations, but activate

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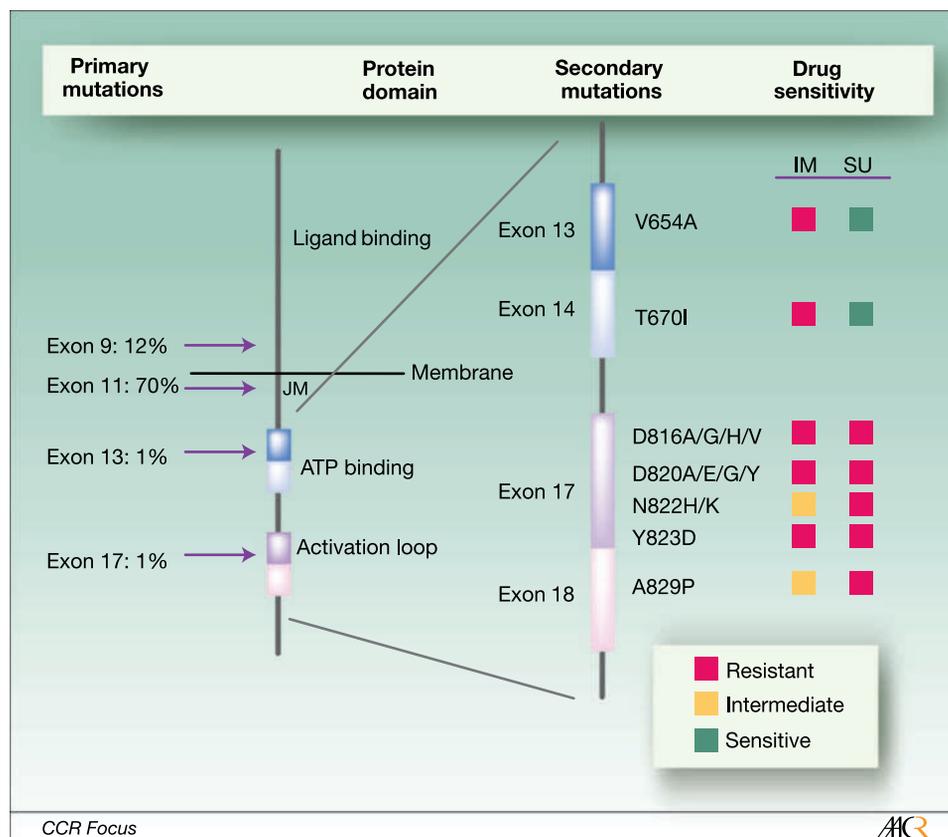


Fig. 1. Location and biochemical properties of secondary KIT kinase mutations in TKI-resistant GIST. The location of primary KIT kinase mutations is shown on the left-most stick figure. The protein domains are indicated to the left of this panel. The center of the figure has an exploded view of the kinase domain (exons 13-18). The relevant *KIT* exon locations are indicated on the figure. The codon location of drug resistance mutations is depicted to the right of the middle panel. The wild-type amino acid for the relevant codons is shown and reported amino acid substitution mutations are shown listed [for example wild-type valine (V) at codon 654 can be mutated to alanine (A) in imatinib-resistant GIST]. The potency of imatinib (IM) or sunitinib (SU) against the various drug resistance mutations is depicted by traffic-light colored boxes that are aligned with the mutations of interest. For example, the V654A mutation is biochemically resistant to imatinib (red light), but remains sensitive to sunitinib (green light). Notably, sunitinib is very potent against V654A and T670I mutations but has no significant activity against mutations of the activation loop (exons 17 and 18). Conversely, imatinib has minimal activity against V654A or T670I KIT mutations, but has variable potency against activation loop mutations (inactive against mutations of codons 816, 820, or 823, but intermediate potency against kinases with mutation of codons 822 or 829).

similar signal transduction pathways that support GIST oncogenesis (17). The remaining 10 to 15% of GISTs do not possess a *KIT* or *PDGFRA* mutation and are commonly termed "wild-type" GISTs.

During the past decade a wide variety of studies have helped delineate the central role of *KIT* and *PDGFRA* mutations in GIST biology. When expressed *in vitro*, the mutant forms of these kinases show constitutively activated signaling activity (18). In extracts of fresh-frozen GIST, the kinases are found to be phosphorylated, indicating *in vivo* activity (19). Mice engineered to express mutant forms of *KIT* form GIST-like tumors; in humans, *KIT* mutations are found in the earliest recognizable forms of GIST (20, 21). Finally, when GISTs become resistant to inhibition by imatinib, it is most frequently on the basis of acquired secondary mutations that directly interfere with drug activity. As discussed in more detail below, this observation indicates that most resistant GISTs are still "KIT-driven," which has implications for further therapy.

Approximately 1 to 2% of GISTs occur in the pediatric population and more than 85% of these tumors are wild-type despite expressing *KIT* at levels similar to adult GIST (22, 23). This sug-

gests distinct mechanisms of GIST oncogenesis between adult and pediatric GIST. GISTs associated with the nonfamilial syndrome Carney's triad are also negative for mutations in *KIT* or *PDGFRA*. The molecular basis of this syndrome (the association of gastric GIST, extra-adrenal paraganglioma, and pulmonary chondroma) is unknown (24). Rare patients have Carney-Stratakis or NF-1 syndromes as an underlying cause of their GIST (25-27).

Targeted Therapy Of GIST With Imatinib

Imatinib mesylate is a very effective agent for the treatment of metastatic or surgically unresectable GIST given its ability to selectively inhibit *KIT* and *PDGFRA*. Imatinib is a competitive inhibitor of ATP binding and blocks kinase enzymatic activity. Notably, imatinib can only bind to the inactive conformation of *KIT* (Fig. 2; ref. 13). As discussed below, this characteristic has significant implications for potential mechanisms for developing drug resistance. Phase I and II trials of imatinib in GIST reported partial response rates of 54% and 68%, respectively, with most remaining patients achieving stable disease

(28). In two large phase III studies comparing imatinib dose levels (400 mg per day versus 800 mg per day), the median progression-free survival (PFS) for either arm was approximately 20 months, and median overall survival was approximately 50 months (29, 30).

Analysis of these studies has revealed that imatinib response in GIST correlates with primary tumor genotype (15, 16, 31, 32). For example, the S0033 trial reported improved response and survival rates for patients with tumors harboring *KIT* exon 11 mutations, but there was no significant difference between patients with exon 9-mutant or wild-type tumors.

Imatinib resistance

Although the majority of GIST patients achieve clinical benefit when treated with imatinib, approximately 10% will progress within 3 to 6 months of initiating therapy. Such cases are regarded as showing primary resistance to treatment. An additional 40 to 50% of patients will go on to develop imatinib resistance within 2 years, after enjoying a partial response or at least disease stabilization during initial follow-up. These patients are classified as having delayed resistance.

Clinical presentation of imatinib resistance. In an effort to improve both early detection and treatment strategies for TKI-resistant GIST, investigators have analyzed patterns of GIST progression. Determination of response, stability, and progression in clinical trials for solid tumors has traditionally relied on the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (33). Interestingly, in approximately 50% of cases of delayed resistance, the initial sign of GIST progression is the development of an enhancing nodule within a previously responding

nonenhancing lesion on contrast-enhanced CT scans (Fig. 3; refs. 34, 35). Although not fulfilling RECIST criteria, most GIST experts would consider this to represent progressive disease despite stability in the overall size of the mass. The time between the detection of nodules and conventionally defined disease progression varies, but one study found a median of 5 months (34, 35).

Primary imatinib resistance. Primary resistance is observed in approximately 10% of patients (28–30, 36). Primary resistance has been observed with all genotypic subtypes of GIST; however, the tumors that are most likely to show primary resistance are those that are *KIT* and *PDGFRA* wild-type, those that have a *KIT* exon 9 mutation, and those that have a *PDGFRA* D842V substitution. The latter can be explained by inherent resistance of the D842V mutation to imatinib, as documented in several *in vitro* studies (15, 37). As is the case with *KIT*, imatinib can only bind to the inactive conformation of PDGFRA. The D842V mutation results in a change in the kinase activation loop that strongly tilts the protein conformation to favor the active conformation (Figs. 1 and 2). In patients with *KIT* exon 9-mutant tumors, inadequate dosing may account for some of the primary resistance observed. It seems that exon 9 mutations generate a kinase conformation that is less amenable to imatinib binding (16, 38). In patients lacking identifiable *PDGFRA* or *KIT* mutations, one potential mechanism for resistance is a mutation in an alternate signaling pathway. Recently, one group identified *BRAF* exon 15 activating mutations in four wild-type GISTs from both imatinib-naïve and -resistant patients (39). *KIT* and/or *PDGFRA* gene amplification has also been implicated as a potential mechanism for either primary

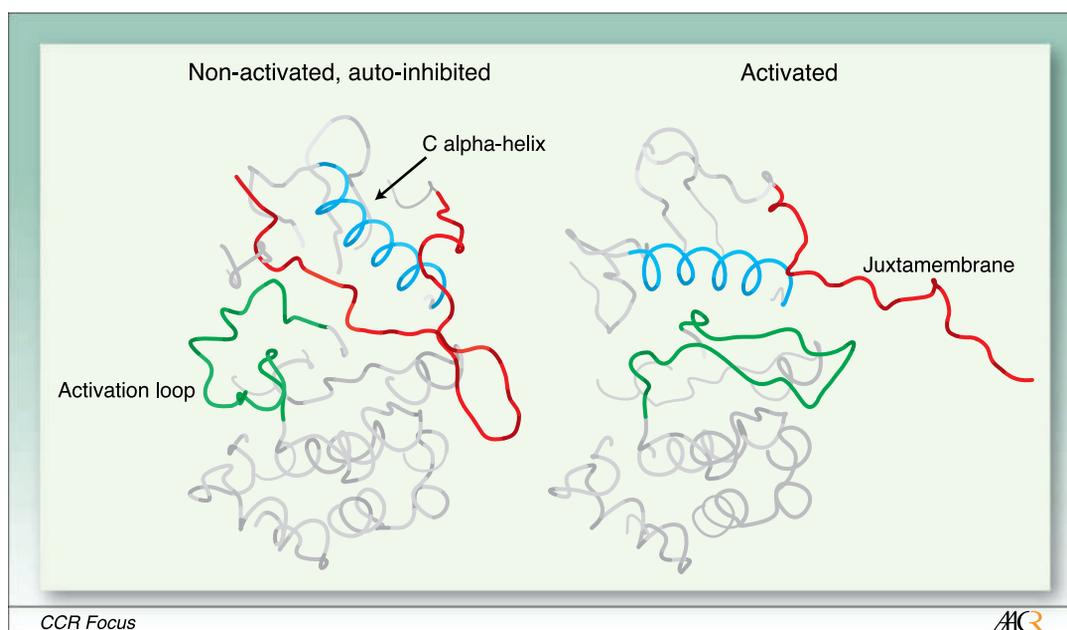
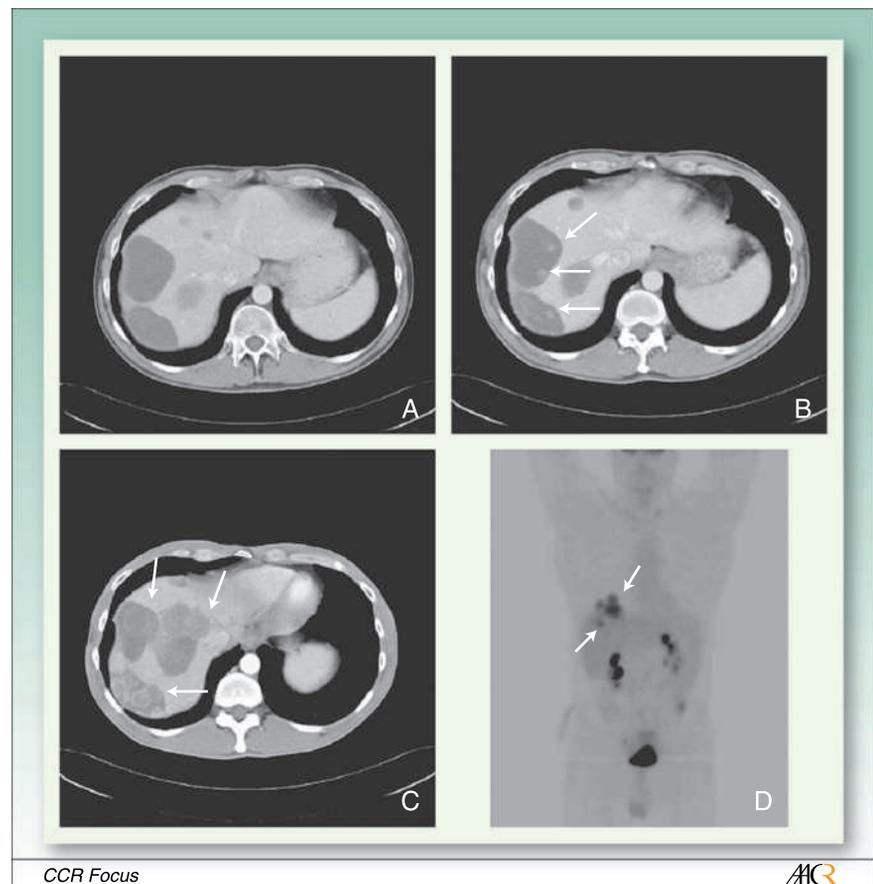


Fig. 2. Overview of the structural biology of KIT. The nonactivated (auto-inhibited) and activated forms of wild-type KIT are shown. Notably, the juxtamembrane domain (red), activation loop (green), and C α -helix (cyan) are oriented differently in the nonactivated and activated states. Tyrosyl-phosphorylation or mutation of the juxtamembrane domain result in a disordered juxtamembrane structure that no longer impedes the activation loop from moving into the active kinase conformation. Reproduced with permission from Gajiwala et al. (52).

Fig. 3. Development of multiple imatinib-resistant clonal nodules in a GIST patient. **A**, computer tomography (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 or characteristics of tumor masses. **C**, CT scan after 15 mo of imatinib. Note the growth of multiple resistant clonal nodules. **D**, 2-deoxy-2-¹⁸F]fluoro-D-glucose positron emission tomography (FDG-PET) scan after 15 mo of imatinib showing FDG uptake by the multiple resistant clonal nodules. Reproduced with permission from Fig. 2 in Desai et al. (34).



or delayed TKI resistance (40–42). Primary imatinib resistance is infrequently associated with the presence of secondary kinase mutations (43, 44).

Delayed imatinib resistance. Unlike primary imatinib resistance, delayed imatinib resistance most often is associated with the expansion of tumor clones with secondary *KIT* or *PDGFRA* mutations (42, 44–47). Analysis of tumors of patients who progressed on the phase II B2222 imatinib trial revealed that 67% of patients with delayed resistance had tumor clones with one or more secondary kinase mutations. All secondary *KIT* kinase mutations were found in GISTs with an underlying primary *KIT* mutation, and the only secondary *PDGFRA* mutation identified arose in a GIST with a primary *PDGFRA* mutation. The secondary *KIT* mutations involved either the ATP binding pocket of the kinase domain (exons 13 and 14) or the kinase activation loop (exons 17 and 18; Fig. 3). No secondary mutations were identified in post-imatinib samples that lacked a primary mutation (wild-type GISTs; ref. 43).

Analysis of specimens from 67 imatinib-resistant patients enrolled on the phase I and/or II sunitinib trial yielded secondary kinase mutations in 33 patients (49%; ref. 48). Notably, this analysis included patients with primary imatinib resistance, resulting in a lower percentage of patients with secondary mutations. Again, the secondary mutations clustered in the *KIT* ATP binding pocket or kinase activation loop. Secondary kinase mutations were significantly more common in

GISTs with primary *KIT* exon 11 mutations than those with exon 9 mutations (73% versus 19%). The underlying mechanism of imatinib resistance varies between the different sites of secondary kinase mutations. On the basis of a number of *in vitro* studies, secondary mutations involving the ATP binding pocket were found to directly inhibit imatinib binding, especially the T670I “gatekeeper” mutation (46, 49, 50). This mutation is homologous to the resistance mutations of the “gatekeeper” threonine residues in BCR-ABL (T315I) and epidermal growth factor receptor (EGFR; T790M; refs. 1, 3). Secondary mutations involving the *KIT* activation loop help stabilize the active conformation of *KIT* (Figs. 1 and 2; refs. 51, 52). As noted above, imatinib can only bind and inhibit the nonactivated (auto-inhibited) conformation of *KIT* (Figs. 1, 3, and 4). Thus, activation loop mutations indirectly induce imatinib resistance by shifting the equilibrium strongly in favor of the active conformation. In the case of chronic myeloid leukemia (CML), there is evidence that drug-resistant ABL kinase mutations may exist at low frequencies in untreated patients. Presumably, these pre-existing mutations are then selected for during TKI therapy (3). An analogous situation likely exists in the case of GIST, although this hypothesis has not yet been experimentally verified.

GIST cell lines derived from imatinib-resistant tumors have been analyzed *in vitro*. Cell lines with secondary *KIT* ATP binding pocket or kinase activation loop mutations remain

KIT-dependent as evidenced by decreased proliferation and increased apoptosis following inhibition of KIT activation by either KIT RNA interference (RNAi) knockdown, alternative KIT kinase inhibitors, or HSP90 inhibitors (Fig. 1; refs. 43, 48, 53).

In TKI-resistant CML, sampling blood and/or bone marrow typically reveals a single dominant clone or evidence of limited oligoclonal resistance (54). This result is presumably due to trafficking of resistant stem and/or progenitor cells and competition of different clones for available bone marrow niches. In contrast, solid tumor metastases represent distinct micro-environments, and there is little biological evidence for tumor to tumor migration of stem and/or progenitor cells. Not surprisingly, resistance in individual, anatomically separate GIST tumors has been shown to emerge independently and may use different molecular mechanisms (Fig. 5; refs. 34, 43, 44, 47). For example, Liegl and colleagues showed substantial interlesional heterogeneity of drug resistance mutations in patients treated with imatinib alone or imatinib followed by sunitinib. In this study, 83% of patients had secondary drug-resistant *KIT* mutations, and in 67% there were two to five different secondary mutations among separate metastases. Perhaps even more sobering was that 34% of the cases showed two different secondary *KIT* mutations within the same metastasis (40). This striking mutational heterogeneity is the reason why genotyping for resistance mutations is not recommended for routine clinical management, as a biopsy of one progressing lesion may not be representative of others. As discussed below, the heterogeneity of delayed resistance has important implications in regard to salvage therapies.

Other mechanisms of imatinib resistance. Other potential mechanisms of clinical resistance are currently being investigated. Some GISTs lacking secondary kinase mutations show genomic

amplification of *KIT* and/or become hemi- and/or homozygous for the primary *KIT* mutation by deleting the remaining wild-type *KIT* allele (40, 41). Interestingly, secondary *KIT* resistance mutations have not been found in *KIT/PDGFRFA* wild-type GISTs, or the more rare *KIT*-negative GISTs. The latter represent GISTs that lose *KIT* expression possibly because other oncogenic pathways are activated. For example, a *BRAF* V600E mutation was identified in an imatinib-resistant peritoneal nodule that no longer expressed *KIT* or *PDGFRA* (39). In another study, gene expression profiling of an imatinib-resistant cell line revealed overexpression of the receptor tyrosine kinase *AXL* and simultaneous down-regulation of *KIT* (55). Correspondingly, strong *AXL* expression was detected by immunohistochemistry in two imatinib-resistant patients whose tumors were *KIT* negative. *AXL* is known to regulate the same signaling pathways as *KIT*, but the mechanism of its regulation in GIST is unknown.

Focal adhesion kinase (*FAK*) may play a role in the survival of imatinib-resistant cells, as well. Sakurama and colleagues showed that an imatinib-resistant cell line with the *KIT* D820Y mutation maintained *FAK* and *AKT* activity, whereas in an imatinib-sensitive cell line with a *KIT* exon 11 mutation imatinib suppressed *FAK* and *AKT* activity. Inhibition of *FAK* activity with an inhibitor resulted in cell death *in vitro* and in mouse xenografts with the *KIT* D820Y mutation (56).

IGF1R amplification may represent another mechanism of imatinib resistance. It is overexpressed in GISTs lacking *KIT* and *PDGFRA* activating mutations and in pediatric GISTs, and its inhibition in GIST cell lines results in cell death regardless of *KIT* mutation status (57, 58).

In both CML and GIST, there is emerging evidence that patients with trough imatinib levels of <1,000 to 1,200 ng/ml may have inferior outcomes compared with patients with higher

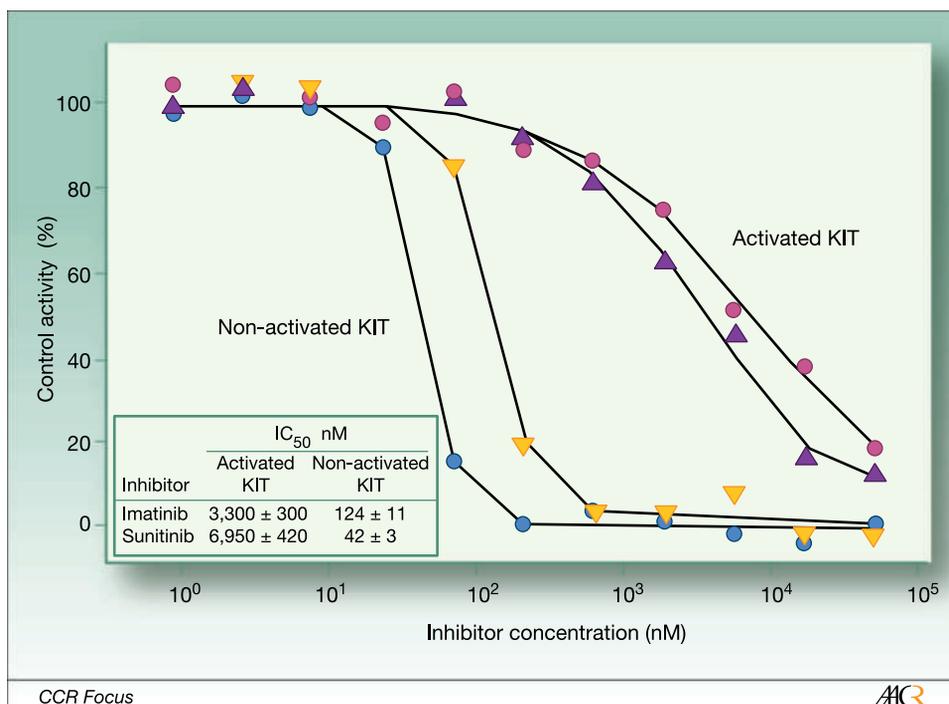
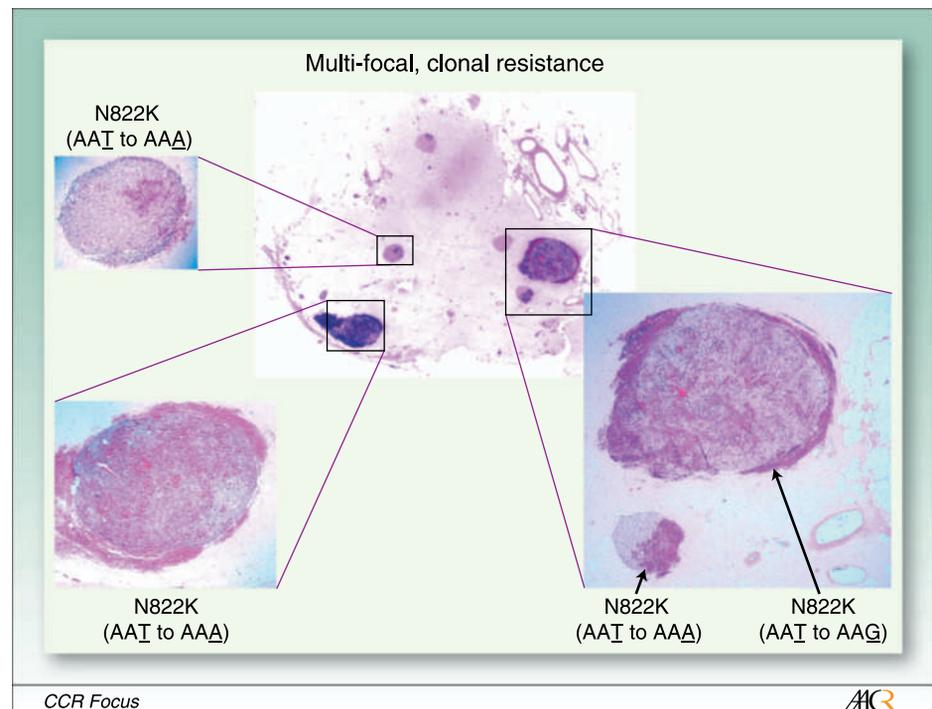


Fig. 4. Activity of sunitinib (circles) or imatinib (triangles) against nonactivated (auto-inhibited) and activated KIT kinase. In this context, nonactivated and activated designations refer to the protein conformations depicted in Fig. 1. Both drugs inhibit the nonactivated KIT kinase more effectively than activated kinase. Notably, the IC₅₀ for imatinib was 124 nM against nonactivated KIT and 3,300 nM for activated KIT. Likewise, the IC₅₀ for sunitinib 42 nM against nonactivated KIT and 6,950 nM for activated KIT. Reproduced with permission from Gajiwala et al. (52).

Fig. 5. Histologic and molecular correlates of multifocal clonal resistance. A GIST lesion was surgically removed from a patient who responded to imatinib. The lesion was largely acellular, but harbored four microscopic foci of viable tumor, each of which had a secondary mutation in *KIT* exon 17 (N822K). Interestingly, there was mutational heterogeneity in the N822K mutations evident at the nucleotide level (AAT → AAA in three lesions, AAT → AAG in top right lesion). It is presumed that each of these foci represents an independent clone of resistant cells. Not depicted here is an additional surgically resected lesion that had a different *KIT* secondary mutation (Y823D).



trough levels. Notably, in a phase II study of imatinib for metastatic GIST, the median time to progression was 11.3 months for patients in the lowest plasma trough quartile (<1,110 ng/mL) compared with more than 30 months for patients with trough drug levels in the higher quartiles ($P = 0.0029$; ref. 59). Imatinib blood level testing is now clinically available and may be useful in optimizing imatinib dosing for individual patients. This strategy will be tested in upcoming clinical studies to optimize tumor response and attempt to delay the emergence of clinical drug resistance.

Treatment of patients with imatinib-resistant GIST

There are an increasing number of options for the management of progressive disease. If a patient manifests global or widespread progression on imatinib, it is recommended that he or she continue kinase inhibition by increasing imatinib dose as tolerated (60). Notably, in the S0033 phase III study, 33% of patients who progressed on 400 mg and crossed over to 800 mg achieved responses and/or stable disease (29). Dose escalation may overcome resistance resulting from decreased imatinib binding affinity (as seen *in vitro* with exon 9 mutations or secondary mutations), *KIT* amplification, or lower plasma drug levels from altered pharmacokinetics (43, 48, 59). For patients in whom a dose increase is ineffective or not tolerated, imatinib should be discontinued and sunitinib should be started.

Targeted Therapy of GIST with Sunitinib

Sunitinib is an inhibitor of KIT, PDGFRs, VEGFR-1, 2, 3, FLT3, and RET. After sunitinib activity was shown in phase I and/or II clinical trials (61, 62), a phase III placebo-controlled

trial was done for imatinib-resistant or -intolerant patients (63). A highly significant improvement in PFS was seen; patients treated with sunitinib had a median PFS of 24.1 weeks compared with 6 weeks for those on placebo. Partial response was seen in 7% of sunitinib patients with 58% achieving stable disease, whereas there were no responses in the placebo group. These data led to approval of sunitinib as second-line therapy for GIST (64). The above results were obtained using a 6-week cycle schedule consisting of 50 mg per day \times 4 weeks, followed by a 2-week rest period. In a more recent phase II study of continuous daily dosing of 37.5 mg in imatinib-resistant or -intolerant patients, median PFS and overall survival were 34 and 107 weeks, respectively (65).

Sunitinib resistance

Sunitinib is approved for the treatment of advanced GIST after imatinib resistance or intolerance. The response to second-line sunitinib correlates with the primary (pre-imatinib) tumor mutation status. Median PFS and overall survival were significantly longer for patients with primary *KIT* exon 9 mutations or a wild-type genotype than for those with *KIT* exon 11 mutations. In an analysis of post-imatinib specimens, among all patients with pre-imatinib *KIT* mutations, the median PFS and overall survival with sunitinib was significantly longer for the patients who had secondary *KIT* exon 13 or 14 mutations than for those with secondary exon 17 or 18 mutations. These results correlate with *in vitro* studies showing that sunitinib potently inhibits the phosphorylation of *KIT* double mutants in which the secondary mutation occurs in the drug-ATP binding pocket, but has little activity versus *KIT* double mutants with secondary mutations in the activation loop (Figs. 1 and 2; ref. 48). Similar to imatinib, sunitinib can only

inhibit the inactive form of KIT (Figs. 1, 2, and 4). In comparing the spectrum of activity of imatinib and sunitinib, one can understand the molecular basis of the mixed clinical responses that are often seen when using sunitinib to treat imatinib-resistant tumors: compared with imatinib, sunitinib has increased potency against imatinib-resistant ATP binding pocket mutations but inferior potency against activation loop mutations (Fig. 1). Other than known imatinib-resistant KIT activation loop mutations, no unique mechanisms of sunitinib-resistance have yet been identified.

Other Tyrosine Kinase Inhibitors that Inhibit KIT and PDGFR

Studies are ongoing to identify additional therapeutic options for those resistant to imatinib and sunitinib. A recent phase II trial reported a response rate of 10% and stable disease rate of 19% when imatinib- and sunitinib-resistant patients are treated with the TKI nilotinib (66). Other TKIs such as dasatinib also show some potentially useful clinical activity (67). Preliminary data on sorafenib from a phase II trial were presented at the 2008 annual ASCO meeting. In imatinib- and/or sunitinib-resistant patients, 76% achieved either partial remission or stable disease (68). Additional data on sorafenib presented at ASCO 2009 showed a 19% response rate with 44% disease stabilization as a fourth-line therapy for patients who had undergone sequential treatment with imatinib, sunitinib, and nilotinib (69).

Local Intervention for TKI-Resistant GIST

For limited progressive disease, surgical resection may be considered if feasible, with continuation of TKI therapy. In one series, surgical debulking combined with TKI therapy resulted in a median PFS of 7.7 months and overall survival of 29.8 months (70). Patient selection is key in identifying patients who are most likely to benefit from surgery. Those with very limited disease progression (one to three lesions) have the best outcomes, whereas those with widespread progression do not seem to benefit from surgical intervention (70, 71). The use of other localized modalities for managing progression has been explored in small studies, including radio frequency ablation and arterial embolization (72–74).

Strategies to Overcome and/or Prevent Resistance

Imatinib was recently approved for adjuvant use in patients at risk for tumor recurrence after primary resection (75). Prolongation of GIST remission through adjuvant therapy is one potential way to prevent resistance, although the alternative possibility, that adjuvant treatment could lead to earlier emergence of drug resistance, has yet to be formally excluded. It is possible that combinations of broad-spectrum KIT and PDGFRA kinase inhibitors could suppress a greater number of tumor clones and provide even longer remissions. The greatest potential advance in KIT TKI therapy would be the clinical development of kinase inhibitors that effectively target the activated KIT conformation or

both the activated and nonactivated (auto-inhibited) conformations (Figs. 1, 2, and 4; ref. 76). It is possible that a combination of inhibitors that target both the active and inactive kinase conformations would yield the best clinical results.

Most individuals with unresectable or metastatic GIST respond to imatinib, with the GIST tumors remaining stable under treatment for several years after achieving an initial clinical response. Imatinib has both pro-apoptotic and antiproliferative effects against GIST, but most individuals have surviving quiescent GIST cells during imatinib therapy (77). It is therefore critical to identify new therapies that can kill these surviving cells. For example, the addition of PI3-K inhibitors to imatinib could maximize inhibition of GIST cell survival pathways; although not all PI3-K inhibitors are known to induce substantial apoptosis (78). As with CML, eradication of these quiescent cells will be required for medical cure of advanced GIST (79).

As noted above, in many cases TKI-resistant GIST remains largely, if not completely, dependent on KIT activation and downstream signaling for cellular proliferation and/or survival. If kinase activation cannot be blocked by small molecule kinase inhibitors, then alternative approaches to inhibit KIT might still prove effective. Studies of GIST cell lines have shown that HSP90 inhibitors have significant activity even against cells harboring secondary imatinib-resistance mutations, presumably by decreasing total cellular KIT expression (53). KIT is a client molecule for the molecular chaperone HSP90, and doubly mutant forms of KIT may be even more HSP90 dependent. Phase I data for an HSP90 inhibitor in the treatment of TKI-resistant GIST were presented at ASCO 2008 and showed promising activity (80). Unfortunately, a phase III trial of this drug was recently closed because of toxicity. However, orally bioavailable HSP90 inhibitors are now entering early phase trials and offer hope for this potential salvage pathway.

Other potential approaches to suppressing GIST growth include RNAi knockdown of KIT, inhibitors of KIT transcription (e.g., flavopiridol, histone deacetylase inhibitors), and/or monoclonal antibodies directed against the KIT extracellular domain (analogous to therapeutic antibodies to HER2 and EGFR; refs. 43, 53, 81–83). In addition to inhibition of the dominant KIT (or PDGFRA) oncoprotein, blockade of downstream signaling pathways may exert an inhibitory effect on GIST proliferation. As noted above, this strategy could be used to maximize the effect of upstream kinase inhibitors or used in isolation. Notably, the PI3-kinase and MEK/MAPK pathways are strongly activated in most GISTs, and are partly dependent on KIT/PDGFR activation (78, 84, 85). Recently, protein kinase C theta (PKC θ) has been identified as a novel therapeutic target in GIST. PKC θ is highly expressed in GISTs, but very few normal cells express large amounts of this enzyme (86). In GIST cell lines, KIT expression is PKC θ -dependent; RNAi knockdown of PKC θ decreases KIT gene transcription, and also decreases mutant KIT expression (87). Although the precise mechanism for KIT regulation by PKC θ remains unclear, PKC θ binds to KIT and KIT regulates phosphorylation of PKC θ (84). Drugs against PKC θ would be expected to have acceptable toxicity, and would not likely be affected by the presence of imatinib-resistant KIT mutations.

Conclusion

In the past decade, GIST has emerged as paradigm for development of targeted molecular therapies against “oncogene addicted” cancer cells (88). Unfortunately, monotherapy with TKIs has been associated with the eventual emergence of drug-resistant clones, which typically have associated secondary mutations of the oncogenic KIT (or PDGFRA) kinases that reduce TKI potency. Structural biology and biochemical studies have revealed the molecular basis of TKI-resistance and have led to the development of new strategies for preventing and/or circumventing such resistance. As new kinase inhibitors enter

the clinical arena, it will be necessary to prospectively study drug resistance to these agents. The continued interplay of drug development, basic biology, and translational studies should lead to new treatment approaches that will further improve clinical outcomes for GIST patients.

Disclosure of Potential Conflicts of Interest

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