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SUPPLEMENT (SPECIAL ISSUE)

Mechanisms of resistance to imatinib and sunitinib in gastrointestinal stromal tumor

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Abstract Gastrointestinal stromal tumor (GIST), the most common mesenchymal neoplasm of the GI tract and one of the most common sarcomas, is dependent on the expression of the mutated KIT or platelet-derived growth factor receptor in most cases. Imatinib mesylate potently abrogates the effects of KIT signaling by directly binding into the ATP-binding pocket of the kinase. It is becoming increasingly apparent that the binding affinity of imatinib for the receptor is dependent on the type and location of mutation. Within KIT, patients whose tumor has an exon 9 mutation are treated by many clinicians with higher doses of imatinib than those patients with mutations within exon 11. Additionally, there are over 400 unique mutations within exon 11 that may have distinctly different binding affinity for imatinib as well as other kinases. Secondary KIT mutations generally occur at a codon where imatinib binds resulting in KIT reactivation and resistance. Sunitinib malate, a second-generation KIT inhibitor is active in imatinib-resistant disease and is FDA-approved for use in this setting. In this review, we describe the biology of the genes and gene mutations responsible for GIST and discuss known and potential clinical implications.

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Introduction

Gastrointestinal stromal tumors (GIST) represent an oncogenic disorder of mesenchymal origin and involve dependence upon an over-expressed and structurally mutated tyrosine kinase receptor. Most commonly, this tyrosine kinase receptor is KIT and of lesser proportion, platelet-derived growth factor receptor-alpha (PDGFR-α) [1, 2]. Originating from the interstitial cells of Cajal, these tumors occupy almost any submucosal region of the alimentary tract, though the most common were the stomach and small intestine [3, 4]. Prior to the discovery of KIT over-expression by immunohistochemistry, GISTs were commonly diagnosed as leiomyosarcomas (LMSs) of the gastrointestinal tract [5]. Whereas anthracycline-based regimens were of therapeutic benefit to those with LMS, GIST is known to be resistant to these chemotherapeutic combinations. This fact was evident in previous trials with response rates rarely exceeding 5% [6].

Fortunately, understanding the molecular underpinnings of GIST coupled with a "druggable" target has resulted in an exemplary example of targeted therapy for cancer patients. Mutations within the KIT gene result in constitutive activation of this tyrosine kinase receptor, leading to unopposed downstream signaling. This activation is ligand-independent and occurs because KIT mutations most commonly affect the juxtamembrane domain (exon 11), an auto-inhibitory region that maintains an "off" conformation in the absence of stem cell factor, the KIT ligand. These mutations alter the conformation of this domain favoring the activated structure. Imatinib mesylate abrogates the effects

of KIT signaling by direct binding of the agent onto the ATP-binding site located within the juxtamembrane domain of Kit [7]. Importantly, the affinity of imatinib to this region depends, in part, on the type of mutation (deletion, point mutation, etc.) and on the codons affected. Whereas imatinib has proven efficacy in GIST, in which most tumors harbor deletions within exon 11, most KIT-expressing mucosal melanomas contain point mutations within exon 11 [8]. The net result is increased apoptosis, senescence, and autophagy. Molecular effects of imatinib are noted within hours of initiation and result in histologic changes, alteration in tumor glucose metabolism, and vascular modifications [9–11].

On a clinical level, tyrosine kinase receptor inhibitors (TKIs) have resulted in an improvement in disease-free survival for patients following surgical resection of their primary tumors and increased response rates and survival for patients with metastatic disease [9, 12, 13]. Unfortunately, most patients will eventually develop resistance to imatinib by several potential mechanisms such as acquisition of secondary mutations within the *KIT* gene, *KIT* gene amplification, loss of the wild-type allele, or inadequate imatinib plasma levels. Secondary *KIT* mutations generally occur in one of the kinase domains of the receptor and, therefore, abrogate imatinib binding to the KIT receptor. Concomitant medications such as St. John's Wort may increase the rate of imatinib metabolism reducing plasma levels. Sunitinib malate, a multikinase receptor inhibitor (including c-Kit), is active in imatinib-resistant disease and is FDA-approved for use in this setting [14]. Despite a superior increase in time to tumor progression with sunitinib versus placebo (27.3 vs. 6.4 weeks, $P < 0.0001$), most patients will become resistant to sunitinib, leaving few options for patients in this situation [14].

In this review, our goal is to describe the biology of the genes and gene mutations responsible for GIST, the clinical implications associated with these genetic aberrations, and to discuss therapeutic strategies. It is apparent that our knowledge of the biological basis of GIST is not only driving our treatment of the disease, but this paradigm has led to increased survival for our patients.

Spectrum of KIT and PDGFR mutations in GIST

As noted in this issue, KIT and PDGFR mutations are the oncogenic driving force in the tumorigenesis of GIST. It is estimated that 80–85% of patients with GIST have an activating mutation in *KIT,* while another 5–7% have a mutation in *PDGFRA*. In our institutional experience, we have found that 73% of GIST patients harbor mutations in *KIT* exon 11, 10% in *KIT* exon 9, 3% in *KIT* exon 13, 1% in *KIT* exon 17, 3% in *PDGFRA,* and 10% have been found to be wild type (Fig. 1a). The slightly different frequency distribution from our institution to that of other publications may be due to our patient population or referral bias. Moreover, we have found over 150 different mutations in KIT exon 11 reflecting extreme diversity in this region. KIT exon 11 mutations may arise as highly variable point mutations, deletions, or insertions that are asymmetrically distributed across the N- to C-terminal regions of KIT exon 11 (Fig. 1b). There is emerging data discussed subsequently that these different mutations within the *KIT* gene may portend different biology and may have different therapeutic implications.

Mechanisms of resistance to imatinib and sunitinib

Resistance to imatinib, and now sunitinib, represents an issue of increasing concern and a focus of research efforts as many patients with gastrointestinal stromal tumors (GISTs) eventually progress under continued targeted treatment (Fig. 2).

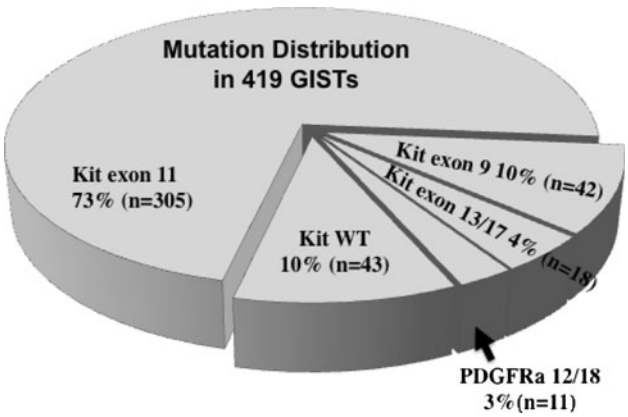

Fig. 1 Distribution of KIT and PDGFR mutation in 419 consecutive patients at MD Anderson Cancer Center

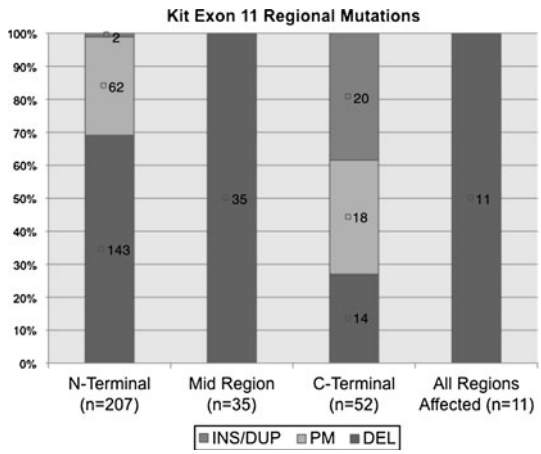

Fig. 2 Distribution and type of mutation in KIT exon 11 for 305 consecutive patients at MD Anderson Cancer Center

Resistance can be divided into primary resistance, or early progression, and secondary/delayed resistance, or late progression. The reported time intervals for early progression vary depending on the study, typically from 3 to 6 months [15]. In general, the tumor continues to progress despite initial exposure to imatinib. This can be detected early in disease course using various imaging modalities as response to imatinib is usually rapid and dramatic. While in secondary/delayed resistance, or late progression, the tumors initially respond to treatment but then re-activate following a latency period [15].

Primary resistance

Of patients with GISTs, 10–15% fail to respond on their initial exposure to imanitib [16–18]. By far, the most commonly reported cause of primary resistance to imatinib is due to the tumor harboring mutations in the molecular target of the drug. Patients with tumors possessing wild-type *KIT* and *PDGFRA* genotypes or those with *KIT* mutations in exon 9 or the *PDGFRA* point mutation D842 V respond less favorably than those with tumors with *KIT* exon 11 mutations [13, 17–19]. In one study, which averaged the results of North American, European, and Asian trials, approximately 71% of patients with tumors with *KIT* exon 11 mutations responded to imatinib with a 5% risk of developing early progressive disease. In contrast, 38% of patients with tumors harboring mutations in *KIT* exon 9 and 28% of patients with tumors harboring wild-type *KIT* and *PDGFRA* genotypes responded to imatinib therapy. Both groups also carry an increased risk of primary resistance (16 and 23%, respectively) [20]. The resistance to exon is relative, as much of this resistance is overcome by increasing the dose of imatinib.

The majority of patients with tumors containing *PDGFRA* mutations fare even worse with imatinib. Approximately 5–7% of patients with GISTs harbor mutations involving *PDGFRA*. These tumors are more likely to arise in the stomach and show epithelioid morphology to be *KIT* negative by immunohistochemical studies. The most common *PDGFRA* mutation (approximately 60% in one study) involves a point mutation at exon 18 resulting in D842 V [2, 21, 22]. Both in vitro and patient studies have demonstrated that tumors with D842 V mutations are virtually completely resistant to imatinib therapy [22–26]. This mutation results in a gain-of-function [23] that favors the activated conformation of *PDGFRA*, making it less susceptible to imatinib inhibition [18]. Despite this, it is equally important to recognize that approximately 30% of patients with GISTs harboring *PDGFRA* mutations will still be susceptible to treatment. Thus, patients with tumors containing *PDGFRA* mutations should not be universally denied imatinib therapy. Some of these patients may have in fact accounted for the positive response previously seen in *KIT* wild-type tumors, attesting to the importance of complete primary mutation analysis [2, 21].

KIT amplification may also play a role in primary imatinib resistance, but this finding has not been found in all studies [27–30]. Low levels of KIT expression as detected by immunohistochemistry does not correlate with imatinib resistance or inferior survival [31]. Involvement of other KIT-independent pathways has also been described. V600E mutations in *BRAF* exon 15, seen in other tumors including melanomas and colonic adenocarcinomas, have been identified in tumors from patients that have wild-type *KIT/PDGFRA* genotypes [32]. These tumors were noted to occur in the small intestine and in women. This finding suggests that alterations in the *RAS/MEK/ERK* pathway, one of the major downstream *KIT*-signaling pathways, may explain imatinib resistance in a small number of these tumors. Insulin-like growth factor 1 receptor was also found to be overexpressed in wild-type *KIT/PDGFRA* genotypes and is particular to young patients [33–35]. Finally, gene expression studies have found that imatinib-responsive GISTs have significant increase in insulin-like growth factor receptor–binding protein-3 as well as a decrease in expression of various genes including a group of genes encoding *KRAB/ZNF* repressors [36]. Further studies need to be done to confirm the significance of these findings to the development of resistance in GISTs.

Secondary resistance

Within 12 to 36 months, approximately 50–70% patients with GISTs will progress on imatinib therapy [16, 37]. The most common cause of secondary resistance (50–80%) is a second mutation involving the same allele as the initial mutation, a phenomenon which has not been documented in tumors with primary resistance [30, 38]. Multiple clones with different secondary mutations have been reported both within the same nodule and in different tumor nodules exposed to imatinib therapy, attesting to the genetic heterogeneity in advanced disease [12, 39–43]. This also has lead some to question the clinical utility of resistance testing in the setting of inhibition therapy with a single agent [18]. It is assumed that the emergence of a second mutation is due to selection of a pre-existing uncommon event in the tumor, though conclusive proof of this notion is lacking. Interestingly, secondary mutations are most often seen in patients with tumors containing *KIT* exon 11 mutations, which are initially the most responsive to imatinib therapy [30, 41]. This finding is compatible with the selection theory of resistance. However, given the great variety of mutations seen in the *KIT* gene in GIST, there may be a source of genetic instability in this gene that provides fodder for selection by the targeted therapy. Larger tumor size, tumors

outside the stomach, high baseline granulocyte count, and low imatinib dose have also been associated with late progression [44].

Secondary, or resistance associated, mutations in *KIT* primarily involve exons 13 and 17 and usually alter single amino acids in the first and second tyrosine kinase domains where imatinib binds and renders the catalytic site insensitive to inhibition [38, 45]. Such mutations in *KIT* exons are very uncommon as primary mutations [30]. A list of secondary mutations is shown in Table 1. These mutations are missense, occur in the same allele as the primary mutation (*cis*-position) [45], and either involve the activation "A"-loop (primarily exon 17) or the ATP-binding domain (primarily exon 13 and sometimes 14) of the tyrosine kinase [20]. These mutations either result in a shift to the active conformation of the receptor or block the binding of imatinib. Both imatinib and sunitinib preferentially bind to the inactive form of the enzyme. Mutations involving exon 17 including D816H/V result in the stabilization of the active conformation of the tyrosine kinase, which reduces the effectiveness of imatinib [20, 46]. Mutations involving KIT exon 13 V654A results in structural changes causing decreased affinity for imatinib to KIT by interfering with drug binding to the ATP active site [38, 47–49]. Mutations involving residue T670 in KIT exon 14 also result in blockage of the imatinib-binding site due to alteration of the gatekeeper threonine of the ATP-binding domain [48, 50].

Other proposed *KIT*-related resistance mechanisms include *KIT* amplification that can result in increased amounts of the kinase [27, 43]. Loss of heterozygosity of the normal wild-type allele has also been reported in metastatic nodules and resistant disease and possibly may also play a role in the development of resistance [30, 51]. However, these findings require further investigation.

Table 1 Summary of resistance-associated mutations in *KIT* and *PDGFRA*

Exons	Mutation	References
KIT Exon 17	D716 N	[29]
	C809G	[39, 40, 42, 45]
	D816G/H/E	[40–43, 45, 59, 73]
	D820Y/E/G/H/N/V	[29, 30, 41, 43, 45, 74–76]
	N822 K/Y	[29, 30, 39–43, 45, 76]
	Y823D	[30, 40–43, 45, 77, 78]
	A829P	[43, 45]
	Arp-Asp 815–816 del	[73]
KIT Exons 16 and 17	K786 N + D816H	[45]
KIT Exon 13	V654A	[27–30, 38, 40–43, 45, 76, 79–81]
	Insertion 643 nucleotide A frameshift	[76]
KIT Exon 14	T670I/E	[27–30, 40, 41, 45, 82]
	S709F	[41]
	H687Y	[76]
KIT Exon 11	V559A	[76]
PDGFRA Exon18	D842 V	[29, 40, 76]
PDGFRA Exon 14	H687Y	[76]

Mechanisms of resistance not involving secondary mutation

Heterologous rhabdomyosarcomatous transformation has been rarely reported to occur in patients and corresponding to resistance to tyrosine kinase therapy. These tumors lacked secondary mutations indicating that alternative mechanisms may be involved in this form of resistance [52]. Imatinib has been shown to be a substrate for P-glycoprotein, multi-drug resistance proteins (MDR), typically involved in tumor drug transport [53], and breast cancer resistance protein (BCRP)/ABCG2, a protein implicated in drug transport in the gut epithelium [54]. Increased expression of these proteins could result in decreased drug levels. Finally, other tyrosine kinases may also be involved. In vitro studies have identified overexpression of AXL, another oncogenic tyrosine kinase, in imatinib-resistant cell lines where KIT expression is downregulated. It is also found to be present in imatinib-resistant tumors by immunohistochemical studies [55]. Focal adhesion kinase, a non-receptor tyrosine kinase associated with invasion and metastasis in other tumors, has also been reported to be expressed in imatinib-resistant cell lines. Therefore, these tyrosine kinases may play a role in tumor survival in imatinib-resistant clones [56]. Promising data with heat shock protein 90 (HSP90) inhibitors on imatinib-resistant GISTs and emerging data on histone deacetylase inhibitors suggest other factors are involved in resistance including the stabilization of KIT by HSP90 [14, 57]. Studies are ongoing.

Sunitnib resistance

Sunitinib is currently being used as second-line therapy for the treatment of GISTs when imatinib fails or drug intolerance is encountered [58]. Patients with mutations in exon 9 and wild-type *KIT* genotype as well as patients with secondary mutations in exons 13 or 14, including V654A and T670I, have a more favorable response [59, 60]. As with imatinib, resistance has recently been documented in patients with prolonged exposure to sunatinib. The most susceptible sites identified in in vitro studies involve mutations to activation loop residues D816 and D820, which can

also be seen in resistance to imatinib [61, 62]. Similar to imatinib, sunitinib preferentially binds to the inactivate form of KIT. Mutations at D816 results in auto-activation and favors an activated enzyme confirmation that would be resistant to sunitinib inhibition [46, 63] (Table 2).

Inadequate steady-state trough imatinib plasma level as a mechanism of progression

The management of GIST patients is continuing to improve upon continued investigation into tyrosine kinase inhibitor resistance mechanisms and development of new therapeutic agents. The next era of therapy for patients with advanced GIST will be to continue to improve outcomes by optimizing management approaches. There may be opportunities to maximize the benefit of the current approved treatments in individual patients. Since imatinib is an oral therapy, the steady-state plasma trough level may be affected by absorption, concomitant medications, and adherence to therapy. Therefore, one approach to maximize therapy is to measure steady-state plasma imatinib trough levels and increase the dose for patients with low levels. This approach is discussed in detail in the article by George and Trent in this issue.

Briefly, factors that may adversely affect adequate imatinib steady-state plasma level include patient characteristics such as allelic variants of imatinib-metabolizing enzymes (ATP-binding cassette proteins and Cytochrome P450 isoenzymes) [64], poor absorption of imatinib (history of extensive gastric or small bowel resection, concomitant medications, emesis), patient physical characteristics (age, weight) [65], and factors in patient plasma that may bind imatinib (hemoglobin, albumin, alpha glycoprotein) [65] and poor adherence to therapy. In addition to imatinib steady-state plasma trough levels, other factors may influence intracellular concentrations of imatinib such as the cellular transporter protein OCT-1.

Recent reports have found that there may be predictive value in the assessment of imatinib plasma levels in terms of clinical outcomes. The B2222 study randomized patients with metastatic GIST to imatinib 400 mg/day or 600 mg/day and measured imatinib steady-state plasma trough level on day 29. Patients in the lowest imatinib quartile (<1,100 ng/mL) had a significantly shorter time to progression (11.3 months) when compared to patients in the upper three quartiles (30.6 months, $P = 0.0029$) [66].

Although purely speculative, the management of GIST patients with tyrosine kinase inhibitors has analogy to the treatment of an infection with antibiotics (i.e, vancomycin) such that a specific minimum steady-state plasma concentration of the inhibitor is required to abrogate an enzyme and kill the organism or cancer cell. Thus, it is appealing to hypothesize that individualized imatinib dosing rather than a fixed-dose schedule may lead to better patient outcomes with less toxicity. This is the subject of the prospective, randomized phase II study of imatinib dosing based on steady-state plasma trough concentrations described in the article by George and Trent of this issue.

Therapeutic implications for KIT primary and resistance mutations

Mutation status of the *kit* or *PDGFR-alpha* gene in GIST has emerged as a prognostic factor and predictor of imatinib response. Patients with GISTs harboring exon 11 mutations, specifically missense mutations, appear to realize the greatest benefit from imatinib [67]. In contrast, patients with tumors harboring kit exon 9, 13, or 17 mutations appear to be less sensitive to imatinib in general [10, 68].

Patients with *kit* exon 9 mutation within their GIST appear to benefit from higher doses of imatinib. Data to support this statement come from sister studies that were performed in North America (intergroup study S0033) [16] and Europe with Australasia (EORTC trial 62005) [37]. Both studies compared 400 mg with 800 mg of imatinib daily with provisions to cross-over to 800 mg if a patient progressed on the 400 mg daily. Comprehensive *kit* mutation analysis was performed on 377 of the patients recruited into the EORTC 62005 study. This analysis led to the observation that exon 9 mutation resulted in inferior objective rates and duration of response for patients treated with imatinib such that the risk of progression was increased by 171% ($P < 0.0001$) and the risk of death by 190% ($P < 0.0001$) when compared to those patients whose tumor encodes an exon 11 mutation [69]. Importantly, patients with *KIT* exon 9 mutation who were treated with imatinib at 800 mg daily had a statistically superior median PFS ($P = 0.0013$) compared to those patients treated with 400 mg daily. Moreover, large deletions in exon 11 resulted in inferior median progression-free survival of patients treated with imatinib. The GIST meta-analysis combined data of 1,640 patients from EORTC 62005 and North American S0033 showed a benefit for the higher dose in *KIT* exon 9 mutant disease ($P = 0.017$) [70]. There was no difference in overall survival for the population, which was likely a result of the cross-over design of the trial that allowed patients who were randomized to imatinib 400 mg to cross-over to 800 mg per day at the time of disease progression.

Although GIST patients harboring *KIT* exon 13 mutation at codon 642 appear to benefit from imatinib therapy, mutation at codon 654 of the same exon within the *KIT* gene is associated with resistance and poor rates of survival [71]. Thus, the phenotype that results from mutation of these

Table 2 Clinical correlations of KIT and PDGFR mutation

Primary Gene/Exon	Site of common gene mutations	Clinicopathologic observation	Author recommendation	NCCN and ESMO recommendations
KIT Exon 9	AY502-3ins	Primary resistance despite in vitro activity; Benefit with imatinib at 800 mg/day; activity noted with sunitinib	Initiate imatinib at 400 mg/day and consider dose escalation to 800 mg/day or the highest dose tolerated; imatinib dose escalation or sunitinib 37.5 mg/day at progression	Initiate imatinib at 400 mg/day but may benefit from 800 mg/day
KIT Exon 11	Codons 550–580	Most common mutation; Most sensitive (in vitro & in vivo) to imatinib at 400 mg/day	Initiate imatinib at 400 mg/day; imatinib dose escalation or sunitinib 37.5 mg/day at progression	Initiate imatinib at 400 mg/day
KIT Exon 13	K642E	Sensitive to imatinib	Initiate imatinib at 400 mg/day; imatinib dose escalation or sunitinib 37.5 mg/day at progression	Initiate imatinib at 400 mg/day (no specific recommendation)
KIT Exon 17		Less sensitivity to imatinib	Initiate imatinib at 400 mg/day; consider a clinical trial at progression	Initiate imatinib at 400 mg/day (no specific recommendation)
KIT WT	N/A	Less in vivo sensitivity to imatinib; IGF1R amplification; subset with B-Raf V600E mutations	Initiate imatinib at 400 mg/day; consider sunitinib or clinical trial of IGF-1R inhibitor or B-Raf inhibitor (if B-Raf mutant) at progression	Initiate imatinib at 400 mg/day (no specific recommendation)
PDGFRA Exon 12	V561D	In vitro sensitivity to imatinib & nilotinib; More in vitro sensitivity to PKC412	Initiate imatinib at 400 mg/day	Initiate imatinib at 400 mg/day (no specific recommendation)
PDGFRA Exon 14		Infrequent	Initiate imatinib at 400 mg/day	Initiate imatinib at 400 mg/day (no specific recommendation)
PDGFRA Exon 18	D842 V, D846 V	Most common PDGFRA mutation in GIST; Primary resistance ex vivo & in vitro evidence of activity with dasatinib, IPI-504, & PKC412	Initiate imatinib at 400 mg/day. If D842V then consider dasatinib or trial with HSP90 inhibitor	Initiate imatinib at 400 mg/day (no specific recommendation)

codons is imatinib sensitivity for 642 and imatinib resistance for 654 despite the minimal 13 codons that separates these two amino acids. Therefore, not all mutations of exon 13 are alike, and a mutant codon 654 but not 642 appears to be critical in the molecular resistance to imatinib. On the other hand, inhibitors such as sorafenib and sunitinib have shown activity in patients whose tumors harbor these imatinib-resistant mutations [72]. GIST patients with secondary KIT exon 13 or KIT exon 14 were noted to be more sensitive to sunitinib compared to GIST with secondary KIT exon 17 or 18 mutants {[13] #256}. PFS was greater within this group as well. Sunitinib resistance was observed in all GIST patients with PDGFRA mutants (exon 12 and exon 18) or KIT exon 17 mutants.

Other TKIs have activity in imatinib-resistant GIST. Nilotinib can inhibit the secondary mutations of KIT exon 13 and exon 14 in cell lines {[61] #447, #448}. In an imatinib-resistant Ba/F3 cell system, nilotinib achieved a superior IC_{50} than dasatinib or sorafenib with double mutants, 560Vdel/V654A and V559D/D280Y. Sorafenib is more effective than dasatinib or nilotinib at inhibition of the double mutant, 557-8WKdel/T670I, and for the KIT exon 14 mutant, T670I. Prospective clinical trials that incorporate molecular correlates will be needed to determine the best treatment for imatinib-resistant disease and sunitinib-refractory disease. Therefore, the identification of specific mutations in *KIT or PDGFR-alpha* may allow selection of active therapies over ones that are inactive.

Thus, it is possible to individualize the dose of imatinib based on whether a patient has an exon 9 mutation in *KIT*. Current efforts are directed toward determining the appropriate dose of imatinib within KIT exon 11 and for mutations within the *PDGFRA*.

Conclusion

Translation of kinase inhibition from a sound theoretical approach in the laboratory to therapeutic reality in the clinic is evidence of a broader conceptual revolution in cancer, whereby non-specific, cytotoxic modalities have given way to rational, targeted therapies. In this regard, GIST is paradigmatic. Whereas GISTs once heralded extremely poor prognoses as a result of resistance to conventional chemo- and radio-therapies, the discovery of KIT or PDGFRA mutation as the oncogenic driving force in GIST, and the advent of safe and efficacious therapy in imatinib mesylate, have resulted in dramatic improvement in patient outcomes.

Ten years of imatinib therapy have revealed a sobering reality, however. Innate- and acquired-resistance mechanisms, together with the cytostatic nature of imatinib, inevitably allow cancer cells to survive and to recur. As discussed herein, various mechanisms of acquired resistance that circumvent therapeutic KIT inhibition have been characterized in GISTs, the most important being the development of isoallelic secondary KIT mutations involving the split kinase domains, which consequently distort imatinib binding and restore oncogenic KIT signaling. KIT amplification and the adoption of alternative signaling mechanisms account for most of the remaining resistance. Through laborious characterization, GIST researchers have defined the wide spectrum of KIT and PDGFR mutations, as well as other gene mutations involved in the pathogenesis and progression of GIST, and elucidated the molecular nature of resistance to imatinib and sunitinib. Overall, the vast genetic heterogeneity of primary and secondary *KIT* and *PDGFRA* mutations occurring in GIST implies that tyrosine kinase inhibition as a sole therapeutic strategy may not be sufficient to eradicate GIST. With individual patients known to harbor numerous genetically diverse TKI-resistant tumor cells, it seems unlikely that second- and third-line therapies based on the same principle (KIT inhibition) will achieve definitive cure.

Thus, it is now apparent that overcoming resistance in GIST will require combinatorial and individualized approaches that consider, and target, other unique tumor characteristics beyond KIT expression. This is a singular opportunity in oncology, as there are only a handful of examples where molecular characterization of individual patient tumors can determine the need for targeted therapy, likelihood of benefit of such treatment, and in many cases guide alternative approaches.

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