Molecular basis and management of gastrointestinal stromal tumors

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Abstract
Molecularly targeted agents have dramatically impacted the management of several cancers. Targeting KIT has led to a new treatment paradigm in gastrointestinal stromal tumors (GISTs). KIT is a cell surface receptor with tyrosine kinases that, upon binding of its ligand, stem cell factor, activates various signaling pathways. Imatinib and sunitinib, both tyrosine kinase inhibitors directed to KIT, were approved for first- and second-line treatment of metastatic and unresectable GISTs. In this article, we will review the molecular pathogenesis of GISTs followed by a discussion of imatinib and sunitinib’s role in the treatment of GISTs. Finally, we will introduce novel therapeutic options for imatinib- and sunitinib-resistant GISTs.

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Key words: Gastrointestinal stromal tumor; KIT; Imatinib; Sunitinib; Nilotinib

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INTRODUCTION
The gastrointestinal stromal tumor (GIST) is the most common (80%) mesenchymal neoplasm of the gastrointestinal tract[1] and represents about 5% of all sarcomas[2]. The annual incidence of GISTs is estimated to be 14.5 per million and prevalence 129 per million[3], with as many as 6000 new cases per year in the United States[4].

GISTs represent a morphological and biological gamut from incidentally discovered, < 1 cm nodules of benign appearance to large sarcomas, although all GISTs are currently accepted as potentially malignant. GISTs most commonly involve the stomach (50%) and small bowel (25%) (Figure 1); however, they may occur anywhere in the GI tract including the mesentery and omentum[5]. Approximately half of the patients present with metastatic disease and nearly two-thirds of those have liver metastases. Extraintestinal and lymph node metastases at presentation are rare, obviating the need for lymph node dissection unless they are directly involved[6].

Until the 1980s, stromal tumors arising from gastrointestinal tract were classified as various entities such as leiomyosarcoma, leiomyoblastoma and bizarre leiomyoma. With the advent of immunohistochemistry, it was realized...
that these tumors lacked immunophenotypic characteristics of smooth muscle. Mazur and Clark showed that a proportion of these tumors stained positively for S-100 and suggested the myenteric nervous system as the cells of origin, introducing the more generic term, “stromal tumor”[5]. In 1998, Hirota and colleagues demonstrated that almost all GISTs expressed KIT and had activating c-kit mutations. They also showed that interstitial cells of Cajal (ICC) were positive for both KIT and CD34 suggesting ICC as the cells of origin of GISTs[8].

**KIT**

KIT encoded by the c-Kit gene (mapped to chromosome 4q12) belongs to the type III receptor tyrosine kinase family and is structurally similar to platelet-derived growth factor receptors (PDGFRs), colony-stimulating factor-1 receptor, and fms-like tyrosine kinase-3 (FLT-3)[9,10]. KIT consists of an extracellular (EC) domain with 5 immunoglobulin-like loops, a transmembrane region, and a cytoplasmic domain with juxtamembrane (JM) region and a split tyrosine kinase (TK) domain. The latter is divided into an adenosine triphosphate (ATP) binding region (TK1) and a phosphotransferase region (TK2) by a hydrophilic kinase insert (KI) (Figure 2).

Normally, KIT is activated by stem cell factor. Ligand binding to the EC domain results in the dimerization of receptors and phosphorylation of tyrosine in the cytoplasmic TK domains. This leads to a phosphorylation cascade and activation of signal transduction pathways including Ras/MAP kinase, Rac/Rho-JNK, PI3K/AKT and SFK/STAT signaling networks[11]. Signaling by KIT plays an important role in erythropoesis, lymphopoesis, mast cell development and function, megakaryopoesis, gametogenesis and melanogenesis.

KIT is expressed in more than 95% of GISTs, including tumors with wild-type KIT and most PDGFR-A mutant GISTs. However, in the latter group, KIT expression may be weaker. KIT mutation in GISTs does not cause KIT expression, but modifies KIT function[12]. About 65%-85% of GISTs have KIT mutations[13-15]. Based on the location, these mutations could be divided into 2 categories: mutations of the receptor regulatory domain (EC and JM) and mutations of the enzymatic domain (TK1 and TK2)[16]. Most involve the JM domain (exon 11) and consist mostly of deletions or point mutations. Mutations in the JM domain affect KIT’s autoregulatory function and promote spontaneous kinase activation[17]. Exon 9 (EC domain) mutations are the second most common mutations followed by exon 13 (TK1 domain) and exon 17 (TK2 domain) mutations.

In approximately 10% of GISTs, no c-kit mutations are found even when the whole coding region is examined. In 2003, Heinrich et al.[18] and Hirota et al.[19] found gain-of-function mutations of the PDGFR-A gene in about half of the GISTs lacking c-kit mutations. A majority of PDGFR-A mutations affect the TK2 domain (exon 18). These mutations change the activation loop, which regulates the ATP-binding pocket and leads to kinase activation[8]. Activated PDGFR-A activates the same signaling pathways that KIT activates, leading to GIST.

**IMATINIB**

Imatinib mesylate (henceforth referred to as imatinib) is a small-molecule TK inhibitor. It works by binding to ATP binding sites of KIT, PDGFR-A, and bcr-abl fusion product, consequently inhibiting their activity[20].

Imatinib is rapidly absorbed in the GI tract, reaching maximum plasma concentrations 2-4 h after oral intake. Absolute bioavailability of imatinib is 98% and food does not affect its absorption[21]. Imatinib is metabolized mainly by the cytochrome P450 (CYP) 3A4 enzymes in the liver, with minor contributions from other CYP enzymes and is eliminated mainly via the feces, mostly in the form of metabolites[22]. As a result of intrinsic variability of CYP enzyme activity, there is a high inter-patient variability for imatinib exposure. Accordingly, imatinib trough levels at 308x338 to 539x569
day 29 were recently reported to be associated with clinical outcome[25]. Concomitant administration of CYP3A4 inhibitors (e.g. ketoconazole) may increase and CYP3A4 inducers (e.g. simvastatin) thereby increasing their exposure. Imatinib may also increase systemic exposure to paracetamol by inhibiting its O-glucuronidation[21,24].

In May 2001, the US Food and Drug Administration (FDA) approved imatinib for chronic myelogenous leukemia (CML) based on excellent responses as first- and second-line treatments[25]. Following demonstration of its activity against KIT and successfu treatment of a patient with a GIST[26], imatinib was evaluated in an open label, randomized, multicenter trial. Of 147 patients with unresectable or metastatic GISTs who were randomly assigned to receive either 400 or 600 mg imatinib daily, 79 (54%) had a partial response and 41 (28%) had stable disease. None of the patients had a complete response. There were no significant differences in the rate or duration of responses between the 2 dose levels of imatinib that were tested. The estimated 1-year overall survival rate was 88% for all patients[27]. As a result of this study, the FDA approved the use of imatinib in advanced GISTs in 2002. Recently, a long-term follow-up analysis of the same trial demonstrated that median duration of response was 27 mo and median overall survival was 58 mo[28].

In the same phase II trial, the 18F-fluoro-2-deoxy-D-glucose uptake in the tumors was found to be decreased markedly from baseline as early as 24 h after a single dose of imatinib. The median time to an objective response was 13 wk[29]. Accordingly, in the Euro-Australasian phase III trial, the median time to best response was 15 wk, with most responses occurring within the first 9 mo. However, best responses were occasionally observed after as long as 2 years of treatment suggesting that responses to imatinib can be seen late in the treatment[30].

Blay et al[31] investigated whether imatinib could be stopped after 1 year in patients who responded to imatinib and concluded that treatment with imatinib should continue until disease progression, patient intolerance or refusal. In this study, 58 patients with advanced GISTs were randomized to continuous and intermittent treatment arms. Twenty-six (81%) of the 32 patients in the intermittent arm had progressed and were restarted on imatinib. Of these 26 patients, 24 had a response or stable disease after imatinib was restarted. At the time of the final analysis, there was no difference in overall survival between continuous and intermittent treatment arms[32].

Adjuvant and neoadjuvant therapy with imatinib
Imatinib showed promising results in adjuvant therapy of GISTs. However, there is an ongoing debate on the duration, dose, and the selection of patients for adjuvant imatinib therapy. It is assumed that GIST patients with a relatively high risk of recurrence would benefit the most from adjuvant treatment. Several models were constructed to estimate the recurrence risk of resected GISTs.

Parameters commonly used were tumor size and mitotic rate[33,34]. Based on the reports of a higher recurrence risk of small bowel GISTs compared to gastric ones[35], a new risk stratification model incorporating tumor location was proposed[36,37] (Table 1). In addition to estimation of the recurrence risk, in the near future, mutation analyses from tumor specimens may help practitioners to select different agents according to different genotypes, customize both the duration and the dose of imatinib or other effective agents in the adjuvant setting.

After a phase II trial (ACOSOG Z9000) demonstrated high tolerability and promising efficacy in high risk (tumor size > 10 cm, tumor rupture, or multifocal disease) GIST patients[36-38], a phase III trial (ACOSOG Z9001) was initiated to compare 400 mg imatinib daily for 1 year with placebo in patients with KIT-expressing GISTs measuring at least 3 cm that were grossly resected. Accrual to the trial was halted early because of the better relapse-free survival (RFS) in the treatment arm in the interim analysis, and these results were presented at the 2007 ASCO meeting leading the FDA to approve imatinib for adjuvant treatment of GISTs in the USA[39]. Final results showed a 1-year RFS of 97% and 83% in imatinib and placebo arms, respectively, with a hazard ratio (HR) of 0.35 (95% confidence interval, 0.22-0.53)[37]. However, the risk reduction in patients with a tumor diameter between 3 and 6 cm was nearly zero. Secondly, there was no difference in overall survival between the 2 groups. It remains unclear whether imatinib prevents GIST recurrence or merely delays it. While 2 phase II trials from Korea and China confirmed the improved RFS in intermediate- and high-risk GIST patients treated with imatinib in an adjuvant setting[39,40], 2 other phase III trials are still ongoing: EORTC 62024 comparing imatinib for 2 years vs placebo, and SSG XVIII /AIO trial comparing imatinib for 3 years vs 1 year. Long-term follow-up results will be needed to demonstrate the adjuvant treatment effect on overall survival, the subsets of patients that would benefit, and the optimal duration of the treatment. Table 2 demonstrates the adjuvant/neoadjuvant trials registered by the National Cancer Institute (USA).

On the neoadjuvant side, early results from the phase II RTOG 0132 trial established the feasibility of the ap-

| Table 1 Risk stratification of primary GISTs |
|---------------------------------------------|
| **Tumor feature** | **Mitotic index** | **Size (cm)** | **Risk of tumor progression** |
|-------------------|------------------|---------------|-----------------------------|
| Stomach           | < 5/50 HPF       | ≤ 2           | Very low                    |
|                   | > 2 ≤ 5          | Low           | Moderate                    |
|                   | > 5 ≤ 10         | Moderate      | High                        |
|                   | ≥ 5/50 HPF       | ≥ 2           | Very low                    |
| Small bowel       | ≤ 5              | Very low      | Low                         |
|                   | > 5              | Moderate      | High                        |
|                   | > 10             | High          | High                        |

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GISTs arising from other sites should probably be stratified as small bowel tumors. GISTs: Gastrointestinal stromal tumors; HPF: High power fields.
Locally advanced, KIT Diameter > 10 cm or mitotic rate Primary: RFS Therapy (Diameter > 2 cm and mitotic rate Imatinib 400 mg daily for 1 year Eligibility 1-year RFS: 83% End points Secondary: RFS and safety Accrual Diameter > 5 cm or mitotic rate Primary: OS Diameter > 3 cm Diameter > 10 cm or tumor EORTC soft tissue and bone sarcoma group (EORTC-62024) randomized phase III trial Scandinavian sarcoma group trial SSGVIII Phase II study of neoadjuvant and adjuvant imatinib mesylate in patients with primary or recurrent potentially resectable malignant GIST (Germany/Austria) Five year adjuvant imatinib mesylate in GIST (Phase II) Phase II study of neoadjuvant imatinib mesylate in patients with locally advanced gastrointestinal stromal tumor (Germany/Austria) Table 2 Adjuvant and neoadjuvant trials of imatinib in patients with GISTs

| Trial | Accrual | Eligibility | Therapy (n) | End points |
|-------|---------|-------------|-------------|------------|
| Phase II study of adjuvant imatinib mesylate in patients with completely resected high-risk primary GIST (ACOSOG-Z9000) | Closed | Diameter > 10 cm or tumor rupture or multifocal | Imatinib 400 mg daily for 1 year (107) | 2-year OS: 97%, 2-year RFS: 73%[36] |
| Phase III randomized study of adjuvant imatinib mesylate in patients with resected primary GIST (ACOSOG-Z9001) | Closed | Diameter > 3 cm | Imatinib 400 mg daily for 1 year (359) Placebo (354) | 1-year RFS: 98%[37] |
| EORTC soft tissue and bone sarcoma group (EORTC-62024) randomized phase III trial | Closed | Diameter > 5 cm or mitotic rate > 5/50 HPF | Imatinib 400 mg daily for 2 years Observation (Total projected 750) | Primary: OS Secondary: RFS and safety |
| Scandinavian sarcoma group trial SSGVIII | Closed | Diameter > 10 cm or mitotic rate > 10/50 HPF or > 5 cm and > 5/50 HPF or tumor rupture | Imatinib 400 mg daily for 36 mo Imatinib 400 mg daily for 12 mo (Total projected 280) | Primary: RFS Secondary: OS, safety |
| Phase II study of neoadjuvant and adjuvant imatinib mesylate in patients with primary or recurrent potentially resectable malignant GIST (Germany/Austria) | Closed | Locally advanced or metastatic/recurrent | Imatinib 600 mg daily for 6-8 wk followed by debulking/resection (52) | 2-year PFS: 80%, objective response rate: 6%, R0 resection in 65%[38] |
| Five year adjuvant imatinib mesylate in GIST (Phase II) | Open | Diameter > 2 cm and mitotic rate > 5/50 HPF or non-gastric GIST > 5 cm | Imatinib 400 mg daily for 5 years (Projected 133) | Primary: Time to recurrence Secondary: Safety |
| Phase II study of neoadjuvant imatinib mesylate in patients with locally advanced gastrointestinal stromal tumor (Germany/Austria) | Open | Locally advanced, KIT expressing, histologically confirmed GIST | Imatinib 400 mg daily/BID (Projected 40) | Primary: ORR Secondary: R0-resectability and organ-preserving resectability |

OS: Overall survival; RFS: Relapse-free survival; PFS: Progression-free survival.

proach in locally advanced and metastatic GIST patients[40]. Fiore et al[39] recently reported that all of the 15 patients who received preoperative imatinib benefited from neo-adjuvant treatment: one patient had a complete response; 3 patients who were initially considered to have unresectable disease underwent complete resection; 7 patients with initial indication for extensive surgery were more conservatively operated on; 4 patients initially deemed at high perioperative risk underwent safe surgery[40]. For patients who do not have access to the ongoing neo-adjuvant trials (Table 2), we consider preoperative imatinib as an option for those with unresectable GISTs or in whom surgical morbidity would be improved by reducing the size of the tumor preoperatively. Positron emission tomography (PET) scans within 2-4 wk of therapy could be a predictive test separating responders from resistant patients. Non-responding patients, if surgically resectable, would be taken to surgery. Patients that are not surgical candidates could be considered for second-line therapy.

Toxicity

Almost all patients in clinical trials with imatinib experienced adverse events; however, most of the events were mild or mild to moderate. Patients treated with 800 mg/d imatinib had more grade 3 or above side effects compared to those treated with 400 mg/d in both phase III trials comparing 2 different doses. Most common grade 3-4 side effects in these 2 phase III trials were anemia, granulocytopenia, fatigue, fluid retention, muscle pain, and gastrointestinal symptoms[29,41]. In the Euro-Australasian trial, dose reductions and treatment interruptions, mostly because of toxic effects, were found to be more likely to occur in patients who received imatinib 400 mg twice daily. Additionally, side effects were mostly recorded during the first 8 wk of treatment[41].

Fluid retention due to imatinib is generally mild, most frequently affects the periorbital region, and can be seen in 70%-80% of patients treated with imatinib. It responds well to intermittent low dose thiazide diuretics. On the other hand, muscle cramps can be seen in up to 40% of patients and can be very troublesome as a result of their long-term course. There are anecdotal reports of patients responding to magnesium/calcium supplements[42], quinine[43], and chloroquine[44]. Hypophosphatemia can also be seen with imatinib use, and routine monitoring of phosphate levels has been suggested[45]. In 2006, 10 individuals were reported to develop severe heart failure after receiving imatinib[46]. However, whether imatinib causes cardiac toxicity in GIST patients is still unclear. Multiple randomized studies failed to show excess cardiotoxicity in patients treated with imatinib postoperatively[37,47].

Tumor hemorrhage is a life-threatening toxicity for which patients with large, bulky tumors have a higher risk. Therefore, hemoglobin levels should be monitored upon starting GIST patients on imatinib.

Imatinib resistance

The advent of imatinib had completely changed the management and survival of patients with GISTs. However, imatinib resistance, both primary and secondary, is still a
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Table 3  Prevalence of c-kit and PDGFR-A mutations and clinical responses in advanced GISTs to imatinib and sunitinib correlated with mutational status

| Genotype                      | Prevalence[52-54] | Clinical benefit from imatinib<sup>[15,58,59]</sup> | Clinical benefit from sunitinib<sup>[57]</sup> |
|-------------------------------|------------------|------------------------------------------------|-----------------------------------------------|
| KIT exon 9 mutation (%)       | 5-14             | 74-81                                          | 60                                            |
| KIT exon 11 mutation (%)      | 57-69            | 83-95                                          | 35                                            |
| KIT exon 13 mutation (%)      | < 5              | 60-100 (few cases)                             | 65                                            |
| KIT exon 17 mutation (%)      | < 5              | 75-80 (few cases)                              |                                               |
| PDGFR-A mutations (%)         | 3-8              | 40-66                                          | 0 (few cases)                                 |
| Both wild-type (%)            | 5-10             | 33-73                                          | 55                                            |

Clinical benefit is defined as complete, partial response or stable disease. In imatinib-resistant GIST.

significant problem. In the Euro-Australasian phase III trial, 12% of patients exhibited initial resistance to imatinib<sup>[56]</sup>. Furthermore, more than 40% of patients who were initially responsive to imatinib developed late resistance after a median follow-up of 25 mo.

Several different mechanisms of imatinib resistance were identified in the literature: (1) KIT or PDGFRA mutations resulting in intrinsic target resistance; (2) genomic amplification leading to target overexpression; and (3) alternate oncoprotein activation supplanting target expression<sup>[24,50,31]</sup>. During imatinib treatment, resistance often develops as a result of secondary mutations, primarily in the kinase domains of KIT or PDGFR-A<sup>[52-54]</sup>. One of the frequent secondary kinase domain mutations, V654A mutation, is intrinsically imatinib-resistant<sup>[55]</sup>.

Depending on the mechanism of the resistance, a higher dose of imatinib may be considered in patients with GISTs resistant to 400 mg/d imatinib. The effect of increasing the dose of imatinib to 800 mg daily in advanced GIST patients was assessed in 2 phase III trials. In the Euro-Australasian trial of 946 patients, Verweij et al<sup>[59]</sup> reported that although there was no difference in response rates between daily and twice daily 400 mg dosing, progression-free survival was significantly better in patients who received the higher dose. On the other hand, the results of the phase III trial in North America did not reveal any difference between daily and twice daily 400 mg dosing in response rates, progression-free and overall survival. However, 31% of patients who progressed on 400 mg daily dosing and crossed over to 400 mg twice daily dosing had a partial response or stable disease suggesting that in a subset of patients increasing the imatinib dose may overcome the resistance to imatinib<sup>[56]</sup>.

In the North American phase III trial, patients with exon 11 mutations had a better response rate, time to progression and overall survival compared to those with exon 9 mutations and the wild-type c-kit gene. Although the survival rates of exon 9, exon 11 or wild-type GISTs were not affected by imatinib dose, the response rate for patients with an exon 9 mutation was significantly higher in those who were treated with a higher dose of imatinib (67% vs 17%, P = 0.02)<sup>[57]</sup>. Furthermore, in a meta-analysis of 2 phase III trials, 800 mg/d imatinib was found to be associated with a significantly better progression-free survival in patients with the exon 9 mutation (median progression-free survival: 1.6 year vs 0.5 year; HR, 0.58, P = 0.017)<sup>[57]</sup>. Table 3 demonstrates the prevalence and response rates of mutations in different exons of KIT and PDGFR-A genes derived from 3 different clinical trials<sup>[55,50,39]</sup>, population<sup>[60]</sup> and institution based studies<sup>[61]</sup>. Lassota et al<sup>[62]</sup> published a detailed review on the role of c-kit and PDGFR-A gene mutations on GIST therapy<sup>[63]</sup>.

**SUNITINIB**

Sunitinib malate, an oral multitargeted inhibitor of KIT, PDGFRs, vascular endothelial growth factor receptors (VEGFR), FLT3 and RET receptor TKs, is FDA approved for treatment of imatinib-resistant GISTs and of advanced renal cell carcinoma. In addition to its antitumor effect through inhibition of KIT and PDGFR, sunitinib may have an antiangiogenic effect on GISTs through inhibition of VEGFR<sup>[64]</sup>.

In a phase I/II trial, sunitinib at different dosages and schedules was administered to 97 GIST patients with imatinib resistance (96%) or intolerance (4%). In phase I, sunitinib 50 mg/d for 4 wk followed by 2 wk off treatment was chosen for further development. Overall, 73% of patients experienced stable disease which lasted > 6 mo and 7% achieved a partial response. The median overall survival was 19 mo<sup>[65]</sup>.

The pivotal, randomized, placebo-controlled, multinational phase III trial of sunitinib in patients with unresectable, imatinib-resistant GISTs had to be unblinded early when interim data analysis showed a significantly longer median time to progression in patients who received sunitinib compared to those who received placebo (27.3 wk vs 6.4 wk; HR, 0.33, P < 0.001). Response rate was better in patients treated with sunitinib compared to those treated with placebo (6.8% vs 0%, P = 0.006). Despite the crossover after unblinding, overall survival was superior in the sunitinib arm (HR, 0.49; P < 0.007). This study established the role of sunitinib as a second-line therapy in patients with advanced imatinib-refractory and imatinib-intolerant GISTs<sup>[66]</sup>.

Although a clinical benefit of sunitinib treatment was observed in all major mutant types, the primary response rate was significantly higher for KIT exon 9 mutants. The inhibitory effect of sunitinib was not substantially affected by KIT mutations in TK1 whereas GISTs with KIT-TK2 mutations were resistant to sunitinib treatment. Specifically, the imatinib-resistant KIT mutation V654A was highly sensitive to sunitinib<sup>[66-67]</sup>. 

Table 4 Novel agents being developed for GIST therapy

| Agent            | Molecular target          | Clinical benefit in pilot studies |
|------------------|---------------------------|----------------------------------|
| Kinase inhibitors|                           |                                   |
| Nilotinib        | KIT, PDGFRs, bcr-abl      | 46%-77%                          |
| Sorafenib        | Raf, KIT, PDGFR-B, VEGFR, FLT3, RET | 71%                              |
| Dasatinib        | Src, ABL, KIT, PDGFRs     | Phase I ongoing in advanced sarcomas and accepting patients |
| AZD2171          | VEGFR, KIT, PDGFRs       | Phase I ongoing, not recruiting   |
| OSI-930          | VEGFR, KIT               | Phase I ongoing, not recruiting   |
| PTK787           | VEGFR, KIT, PDGFRs       | Phase I ongoing, not recruiting   |
| XL820            | KIT, PDGFR-B, VEGFR      | Phase I ongoing, closed recruitment |
| AMG706           | VEGFR, KIT, PDGFRs, RET  | 24%-27%                          |
| mTOR and AKT inhibitors |                 |                                   |
| Perifosine       | AKT                      | Phase II ongoing in combination with imatinib |
| Everolimus       | mTOR                     | 26%                              |
| Temsirolimus     | mTOR                     | Phase II ongoing, closed recruitment |
| Others           | Hsp90                    | 78%                              |
| Flavopiridol     | Transcription inhibitor  | Phase I ongoing in combination with doxorubicin |

Clinical benefit is defined as complete or partial response or stable disease.

Sunitinib was generally well tolerated in patients with GISTS, with adverse events mild to moderate in severity. In the phase III trial, the most frequent treatment-related adverse events were fatigue, diarrhea, hand-foot syndrome, rash, nausea, anorexia, and skin discoloration. Hypertension occurred in about 20% of treated patients, 5% being grade 3/4 in severity. Treatment discontinuation because of adverse events occurred in 9% and 8% of sunitinib and placebo recipients, respectively[65]. Hyothyroidism, possibly secondary to inhibition of the protein product of the RET proto-oncogene found in normal thyroid has been described in as high as 36% of sunitinib-treated GIST patients[66].

**FUTURE DIRECTIONS**

Currently, there is no established third-line treatment in patients with GISTS who failed to respond to both imatinib and sunitinib. Table 4 demonstrates the drugs in the pipeline for GIST therapy[69-70]. Nilotinib, a second-generation TK inhibitor engineered to inhibit KIT, PDGFR-A, and bcr-abl, is approved for the treatment of imatinib-resistant CML. In a phase I study of nilotinib in imatinib-resistant GISTS, 13 (72%) of the 18 patients who received nilotinib experienced stable disease lasting more than 6 wk. One patient achieved a partial response. Median progression-free survival was 25 wk. Nilotinib 400 mg twice daily was the dose recommended for future studies[69]. Recently, Montemurro et al[71] reported a retrospective analysis of 52 patients treated with nilotinib 400 mg twice daily as compassionate use in 12 European centers. All patients had failed both imatinib and sunitinib either due to resistance (96%) or intolerance (4%). One and 4 patients achieved complete and partial responses, respectively; whereas 19 had disease stabilization. The median progression-free survival was 12 wk (range 2 d-104 wk) and the median overall survival was 34 wk (range 2-135 wk). Most patients tolerated nilotinib well except 6 (12%) patients discontinued treatment due to grade 2-3 adverse effects[70].

The efficacy of sorafenib, a multi-kinase inhibitor of raf kinase, VEGFR, PDGFR, and KIT, in imatinib- and sunitinib-resistant GISTS was studied in a phase II trial of 26 patients. Three (13%) patients achieved a partial response and 14 patients (58%) experienced stable disease. Median progression-free survival was 5.3 mo and median overall survival was 13.0 mo. The most common side effects were hand-foot syndrome (28%), hypertension (24%), and rash (20%)[71].

Heat shock proteins (Hsp) control the proper folding, function, and stabilization of various proteins. Laboratory studies have demonstrated that inhibition of Hsp90 results in selective destruction of the mutated KIT in human GIST cell lines. In a phase I trial of IPI-504, an intravenous Hsp90 inhibitor, 78% of evaluable patients with imatinib-resistant (100%) and sunitinib-resistant (95%) GISTS experienced stable disease[72]. However, a phase III trial of IPI-504 ended early because of safety concerns. Other strategies to inhibit growth of GISTS is to abrogate KIT mRNA expression with flavopiridol, a transcriptional inhibitor[73]; and inhibition of the AKT-mTOR pathway by mTOR inhibitors such as everolimus[74].

**CONCLUSION**

The discovery of near universal KIT protein expression, and activating KIT and PDGFR-A mutations advanced our understanding of GISTS significantly. Later, the finding of the high efficacy of imatinib in the treatment of GISTS changed the management and prognosis of this once very deadly malignancy. Imatinib is currently approved for the treatment of unresectable or metastatic GISTS, however, many centers around the world, including our own, use imatinib also in adjuvant and neoadjuvant settings. PET scans may be especially helpful in identifying imatinib-resistant tumors during neoadjuvant treatment. Further
studies are needed to tailor the imatinib treatment in these settings. On the other hand, imatinib should be continued until disease progression or intolerability in patients with metastatic or unreseetable GISTs.

The standard therapy for metastatic GISTs resistant to imatinib is sunitinib. The efficacy of sunitinib in the first-line treatment of advanced GISTs and as adjuvant/neoadjuvant treatment should be studied in randomized trials. Resistance to imatinib and sunitinib continues to be a challenging issue. Upcoming treatment options are second-generation kinase inhibitors and inhibition of the growth of GISTs via pathways other than KIT and PDGFR-A. We believe the combination of Hsp90 inhibitors and kinase inhibitors could yield superior results.

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