Gastrointestinal Stromal Tumor: A Clinical Overview

Richard Quek, MDa,b, Suzanne George, MDa,c,*

KEYWORDS
• Gastrointestinal stromal tumors • GIST • Review
• Imatinib • Sunitinib • Tyrosine kinase inhibitor

HISTORICAL PERSPECTIVE

Following descriptions in the 1940s by Stout and others, stromal tumors arising from the gastrointestinal tract were classified as smooth muscle neoplasms.1,2 These rare tumors were classified as various entities including leiomyosarcoma, leiomyoblastoma and bizarre leiomyoma, until, at least, the 1960s. With the advent of electron microscopy (EM) in the late 1960s, smooth muscle features were seen only in occasional GIST cells, raising into question the smooth muscle origin of this entity.3,4 In addition, several authors reported ultrastructural features reminiscent of autonomic nerve structures, with schwannian and neuroaxonal characteristics, in tumor specimens microscopically indistinguishable from GIST.5

With the introduction of immunohistochemistry in the early 1980s, it was soon appreciated that many of these tumors lacked immunophenotypic features of smooth muscle, and conversely, a proportion of tumors stained positively for S-100 protein, a marker for neuroectodermal differentiation.6 This led Mazur and Clark to suggest the myenteric nervous system as a possible cell of origin and to introduce a more generic term, “stromal tumor.” In 1989, a distinctive subset of gastrointestinal tumors showing autonomic neural features was described and termed “plexosarcoma”7 and subsequently became better known as gastrointestinal autonomic nerve tumor (GANT).8 By the early 1990s, there was considerable confusion as to the lines of
differentiation of these tumors. Some were obviously neurogenic, some myogenic, others displayed bidirectional differentiation and a subgroup with null phenotype. To further complicate matters, there was a distinct lack of histologic prognostication methods, with great difficulty classifying GISTs even into benign and malignant categories. Tumors showing the usual histologic criteria for malignancy did not uniformly behave aggressively, and on the other hand, some tumors with benign features gave rise to metastases.

From 1994, it became apparent that a significant proportion of GANTs were immunopositive for CD34, and for a while, CD34 was hailed as the marker for GIST.9,10 This finding also raised the possibility that GIST might be related to the interstitial cells of Cajal (ICC) on the basis of CD34 immunopositivity. Interstitial cells of Cajal, sometimes known as the pacemaker cells of the gastrointestinal tract, form the interface between the autonomic nervous system and the smooth muscle. They possess the immunophenotypic and ultrastructural characteristics of both the neural and smooth muscle elements. However, over the next several years, it also became apparent that not more than 70% of GIST cases were truly positive for CD34. This was further confounded by the fact that Schwann cell, and other smooth muscle tumors, were also variably CD34 positive, thus obviating the diagnostic efficacy of CD34. Up until 1998, it was unclear what the cell of origin GIST derived from, how best to accurately diagnose GIST, or even to distinguish malignant from benign GIST. In parallel to developments in GIST, by the mid-1990s, various reports emerged describing gain-of-function mutations, and consequently, constitutive activation of KIT receptors in several human tumor mast cell lines.11,12

Finally in 1998, in a landmark publication, Hirota and colleagues13 made two key discoveries: a near-universal expression of KIT in GIST and the presence of activating c-Kit mutations in GISTs. In Hirota’s series of 49 GIST samples, 94% of cases expressed KIT. Mutations in the juxtamembrane domain of c-KIT were detected in five of six samples of GISTs, resulting in constitutive ligand-independent activation of the KIT receptor tyrosine kinase. The oncogenic role of KIT was confirmed when stable transfection of the mutant c-KIT cDNAs induced malignant transformation of murine lymphoid cells. In addition, 82% (40 of 49) of GISTs were CD34-positive and 78% (38 of 49) were positive for both CD34 and KIT. ICC were also found to be positive for both KIT and CD34, suggesting close morphologic relations between ICC and GIST. In the same year, work by Kindblom and colleagues14 corroborated findings from Hirota and colleagues, showing that 78 of 78 GISTs studied were immunoreactive for KIT, and shared striking ultrastructural and immunophenotypic similarities with ICC. This work again supported the hypothesis that GIST may indeed develop from stem cells that differentiate toward ICC phenotype and confirmed KIT as an accurate diagnostic tool for GIST.

The next decade saw phenomenal growth in the understanding of GIST biology and therapeutics, beginning with a single patient with multiply treated, advanced refractory GIST, displaying early, rapid, and sustained response to a small molecule tyrosine kinase inhibitor (TKI) with potent activity against the transmembrane receptor KIT, ABL kinase and chimeric BCR-ABL fusion oncoprotein product of chronic myeloid leukemia, imatinib.15 Imatinib occupies the ATP binding pocket of KIT, thereby preventing substrate phosphorylation, downstream signaling, and thereby inhibiting cell proliferation and survival. The remarkable, early clinical results led to the conduct of large-scale, rationally designed clinical trials of imatinib in patients with metastatic or unresectable GIST, aided by accurate diagnoses using CD117 expression (a marker of KIT-receptor tyrosine kinase), ultimately confirming the benefit and subsequent approval of imatinib in this indication by the US Food and Drug Administration in
Median progression-free survival of GIST patients on first-line imatinib is between 18- to -24 months. At the time of imatinib failure, sunitinib has successfully demonstrated clinical activity in an international randomized placebo-controlled phase 3 trial, leading to its approval in January 26, 2006, for use in patients with imatinib-refractory or intolerant GIST.

**EPIDEMIOLOGY**

Gastrointestinal stromal tumors represents about 5% of all sarcomas and is the most common (80%) mesenchymal neoplasm of the gastrointestinal tract. Using a Swedish population-based study, the annual incidence of GIST is estimated to be 14.5 per million and prevalence 129 per million, with as many as 5000 to 6000 new cases per year in the United States. Median age of onset is about 60 with no gender predilection. GISTs may occasionally affect children and rare familial cases have been reported in the literature, but the vast majority of cases are sporadic in nature and risk factors are relatively unknown.

**CLINICAL FEATURES**

From a large population-based study, about one third of GIST cases were detected incidentally, with approximately 20% found during surgery for other unrelated condition and remaining 10% found at autopsy. The majority of GISTs, 50% to 60%, arise in the stomach, 20% to 30% in the small bowel, 10% in the large bowel, 5% in the esophagus and 5% from elsewhere in the abdominal cavity (eg, mesentery, omentum). A peculiar feature of GIST is that it is an essentially intra-abdominal disease for the length of its natural history. Fifteen to 47% of patients present with overt metastatic disease. Common sites of metastases include liver, peritoneum and omentum. Unlike adenocarcinoma, lymph node metastases are rare. In contrast to other sarcomas, lung and bone metastases are unusual and appear late in the course of disease, if at all. Brain metastases are exceedingly rare. For symptomatic cases, presenting symptoms are invariably related to the gastrointestinal tract or mass effect within the abdominal cavity, and include vague abdominal discomfort, early satiety, palpable abdominal mass, or secondary symptoms of tumor bleeding and associated anemia, bowel obstruction or perforation and dysphagia. Ensuing investigations include appropriate radiological imaging with either computed tomography (CT) or magnetic resonance imaging (MRI) scans of the abdominopelvic cavity, or functional imaging with positron emission tomography (PET), and endoscopies as indicated.

**RISK STRATIFICATION**

For many years, there was little consensus on how best to distinguish benign from malignant GIST. As alluded to earlier in this discussion, some tumors with morphologically malignant features did not display the expected aggressive behavior and some tumors with histologically benign features develop metastases, sometimes years later. Most experts now consider all GISTs to have malignant potential, instead of segregating them into distinct categories of benign and malignant. Many factors have been extensively studied and proposed to predict for outcome, but tumor size and mitotic rate are the two most widely accepted indices, stratifying patients into four risk groups. Anatomic location of primary GIST tumor is also recognized as an independent prognostic factor, with small bowel lesions carrying a higher risk of progression than gastric primaries of similar size and mitotic rate. Miettinen and colleagues
have incorporated site of primary lesion (gastric versus small bowel) into a revised version of the risk assessment schema. This more recent risk assessment is now considered the standard risk assessment model.25

**MOLECULAR BIOLOGY**

Since the first discovery of activating \textit{KIT} mutations by Hirota and colleagues, much progress has been made in the understanding and characterization of the various forms of \textit{KIT} mutants. Eighty to 88% of GISTs are associated with a \textit{KIT} mutation in either the exons 11, 9, 13, or 17. Exon 11 mutations are most common, occurring in approximately 65% of all cases, followed by exon 9 mutations (15%), with exon 13 and 17 representing approximately 1% of tumors each.26–28 In 2002, Heinrich and co-workers reported an analogous gain-of-function mutation in a closely related receptor tyrosine kinase, platelet-derived growth factor receptor-\(\alpha\) (PDGFRA), in approximately 35% of GISTs lacking \textit{KIT} mutations. These PDGFRA mutant tumors were indistinguishable from \textit{KIT} mutants with respect to activation of downstream signaling intermediates and cytogenetic changes related to tumor progression.29 Based on this finding, subsequent mutational studies estimated frequency of PDGFRA mutations to be between 2% to 7%, and the remaining 7% to 13% of GISTs being wild-type for both \textit{KIT} and PDGFRA. The significance of mutational status of GIST, as will be detailed later, lies in its correlation with clinical outcome in TKI treated patients.

Based on work by Corless and colleagues,30 it is likely that activating \textit{KIT} mutations are acquired early in the development of GISTs. In a cohort of 13 morphologically benign, small (4 mm–10 mm) asymptomatic GISTs identified incidentally, 11 samples harbored confirmed KIT mutations. In parallel to these findings, it is not unusual to find characteristics cytogenetic aberrations (deletions in 14q and 22q) in subsets of \textit{KIT} mutant GISTs, but conversely some \textit{KIT} mutant GISTs have entirely normal cytogenetic profiles. This would suggest that \textit{KIT} activating mutations occur early in the course of disease but further chromosomal changes, including deletions in 14q, 22q, 1p, 11p and 9p, as well as gains in 8p and 17q, are necessary to effect overtly malignant phenotype and progression of disease.31

**UNCOMMON PRESENTATIONS OF GIST**

**Pediatric GIST**

Pediatric GIST is a rare childhood malignancy occurring preferentially in females. Evidence suggests that it may be biologically distinct from adult GISTs. Although pediatric GISTs express KIT at levels comparable to adult GISTs, fewer than 15% of tumors harbor activating \textit{KIT} or PDGFRA mutations, in contrast to the more than 85% noted in adult GISTs. In addition, pediatric GISTs respond poorly to standard imatinib treatment, the cornerstone for adult GIST therapeutics. Interestingly, pediatric \textit{KIT}-wild type GISTs display levels of KIT activation similar to that seen in both pediatric and adult \textit{KIT}-mutant GISTs, suggesting that a separate biological mechanism may be responsible for its oncogenesis.32 Recently, insulin-like growth factor-1 receptor (IGF-IR) amplification and protein expression has been detected in pediatric and wild-type GIST,33,34 and is hypothesized to be associated with the oncogenesis of such tumors. This finding, if confirmed, may have therapeutic implications especially in the subset of tumors that respond poorly to imatinib-based therapy.
Familial GIST

Heritable mutations in KIT and PDGFRA, likely of autosomal dominant inheritance pattern, have been widely reported in the literature.35–37 Affected kindreds with familial GIST may present with multi-focal disease, and in some cases, may be associated with cutaneous and mucous membrane hyperpigmentation, mast cell disease, urticaria pigmentosa and diffuse spindle cell hyperplasia in the myenteric plexus of the gastrointestinal tract. Carney’s triad, a rare and possibly familial tumor syndrome, of unidentified genetic mechanism, predominantly affects young women, and comprises of gastric stromal sarcoma (GIST), pulmonary chondroma and extra-adrenal paraganglioma.38 Neurofibromatosis type 1 has also been associated with development of GIST. In a Swedish population based study of 70 patients with NF-1, 7% of patients were diagnosed with GIST. These tumors are frequently multifocal, often affect the small bowel, and are often KIT/PDGFRA mutation negative.39,40

Treatment of Localized Disease

Standard treatment for localized, resectable GIST remains complete surgical resection. As GIST tends to be exophytic rather than diffusely infiltrative, wedge resection is oftentimes sufficient. In locations where wedge resection is not technically feasible, wide resection (esophagus GIST) and en-bloc (omental GIST) resections are recommended, aiming to achieve complete gross resection.41 Lymphadenectomy is not warranted unless there is gross nodal involvement. In cases of unresectable or marginally resectable disease, neoadjuvant therapy with imatinib should be considered.25,41

The role of adjuvant imatinib therapy is being actively investigated. In the ACOSOG Z9000 trial, a United States intergroup phase 2 single-arm trial of adjuvant imatinib in patients with high-risk, completely resected GIST, one year of adjuvant imatinib prolonged recurrence-free survival compared with historical controls.42 In a parallel phase 3 placebo-controlled study of adjuvant imatinib in patients with completely resected GIST, 3 cm or larger, ACOSOG Z9001, one-year of adjuvant imatinib significantly improved relapse-free survival compared with placebo, 97% 1-year relapse-free survival compared with 83% achieved with placebo. Notably, there was no significant difference in overall survival at a median follow-up of 15 months.43

Treatment of Advanced Disease

Before 2000, metastatic GIST was a uniformly fatal disease with few therapeutic options. Response to chemotherapy was invariably poor, with one study reporting an abysmal response rate of 1.8% despite aggressive combination chemotherapy.44 Imatinib is a small molecule tyrosine kinase inhibitor (TKI) with potent activity against the transmembrane receptor KIT, ABL kinase and chimeric BCR-ABL fusion oncprotein product of chronic myeloid leukemia. Imatinib occupies the ATP binding pocket of KIT, thereby preventing substrate phosphorylation, downstream signaling and inhibiting cell proliferation and survival. Imatinib was first approved in 2002 for use in advanced GIST following impressive clinical activity demonstrated in a phase 2 study of 147 patients.16 Overall, objective response rates of 53.7% and stable disease in 27.9% were achieved in this study population with very manageable toxicities. This represented a remarkable advancement in therapy for patients with metastatic GIST. With longer follow-up, these results continue to hold true. Overall median time to progression being 24 months and median overall survival reported as 57 months. Overall survival was not different in patients who achieved an objective response or stable disease.45
As the maximum tolerated dose of imatinib in a European phase 1 dose escalation study was 800 mg per day, there were concerns amongst GIST experts worldwide that patients might achieve greater benefit with higher dosing.\textsuperscript{46} As such, two separate large phase 3 randomized studies were conducted on either side of the Atlantic, comparing imatinib 400 mg daily (standard dose) versus 800 mg daily, administered at 400 mg twice per day (high dose); crossover to the high-dose arm at time of disease progression was permitted for patients randomized to the standard dose.\textsuperscript{47,48} Toxicities were greater in the high-dose arm, with more patients requiring dose reductions (16% in the standard arm versus 58%–60% in the high-dose arm) and dose interruptions (38%–40% in the standard arm versus 59%–64% in the high-dose arm). Common imatinib toxicities include edema, fatigue, nausea, rash and diarrhea. In a pooled analysis, a small but statistically significant progression-free survival (PFS) benefit was noted in the high-dose arm approximately 19 months versus 23 months, with results consistent in both studies (but significant only in the European study). For patients with \textit{KIT} exon 9 mutation, PFS benefit was detected in the high-dose arm in the European study (19 months versus 4 months), not confirmed in the United States study, but nevertheless, remained significant in the pooled meta-analysis (19 months versus 6 months). There was no benefit seen for high-dose imatinib in patients with primary exon 11 mutations. Overall survival was identical in standard- and high-dose arms, independent of genotype.\textsuperscript{49} Thus, a high-dose imatinib starting dose may reasonably improve PFS in patients with \textit{KIT} exon 9 mutation, but is associated with greater toxicity, with no added survival benefit.

Sunitinib, a small molecule, oral, multitargeted tyrosine kinase inhibitor with potent anti-angiogenic and anti-tumor activities, targets receptors of \textit{KIT}, vascular endothelial growth factor receptor (VEGF1, 2, 3), platelet-derived growth factor (PDGFA and B), Fms-like tyrosine kinase-3 (FLT3), and the receptor encoded by ret proto-oncogene (RET). Because of this broad spectrum of inhibition, sunitinib may have both antitumor and antiangiogenic effects in GIST. A randomized, placebo-controlled, multinational trial evaluated the benefit of sunitinib administered 50 mg daily, 4 weeks on and 2 weeks off. In this study, 312 patients with imatinib refractory or intolerant GIST were randomized in a 2:1 ratio to receive sunitinib (n = 207) or placebo (n = 105). The trial was unblinded early when an interim data analysis showed a significantly longer median time to progression (TTP) with sunitinib (6.8 months versus 1.6 months). The majority of patients on sunitinib (58%) achieved stable disease as their best response, with only 7% of patients demonstrating a partial response. Despite the cross over design of the trial, overall survival obtained with initial sunitinib was superior to that obtained with placebo (hazard ratio 0.49, \textit{P}<.007). This pivotal study established the role of sunitinib as second-line therapy in patients with advanced imatinib-refractory or imatinib-intolerant GIST.\textsuperscript{17}

Work by Van den Abbeele and colleagues,\textsuperscript{50} using \textsuperscript{18}F] fluorodeoxyglucose-emission tomography (FDG PET) to study the effects of sunitinib on GIST, when administered on a 4-week on and 2-week off schedule, revealed that FDG responses were noted as early as 7 days. But this suppression was accompanied by a rebound during the 2-week off period, suggesting a flare in disease activity, consistent with lack of TK inhibition during the wash-out period. Thus, clinical studies employing continuous daily dosing of sunitinib have been undertaken in an attempt to provide consistent TK inhibition. Starting dose of sunitinib at 37.5 mg daily was chosen to reduce toxicity. In a report by George and colleagues,\textsuperscript{51} continuous daily dosing was found to be safe and well tolerated. Median PFS of 32 weeks was achieved, comparable to results obtained from the 4-week on and 2-week off schedule. Longer follow-up for efficacy assessment is required.
Common sunitinib toxicities include fatigue, diarrhea, hand-foot syndrome, rash, and skin discoloration. Hypertension, likely a class effect of anti-angiogenic agents, is relatively common, and occurs in about 20% of treated patients, 5% being grade 3/4 in severity. Hypothyroidism, possibly secondary to a drug-related destructive thyroiditis process, via inhibition of the protein product of the RET proto-oncogene found on normal thyroid has been described in as high as 36% of sunitinib-treated GIST patients. Cardiotoxicity has recently been reported to be associated with sunitinib use, although its frequency and significance varies considerably.

FUTURE DIRECTIONS

Currently in ongoing trials, sorafenib tosylate, a small molecule Raf kinase and VEGF-receptor kinase inhibitor, has demonstrable activity in TKI-treated patients, yielding a 13% partial response rate in a group of 26 patients, 77% of whom were imatinib and sunitinib refractory. Progression-free survival and median overall survival are 5.3 months and 13 months respectively. Heat shock proteins (HSP) control the proper folding, function, and stabilization of various “client” proteins. Many of these client proteins (eg, KIT and PDGFR-α) are oncoproteins or important cell signaling proteins. Inhibition of KIT signaling by targeting its molecular chaperone is an area of active research. Recently, IPI-504, a novel potent inhibitor of HSP-90, demonstrated clinical activity in a phase 1 dose escalation trial, achieving a 23% response rate (judged by positron emission tomography scans) and a median PFS of 12 weeks, in a cohort of heavily pretreated GIST patients. At the time of this writing, an international phase 3 placebo-controlled study with IPI-504 in patients with imatinib and sunitinib refractory GIST is being planned. IGF-IR inhibitors are a new promising class of anti-cancer agents. In light of the finding of IGF-IR up-regulation in wild-type and pediatric GISTs, further studies are eagerly anticipated.

SUMMARY

The last decade marked an important era in the history of GIST, culminating from the discovery of near universal KIT protein expression and activating KIT mutations, in advancement of diagnosis of GIST and our understanding of its oncogenesis; to the development of risk stratification models, refining prognostication, and consequently, influencing treatment strategies; to the translation of laboratory successes into biologically relevant therapeutics, dramatically improving patient outcomes. It is with optimism that patients, clinicians, and researchers alike, stride into the next decade, working to improve on the remarkable achievements of the last.

REFERENCES


42. DeMatteo RP, Owzar K, Antonescu CR, et al. Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal


