CLINICAL INVESTIGATION

Pharmacological treatment of gastrointestinal stromal tumors: update from recent clinical trials

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract and until recently were uniformly found to have poor prognoses with no successful treatment options aside from surgical resection. Cytotoxic chemotherapeutics evaluated in this disease revealed minimal clinical responses. Given the clearer understanding of the distinct molecular abnormalities and biology of the tumor, treatment strategies to overcome this lack of clinical response have been achieved. As the field of oncology has shifted from the development of cytotoxic chemotherapeutics to the emergence of targeted agents, treatment options are available and are becoming effective at delaying progression of disease and decreasing mortality. GISTs can now be classified as a treatable malignancy. This review seeks to provide a comprehensive overview of GISTs, with a focus on recent clinical trials of pharmacological agents in their treatment.

Keywords: gastrointestinal stromal tumor • HSP90 • imatinib • PI3K pathway • sunitinib • switch pocket • targeted therapy • tyrosine kinase inhibitor

Epidemiology

Sarcomas, as a whole, are a relatively uncommon neoplasm; however, gastrointestinal stromal tumors (GISTs) are the most common sarcomatous tumors of the GI tract and 3000–6000 new cases are diagnosed yearly in the USA [1,2]. With respect to demographics, GISTs show no sex bias, with the majority of men and women presenting after the age of 50 and median age documented at 58 years [3]. GISTs can occur anywhere throughout the GI tract, but show predilection for specific sites: 50% arise in the stomach, 25% in the small bowel and 10% in the colon and rectum [2], with the remaining primary sites including the mesentery, omentum and retroperitoneum. As is similar to other sarcomas, lymphatic spread of GISTs is extremely uncommon, with current guidelines recommending against lymph node biopsy at the time of GIST resection [4]. If metastases develop, they typically occur in the abdominal cavity or liver. Metastases outside the abdomen are very uncommon at presentation and reasonable attempts should be made to rule out another concurrent malignancy. Metastases to either lungs or bones are exceedingly rare and reflect an aggressive, more advanced disease process [5].

Symptoms at presentation are often nonspecific. Patients may experience bloating, fatigue, early satiety, obstruction, pain and GI bleeding. Given the location and presentation of the tumor, a normal physical exam should prompt further exploration with both endoscopy and computed tomography, with final diagnosis confirmed by pathology.

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Etiology

Basic science data would suggest that oncogenic mutations are critical in the development of sarcomas and, specifically, GISTs. GISTs are primarily defined by activating mutations in the *KIT* or *PDGFRA* receptor tyrosine kinases. KIT is a type III receptor tyrosine kinase highly expressed in interstitial cells of Cajal (ICC) – the presumed cell of origin for GISTs – as well as in hematopoietic stem cells, melanocytes, mast cells and germ cells. The natural process for these tyrosine kinase receptors is for the ligand to bind, thus activating the receptors and causing an activation of the downstream signaling pathways through the process of phosphorylation. Cell growth, proliferation and metastases then form. In the setting of tyrosine kinase receptor mutations, a constitutively activated receptor develops and leads to unopposed cell growth and proliferation. This phenomenon holds true for KIT, whereby a mutation also leads to constitutive activation of KIT in the absence of a ligand, unstoppable cell growth and tumor formation. The oncogenic mutation seen in most GISTs is gain-of-function. This serves as the major initiating event that drives the pathogenesis for GISTs. A gain-of-function oncogenic mutation in PDGFRα, also appears to activate GISTs. KIT-activating mutations are found in 85–90% of GISTs [6,7], thus enabling this to be a distinguishing feature to further separate this tumor from leiomyomas, leiomyosarcomas and schwannomas. The most commonly reported *KIT* mutations associated with GISTs often involve exon 9 or 11, whereas mutations in the split kinase domains (exons 13 or 17) are uncommon (<5%) [8]. These mutations are not monolithic and include deletions, insertions and missense mutations. Approximately 4% of GISTs completely lack KIT immunoreactivity. For these KIT-negative GISTs, most harbor activating mutations in *PDGFRA* [9,10]. Of these mutations in *PDGFRA*, 85% occur in the second kinase domain (exon 18), of which almost two thirds consist of a single point mutation. Other less commonly detected mutations include, exon 12 (juxtamembrane domain) or exon 14 (first kinase domain) mutations [11]. Nearly all *PDGFRA* mutant GISTs arise in the stomach, omentum or mesentery, and show epithelioid morphology [12–15]. The complexity of GIST biology and variable responses to treatment can be attributed to the different KIT or PDGFRα mutations harbored [16]. Wild-type (WT) GISTs refer to those tumors that have neither KIT nor PDGFRα mutations. *BRAF* mutation has been detected in 7–13% of WT GISTs. Mutations of the *BRAF* gene are mainly localized to exon 15 (nucleotide 1799), replacing a valine at position 600 with an aspartic acid. This modification mimics the phosphorylation of the kinase activation domain leading to permanent activation of the kinase. The significance of *BRAF* mutations in GISTs negative for *KIT* or *PDGFRA* mutation is unknown, although there should be a biologic impact in the tumor because this mutation has been selected during tumor development [17,18]. In recent years, *KIT* mutational status has become important as a predictive marker of how well patients with GISTs will respond to biologic therapies to counter their cancer. Current and future clinical trials will definitely incorporate mutational status testing in their study design.

Further exploration of the etiology of GISTs formation would suggest an additional mechanism of oncogenesis. Chi *et al.* have recently concluded that GISTs may arise when a normal developmental gene is converted into a tumor-promoting factor by a cooperating oncogene [19]. This finding has implications for diagnostics and therapeutic development. GISTs are presumed to arise in ICCs, which are located in the GI tract. A study has shown that the transcription factor ETV1 promotes GIST development, and is also needed for ICC development. GISTs are known to carry mutated versions of the cancer-promoting gene *KIT*, and the study suggests that ETV1 cooperates with this oncogene to drive the cancer. The fact that ETV1 seems to be present in high levels in all GISTs makes it immediately useful as a candidate diagnostic biomarker. Furthermore, molecules that block ETV1 may prove useful against drug-resistant GIST.

Treatment

Treatment options for GISTs vary based on presentation of the patient. Factors that need to be elucidated include whether the tumor is local or metastatic and whether or the tumor is thought to be resectable or not. For localized lesions, treatment consists of complete surgical resection, for curative intent. As previously mentioned, lymph-node involvement is exceedingly rare and, as such, lymphadenectomy is not recommended. Complete surgical resection with negative margins is the mainstay of treatment and confers a 5-year survival rate of 20–44% [20].

The prognosis for patients with newly diagnosed GISTs has been well characterized and studied. Prognosis and risk of recurrence or metastatic disease is established by evaluation of tumor location, size of the primary tumor, mitotic index and evidence of tumor spillage. Tumors are stratified based on sizes of <2, 2–5, 5–10 and >10 cm. A mitotic index of less than 5 per 50 high powered fields is felt to confer a better

prognosis than an index greater than or equal to 5 per 50 high powered fields. Disease site also has prognostic significance, with tumors of the duodenum, jejunum, ileum and rectum having a higher risk for aggressive behavior, as compared with gastric tumors. Finally, tumor spillage, whether iatrogenic or spontaneous, portends a dismal outcome, with survival similar to patients who present with metastatic disease [21,22].

Imatinib

The initial interest in imatinib for patients with GISTs stems from a case report, published in the *New England Journal of Medicine*, describing a single patient with metastatic GISTs, treated with imatinib, a tyrosine kinase inhibitor (TKI) that had previously only been used and approved for the treatment of chronic myelogenous leukemia [23]. Imatinib is a TKI that specifically affects the receptors of BCR-ABL, PDGFRα, PDGFR-β, c-FMS, c-KIT, and receptors encoded by the RET proto-oncogene [24]. This one-case report led to the further evaluation of imatinib in patients with GISTs and several large clinical trials to assess the best treatment regimen for metastatic and/or unresectable GISTs.

A pivotal, open-labeled, randomized, controlled trial was conducted at multiple centers and randomly assigned 147 patients to either imatinib 400 or 600 mg, administered once daily [25]. Response rate to treatment was reported as 54%, with 28% of patients achieving stable disease (SD) for a disease control rate of 82%. Two separate Phase III trials randomized patients to receive either imatinib 400 or 800 mg/day. While no survival advantage was found, an increase in toxicities was observed with the patients randomized to the high-dose treatment arm. Further subset analysis, taking into account the mutation status of the tumor specimens, suggested that patients with mutations in *KIT* exon 9 may have improved disease-free survival with initial imatinib dosages of 800 instead of 400 mg [26]. The responsiveness to imatinib does correlate closely with the mutational status. GISTs that harbor the *KIT* exon 11 mutations show an 85% response rate and those that have the *KIT* exon 9 mutations have a 45% response rate [27].

Subsequent to its approval in the metastatic setting, imatinib's potential role in the adjuvant setting was naturally questioned. Dematteo *et al.* postulated that the administration of imatinib would show an increased recurrence-free survival, when compared with placebo after complete resection of primary, localized GISTs. They conducted a randomized, double-blinded, Phase III multicenter trial in which patients were randomized to placebo versus imatinib 400 mg daily for 1 year (ACOSOG Z9001). They observed that the patients with imatinib had 98% recurrence-free survival at 1 year compared with 83% in patients on placebo ($p < 0.0001$). The overall survival (OS), however, was similar at 1 year; 99.2% in the treatment group versus 99.7% in the placebo group (follow-up is planned for 3 years) [28,29]. This study led to the US FDA approval of imatinib in GISTs for treatment on the adjuvant setting [30].

Sunitinib

Sunitinib (Sutent®, SU11248) is an oral multitargeted tyrosine kinase receptor inhibitor that has antiangiogenic and antitumor activities. These specific effects of sunitinib are related to its tyrosine kinase receptor inhibition of KIT, PDGFRs, VEGFR-1, -2 and -3, FLT3 and the RET and all downstream signaling pathways from these receptors [31–35]. Despite both sunitinib and imatinib binding within the ATP-binding domain of both KIT and PDGFR, they each have different binding characteristics and affinities, thus distinguishing these two drugs from each other. A randomized, controlled trial of 312 patients evaluated the efficacy and safety of sunitinib versus placebo, in patients with advanced GISTs who had progressed on imatinib [36]. Results confirmed the role of sunitinib as a second-line agent in the metastatic setting by showing a statistically significant prolonged median time to tumor progression for patients taking sunitinib – 27.3 versus 6.4 weeks in the placebo arm.

Update from recent clinical trials: metastatic disease

■ Imatinib

The effect of imatinib discontinuation on progression-free survival (PFS) and OS in long-standing responders with advanced GISTs is unknown. Thus, a Phase III trial has recently been reported in patients with nonprogressive disease according to RECIST criteria after 3 years of imatinib. In an open-labeled, national, multicenter Phase III study in France, patients with GISTs free of progression after 3 years of imatinib 400 mg/day, were randomly assigned to continue or interrupt imatinib treatment. Analysis was done according to the intention-to-treat principal. Findings showed that the 434 patients were enrolled in the trial between 2002 and 2009. Subsequently, 50 patients with no progressive disease (PD) who had received 3 years of treatment with imatinib were randomly assigned to continue or interrupt their treatment, with 25 patients in each group. After a median follow-up of 35 months after random assignment, 2-year PFS was 80% in the continuation group and 16% in the interruption

group. The interpretation from the trial confirmed that imatinib interruption after 3 years in responders resulted in a high risk of rapid progression in patients with advanced GISTs. Discontinuation of imatinib is not recommended outside clinical trials unless patients experience significant toxic effects [37].

Imatinib & everolimus

While imatinib is standard therapy for advanced GISTs, most patients develop resistance. A Phase I–II study was conducted to assess the safety and efficacy of coadministering an inhibitor of mTOR, everolimus, with imatinib in imatinib-resistant GIST patients. In the Phase I portion, patients received imatinib combined with weekly or daily everolimus to determine the optimal dose. In Phase II, patients were divided into two strata based on prior therapy and received the recommended Phase II dosing of everolimus 2.5 mg/day plus imatinib 600 mg/day. The study found that combination treatment was well tolerated. In the Phase II study (strata 1 and 2) four of 23 (17%) and 13 of 35 (37%) assessable patients, respectively, were progression-free at 4 months; median PFS was 1.9 and 3.5 months, and median OS was 14.9 and 10.7 months, respectively. In stratum 1, 36% had SD and 54% PD, while in stratum 2, 2% had partial response, 43% SD and 32% PD. The combination of everolimus and imatinib after failure on imatinib and sunitinib merits further investigation in GISTs [38].

Masitinib

Masitinib is another TKI but with greater *in vitro* activity and selectivity for the WT c-KIT receptor and its juxtamembrane mutation than imatinib. A Phase II study was published, presenting the results of masitinib as a first-line treatment in advanced GISTs. Imatinib-naive patients with advanced GISTs received oral masitinib at 7.5 mg/kg/day. Efficacy end points included response rate at 2 months, best response according to the response evaluation criteria in solid tumors (RECIST), metabolic response rate, disease control rates, PFS and OS rates. In total, 30 patients were enrolled. Response rate at 2 months of therapy was 20% according to RECIST and 86% according to FDG-positron emmision tomography response criteria. Best responses were complete response in one patient, partial response in 15 patients, SD in 13 patients and PD in one patient. Median time-to-response was 5.6 months, with an estimated median PFS of 41.3 months with PFS rate of 59.7 and 55.4% at 2 and 3 years, respectively. The OS at 2 and 3 years was stable at 89.9%. The conclusion from the trial indicates that masitinib appears to be effective as a first-line treatment for advanced GISTs with compatible results to imatinib in terms of safety and response. PFS, in particular OS, data show promise that masitinib may provide substantial benefits [39]. A prospective, multicenter, randomized, open-labeled, active-controlled, two-parallel group, Phase III study to compare efficacy and safety of masitinib at 7.5 mg/kg/day with imatinib at 400 or 600 mg/day in treatment of patients with GISTs in first-line medical treatment will establish whether or not there is a role for masitinib in first-line therapy.

A prospective, multicenter, randomized, open-labeled, active-controlled, two-parallel group, Phase II study to compare efficacy and safety of masitinib at 12 mg/kg/day with sunitinib at 50 mg/day in treatment of patients with GISTs resistant to imatinib is complete and information related to the results of the study have been released by the company. The results reported are encouraging. Masitinib significantly improved OS in patients with imatinib-resistant GISTs as compared with sunitinib. In this study, 44 patients with inoperable, locally advanced or metastatic GISTs and showing disease progression while treated with imatinib, received either masitinib (23 patients) or sunitinib (21 patients) until progression. After a median follow-up of 14 months, median OS was not reached for masitinib versus 15 months for sunitinib ($p = 0.022$). After 18 months, 79% of patients treated with masitinib were still alive, versus 20% for patients treated with sunitinib. After 2 years, 53% of patients treated with masitinib were still alive, versus 0% for the patients treated with sunitinib.

Vatalanib

Recently, Joensuu *et al.* published their work with vatalanib in patients with advanced GISTs [40]. As a similar drug to both imatinib and sunitinib, vatalanib is a TKI with an inhibitory effect on KIT, PDGF-R and VEGF-R. Their Phase II study was conducted with a primary end point of efficacy and secondary end point evaluating the safety of vatalanib in patients with advanced GISTs resistant to imatinib or both imatinib and sunitinib. A total of 45 patients with metastatic GISTs who had progressed on imatinib were enrolled. A total of 19 patients had also received prior sunitinib therapy. Vatalanib 1250 mg was administered orally daily. Clinical benefit was experienced by 18 patients (40%), including two confirmed partial responses (PR) and 16 SD. Out of 26 patients who had only received prior imatinib, 12 achieved either PR or SD compared with six out of the 19 patients who received prior imatinib and sunitinib treatment. The median time to progression was 5.8 months in a subset without prior sunitinib and 3.2 months among those with prior imatinib and sunitinib. Vatalanib

was generally well tolerated. The Phase II clinical trial thus established vatalanib as an active agent in patients with documented imatinib-resistant GISTs or with imatinib-and-sunitinib-resistant GISTs [40].

Regorafenib

Regorafenib is a novel oral kinase inhibitor that blocks VEGFR2–3, c-KIT, TIE2, PDGFR-β, FGFR1, RET, RAF and p38 MAPK and has a broad spectrum of antitumor activity in preclinical and early-phase trials. A multicenter Phase II study of regorafenib in patients with advanced GISTs, after therapy with imatinib and sunitinib, was recently reported in abstract form [41]. Eligible patients (34) received regorafenib 160 mg/day orally on days 1–21 of each 28-day cycle. At the time of evaluation, 22 eligible patients had been on protocol for at least 16 weeks. Clinical benefit was noted in 12 patients (two PR, ten SD) for a clinical benefit rate of 54.5% (90% CI: 35.3–72.9%). Benefit was seen in patients whose tumors had primary *KIT* exon 11 mutations, *KIT* exon 9 mutations or WT kinase genotype. Immunoblotting of prestudy and day-15 matched biopsies demonstrated a 50% inhibition of KIT and AKT phosphorylation in three out of four patients, all with SD for at least four cycles. Regorafenib seems to have significant activity in pretreated patients with advanced GISTs. An international Phase III trial is currently underway in this patient population.

Sorafenib

A Phase II study of the Korean GIST study group has recently reported on sorafenib in patients with metastatic GISTs who failed two or more prior TKIs [42]. A total of 31 patients with measurable metastatic GIST who failed both imatinib and sunitinib were accrued. Sorafenib was administered orally at 400 mg twice daily until disease progression or development of intolerance. Results confirmed four patients achieved PR (response rate 13%), and 16 had SD (52%). At 24 weeks of treatment, disease control rate was 36%. Median progression-free and OSs were 4.9 and 9.7 months, respectively. Sorafenib showed antitumor activity in this population of imatinib and sunitinib pretreated GIST.

A second publication, evaluating patterns of care, prognosis and survival in patients with metastatic GISTs refractory to imatinib and sunitinib, has demonstrated the efficacy of sorafenib in third-line therapy [43]. Medical records of 223 imatinib- and sunitinib-resistant GIST patients who were treated in 11 major referral centers were reviewed. Sorafenib was prescribed to 55 patients in this setting. After adjustment for prognostic factors, nilotinib and sorafenib provided the best PFS and OS. Sorafenib was found to have significant clinical activity in imatinib- and sunitinib-resistant GISTs and further evaluation is merited.

Nilotinib

The evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib has recently been reported in three reports, two Phase II trials and a Phase III trial. Nilotinib, a second-generation TKI, was tested in a single-center, open-labeled, Phase II study with the primary objective of determining PFS at 6 months [44]. A total of 13 patients were treated; 11 had received only prior imatinib and sunitinib. No measurable responses were observed; median time to progression was 2 months. Mutation testing is available from ten primary tumors with seven exon 11 mutations, one exon 9 mutation and two without *KIT*/*PDGFR* mutations. While nilotinib was well tolerated in these patients with advanced GIST, accrual was halted due to insufficient clinical benefit.

A second Phase II study, evaluating nilotinib as third-line therapy for patients with GISTs was conducted as a single-arm, open-labeled trial in eight Japanese hospitals [45]. The key eligibility criteria included resistance or intolerance to both imatinib and sunitinib treatment. A total of 35 patients were enrolled and treated with nilotinib 400 mg twice daily. The disease control rate at week 24 was 29%. The median PFS was 113 days and the median OS was 310 days. The objective response rate was 3%, comprising one PR in a patient with a GIST possessing both a *KIT* exon 11 mutation and an imatinib- and sunitinib-resistant *KIT* exon 17 mutation. A total of 23 patients (66%) had SD (≥6 weeks) as the best response. These results suggest that nilotinib has encouraging antitumor activity in patients with GIST who failed both imatinib and sunitinib.

A Phase III study of nilotinib versus best supportive care with or without a TKI in patients with GISTs resistant to, or intolerant of, imatinib and sunitinib was recently published [46]. Patients were randomized to nilotinib 400 mg twice daily or best supportive care, with or without either imatinib or sunitinib. The primary efficacy end point was PFS. A crossover to nilotinib was permitted. The study enrolled and evaluated 248 patients. Median PFS was similar between arms; 109 and 111 days for nilotinib and best supportive care, respectively. A trend in longer median OS was noted with nilotinib, but this was not statistically significant. With no significant difference in PFS, the role for nilotinib in third-line therapy is debatable.

Update from recent clinical trials: adjuvant

therapy

■ Imatinib

While lifelong imatinib therapy is recommended, as documented above, in the metastatic setting, the optimal duration of adjuvant therapy with imatinib is still relatively unknown. The Scandinavian Sarcoma Group recently reported at the American Society of Oncology national meeting, results of their randomized, prospective, Phase III, multicenter study of 400 patients, with KIT-positive resected GISTs (SSG XVIII trial). Eligibility for these patients included an ECOG performance status ≥2, and enrollment within 12 weeks of surgery. Patients were randomly assigned to receive 400 mg of imatinib daily for either 12 or 36 months, with 200 patients assigned to each cohort. Patients who received 36 months of imatinib had a documented improvement in 5-year OS, 92 versus 81.7% in patients who were treated for 12 months (hazard ratio: 0.45; 95%CI: 0.22–0.89; p = 0.019) [47]. These study results differ from ACOSOG Z9001, which reported improvement in disease-free survival without a documented OS advantage.

Conclusion

Since the recognition of the therapeutic benefit of imatinib, the evolution of treatment for GISTs, initially metastatic and unresectable and now in the adjuvant setting for resected tumors, has been remarkable and impressive. Treatment of this disease has advanced from previous ineffective cytotoxic chemotherapy to oral TKIs that are quite efficacious. The medical community's understanding of the diagnosis, molecular biology, treatment and surveillance of GISTs has dramatically changed over the last decade; however, the story is certainly not over.

Although a remarkable improvement in treatment has been seen with imatinib, sunitinib and other TKIs, primary and acquired resistance has limited their effectiveness and the continued development of alternative therapies both as alternatives and as synergistic adjuncts remains of utmost importance. With new trials being conducted to identify new therapeutic agents for GISTs, further changes and challenges are likely to emerge. While data are available to showcase the benefits of TKIs to the abovementioned targets, novel drugs with new targets are currently being explored. Over the next few years, information should emerge on the roles of these agents. One interesting pathway to be explored is the switch pocket, which is an area on KIT and other kinases that is adjacent to the ATP pocket. The switch pocket binds to the activation loop, which acts as the major on–off switch on a kinase. The kinase will be active when the activation loop switch is bound to the switch pocket. A switch-pocket inhibitor can prevent a kinase from turning on or can even turn off an already active kinase. This approach is complementary to more traditional TKIs that bind to the ATP pocket of a kinase. Switch control pockets are different among kinases. These differences provide the opportunity to design drug candidates with unprecedented and unique selectivity profiles.

The PI3K pathway (which includes AKT and mTOR) is immediately downstream from KIT. PI3K appears to be a major signaling protein in GIST, promoting cell survival and blocking cell death. An inhibitor of PI3K might circumvent imatinib-resistant GISTs when imatinib resistance results from a heterogenous mix of secondary mutations within the *KIT* gene, which would be difficult to treat by a single agent KIT inhibitor. Furthermore, many different cell surface receptors stimulate the PI3K pathway. Thus, inhibiting PI3K might be a way to stop GISTs that are driven by an unknown cell-surface receptor as in WT GIST. At least six PI3K drugs are being evaluated in Phase I trials.

Laboratory studies have demonstrated that inhibition of the HSP90 chaperone protein results in selective destruction of the mutated KIT kinase in human GIST cell lines across multiple genotypes that confer TKI resistance. HSP90 helps proteins to fold into their correct 3D shapes, stabilizes a variety of other proteins, many of which are involved in the development of cancer and protects them from degradation. Preclinical work has shown that mutant proteins can be effectively inhibited by interrupting the HSP90 function, thus making it a target of interest for GISTs. A Phase I clinical trial has reported on the treatment of 54 patients with HSP90 agent IPI-504 in patients with metastatic GIST following failure of TKIs [48]. Targeting HSP90 represents a novel therapeutic strategy for patients with metastatic GISTs and is currently being evaluated in Phase II clinical trials.

In the adjuvant setting, a survival advantage has now been established for 3 years of imatinib in a select group of patients. To further characterize which patients will benefit is of utmost importance. The ACOSOG Z9001 trial tested only the 400-mg daily dose in the adjuvant setting. In randomized trials, patients with advanced GISTs and *KIT* exon 9 mutations have improved outcomes with 800-mg daily doses. Whether doses greater than 400 mg should be used in the adjuvant setting will require a prospective study, but until such studies are completed, patients with exon 9 mutations may benefit from 600–800 mg of imatinib daily rather than 400 mg daily.

Lastly, the duration of therapy that is optimal is still uncertain. In addition to the aforementioned ACOSOG Z9001 trial and the SSG XVIII trial, the Intergroup

Executive summary

Epidemiology

- Gastrointestinal stromal tumors (GISTs) are the most common sarcomatous tumors of the GI tract and can occur anywhere throughout the GI tract.

Etiology

- Both oncogenic mutations and transcription factors play a roll in the development of GISTs.

Treatment

- Current approved drugs for the treatment of metastatic GISTs include imatinib and sunitinib, while only imatinib is approved in the adjuvant setting.

Update from recent clinical trials: metastatic disease

- Further evaluation of imatinib, either alone or in combination with a mTOR inhibitor has recently been reported. In addition, data have recently been reported on several newer tyrosine kinase inhibitors, including masitinib, vatalinib, regorafenib, sorafenib and nilotinib.

Update from recent clinical trials: adjuvant therapy

- Results of the SSG XVIII trial have now been reported and show a survival advantage associated with the use of 3 years of adjuvant imatinib in a subset of patients.

EORTC 62024 trial, a randomization between 2 years of imatinib and observation alone, has been completed and is awaiting data maturation. A single-arm, Phase II, 5-year adjuvant imatinib trial (PERSIST5) has also completed accrual with data pending. We anticipate that the story of GISTs has just begun to be written. In the interim, consideration should be given, especially in difficult cases, for multidisciplinary consultation at a high-volume sarcoma center and enrollment into clinical trials, which will further give insight into a disease that has completely changed over the last few decades.

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- ▪ of interest
- ▪▪ of considerable interest

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