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Molecularly Targeted Therapy: Imatinib and Beyond

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1. Introduction

This chapter will focus on the molecular biology of gastrointestinal stromal tumors, with a focus on therapy targeting the primary activating mutations in the KIT proto-oncogene. The studies that have led to the approval of imatinib and sunitinib will be reviewed. Additional novel agents under development will be discussed.

2. Background and histology

Gastrointestinal stromal tumors (GISTs) are rare tumors, with an estimated incidence of 1.5/100,000 persons per year (Nilsson, 2005). This number accounts for clinically relevant tumors, there is a much higher number of microscopic lesions that can be detected on pathologic specimens. The incidence of such microscopic subclinical lesions approaches 20% in surgical and autopsy specimens (Agaimy, 2007). GISTs account for the overwhelming majority of mesenchymal tumors arising in the GI tract. GISTs arise most frequently in the stomach (approximately 60%), and small bowel (30%), but these tumors can arise anywhere in the GI tract (DeiTos, 2011). GISTs are thought to originate from the interstitial cells of Cajal (GI pacemaker cells). These subepithelial neoplasms share a unique molecular and immunohistochemical signature. Morphologically, GISTs are subdivided into spindle cell, epithelioid cell, and mixed types, but these distinctions have little clinical relevance. Overt cytologic atypia and dedifferentiation are quite rare, and should lead to considerations of alternative diagnoses (DeiTos, 2011). Nearly all GISTs express immunoreactivity to c-KIT, also known as CD117 or stem cell growth factor receptor (SCFR). The KIT receptor is a membrane-bound class III receptor tyrosine kinase (RTK) encoded by the *KIT* proto-oncogene. This RTK is activated by the binding of mast cell growth factor (MGF), also known as stem cell factor. About 95% of GISTs overexpress KIT. DOG1 has also been used as a very sensitive and specific immunomarker. In a large pathology series, the overall sensitivity of DOG1 and KIT in GISTs was nearly identical: 94.4% and 94.7%, and results in GISTs were generally concordant. Gastric spindle cell GISTs were nearly uniformly positive for both markers, whereas DOG1 performed slightly better in gastric epithelioid GISTs that included a higher percentage of platelet derived growth factor receptor alpha (PDGFRA)-mutant GISTs. In the intestinal GISTs, KIT was slightly more sensitive than DOG1. Negativity for both DOG1 and KIT was observed in 2.6% of GISTs (Miettinen, 2009). In 80%

of cases, KIT overexpression is the result of activating mutations in exons 9, 11, 13 and 17 in the *KIT* proto-oncogene (Corless, 2008). Most *KIT* mutations (70%) affect exon 11 within the juxtamembrane domain, and result in constitutive activity of the RTK (Heinrich, 2008). Another clinically important mutation occurs in exon 9, part of the extracellular domain, and occurs almost exclusively in intestinal GIST (Ganjoo 2011). Over-expression without identifiable mutations also occurs, and the mechanism for over-expression of KIT in such cases is presently unclear. Approximately 5% of cases of GIST are immunohistochemically negative for KIT. Activating mutations in a related RTK, PDGFRA, account for most of these cases. KIT and *PDGFRA* mutations do appear to be mutually exclusive oncogenic mechanisms in GISTs. However, a small percentage of GISTs lack mutations in either RTK, and the molecular pathogenesis of these tumors remains unknown at this time. Although most GISTs are sporadic, familial cases with heritable mutations in the *KIT* gene have been identified. Rare syndromes include the Carney triad, which involves GIST, extra-adrenal paraganglionomas, and pulmonary chondromas. In the Carney-Stratakis syndrome, which is transmitted in an autosomal dominant fashion, only GISTs and the paraganglionomas are seen. There is also an increased risk of GIST in patients with neurofibromatosis type I (Kinoshita, 2004.) Pediatric GIST tumors are a distinctive subset, occur mostly in females, are *KIT/PDGFRA* wild-type, and generally follow an indolent course (Dei Tos, 2011).

3. Clinical presentation and staging

Common presentations of GISTs include an abdominal mass, pain or GI bleeding. Histologically, 70% are the spindle cell type, 20% the epithelioid type, and a mixed pattern is encountered in 10% of cases. Tumor size and mitotic rate are the most important determinants of aggressiveness, although location within the GI tract also matters. In general, intestinal GISTs are more aggressive than are gastric tumors. Indeed, there are different stage groupings for gastric, omental and small bowel, esophageal, colorectal and mesenteric primaries in the tumor-node-metastasis (TNM) system. A contrast-enhanced computed tomographic (CT) scan is generally the preferred initial imaging study for screening and staging, although magnetic resonance imaging (MRI), upper GI endoscopy, endoscopic ultrasound (EUS) and positron emission tomographic (PET) scanning using fluorodeoxyglucose (FDG) all have potential utility, depending on the clinical scenario. For example, EUS is the most accurate modality for distinguishing leiomyomas from other submucosal lesions. Preoperative biopsy is not generally recommended for a resectable lesion that is highly suspicious for GIST, unless metastatic disease is suspected, or neoadjuvant imatinib is being considered. Surgery remains the mainstay of local treatment of GIST. All localized GISTs ≥ 2 cm should be completely resected. There is no consensus on the management of smaller lesions. For potentially resectable GISTs, segmental (rather than peritumoral) visceral resection is preferred. Routine lymphadenectomy is unnecessary because nodal metastases are rare.

4. Targeting KIT in GIST

Imatinib mesylate is a competitive inhibitor of the Bcr-Abl, KIT and PDGFRA RTKs. The dramatic results of the IRIS (International Randomized Study of Interferon and STI571) trial in patients with chronic myelogenous leukemia (CML) revolutionized the treatment of that

disease and ushered in a new era of molecularly targeted therapy in oncology (O'Brien, 2003). It subsequently became evident that imatinib induced dramatic, rapid and sustained clinical benefit in advanced GISTs as well. GISTs are exquisitely dependent on signaling via KIT or PDGFRA because of the activating mutations discussed above, a phenomenon termed "oncogene addiction". Molecularly targeted therapy with tyrosine kinase inhibitors (TKIs) such as imatinib or sunitinib blocks such signaling, and consequently also the downstream pathways. (**Figure 1**)

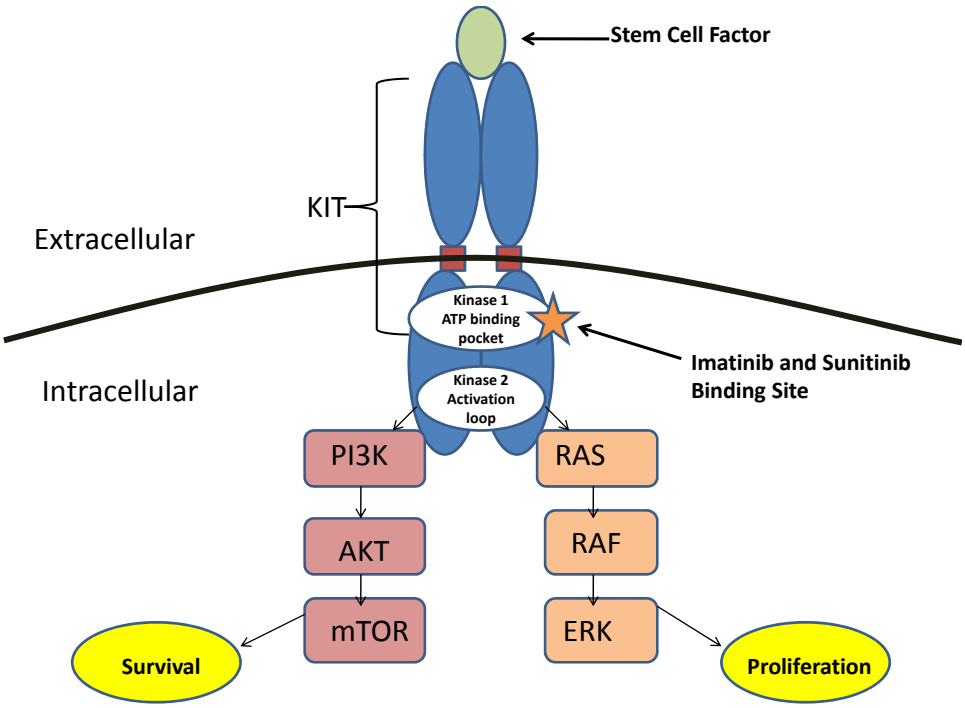

Fig. 1. A simplified schematic diagram of the KIT transmembrane receptor tyrosine kinase and downstream signaling pathways. Constitutive activation of KIT is caused by mutations in the extracellular domain (exon 9), the juxtamembrane domain (exon 11), or the intracytoplasmic kinase domain (exons 13 and 17) that result in different profiles of drug sensitivity/resistance. Activation of KIT leads to ERK activation, mTOR activation and JAK/STAT activation (not shown).

5. Characterization of response

An important consideration in the development of clinical trials in the modern era of targeted therapy is the measure of response. In 2000, a group of international experts agreed on standard criteria for measuring tumor response, called Response Evaluation Criteria in Solid Tumors (RECIST). Each lesion that is identified as a target lesion (>1 cm) is measured in one dimension, the longest diameter. A complete response (CR) is the disappearance of all target tumors. A partial response (PR) is a 30% or larger decrease in the sum of the

longest diameters of the tumors. Progressive disease (PD) is a 20% or greater increase in the sum of the diameters. Stable disease (SD) refers to changes in tumor size that do not meet any of these criteria. RECIST has numerous shortcomings but remains the standard for evaluating response in clinical trials, although that is beginning to change. An increasing number of drugs in development inhibit tumor cell growth (cytostatic) and thus do not shrink the tumor, unlike conventional chemotherapeutic agents, which kill tumor cells (cytotoxic). Criticisms have been raised that tumor density or metabolic activity are not related to diameter, and clinically relevant responses are missed when using uni-dimensional measurements. To address this weakness, alternative criteria, including the Choi criteria, have been proposed. In GIST, tumors only rarely shrink greater than the 30% required for response characterization by RECIST, yet survival benefit of therapy is proven. Changes in tumor density rather than size appear to correlate better with response to these drugs, and prolonged disease stabilization rather than frank tumor shrinkage may be seen on imaging studies. Choi criteria use a 10 percent decrease in unidimensional tumor size or a 15 percent decrease in tumor density on contrast-enhanced CT scans (as reflected by differences in x-ray attenuation between a given material and water, expressed in Hounsfield units), to determine response. In one comparison study looking at RECIST criteria versus Choi criteria in 58 patients with GIST, responses by Choi criteria predicted disease-specific survival while RECIST criteria did not. Using RECIST, 28 (48%) patients showed response and 30 (52%) were nonresponders. Yet there was no statistically significant difference in time to progression between the two groups (P = .2). By the Choi criteria, however, 49 (84%) were good responders and 9 (16%) were not. The good responders had a longer time to progression than the poor responders (P = .0002). The Choi criteria also more accurately predicted disease-specific overall survival (OS) than did the RECIST criteria (Benjamin, 2007). Additional response criteria in use include the Southwest Oncology Group (SWOG) criteria, which monitors disease control rate, and characterizes anything that is not tumor growth as a response. Another approach is to evaluate metabolic activity using FDG-PET. In a study of 23 patients getting second line therapy with sunitinib after progression on imatinib, tumor metabolism was assessed with FDG-PET before and after the first 4 weeks of sunitinib therapy. Treatment response was expressed as the percent change in maximal standardized uptake value (SUV). The primary end point of time to tumor progression on the basis of RECIST criteria was compared with early PET results. Progression-free survival (PFS) was correlated with early FDG-PET metabolic response (P < .0001). Using -25% and +25% thresholds for SUV variations from baseline, early FDG-PET response was stratified into metabolic partial response, metabolically stable disease, or metabolically progressive disease; median PFS rates were 29, 16, and 4 weeks, respectively. Similarly, when a single FDG-PET result was considered after 4 weeks of sunitinib, the median PFS was 29 weeks for SUVs less than 8 g/mL versus 4 weeks for SUVs of 8 g/mL or greater (P < .0001). None of the patients with metabolically progressive disease subsequently responded according to RECIST criteria. Multivariate analysis showed shorter PFS in patients who had higher residual SUVs (P < .0001), primary resistance to imatinib (P = .024), or nongastric GIST (P = .002), regardless of the mutational status of the KIT and PDGFRA genes (Prior, 2009). To summarize, imaging evaluations of response to targeted therapy in GIST are evolving. It is important to keep in mind that tumor shrinkage alone may not correlate with response or survival in GIST in the context of the current arsenal of therapeutic agents.

6. Imatinib in the treatment of GIST

Imatinib is the standard of care for advanced, unresectable or metastatic GIST. It has improved median overall survival from 18 to 57 months, vastly changing the outlook for patients with this disease (Figure II). A single case was reported by Joensuu and colleagues showing a dramatic response to imatinib in a patient with metastatic GIST (Joensuu, 2001). This led to the subsequent treatment of 35 patients in a phase I study conducted by the European Organization for Research and Treatment for Cancer (EORTC), which showed a 54% PR and 37% SD rate (van Oosterom, 2002). In a subsequent large multicenter, randomized, open-label phase II study, patients with metastatic or unresectable GIST were treated with either imatinib 400 or 600 mg daily (Demetri, 2002). Patients whose tumors progressed on imatinib 400 mg were allowed to take the higher dose. Of the 147 patients treated, 53.7% had a PR and 27.9% had SD. Efficacy was based on the SWOG criteria and the median time to response was 13 weeks. The results of this trial led to Food and Drug Administration (FDA)-approval of imatinib for the treatment of unresectable or metastatic GIST in the United States (**Table 1**, page 6). Long-term follow-up analysis showed a 5-year OS rate of 57% in patients who responded to imatinib, and only a 9% 5-year OS rate in those who progressed. There also appears to be molecular heterogeneity in terms of survival on imatinib. Median OS was 63 months in patients with the more common c-KIT exon 11 mutation, compared with 44 months in patients with exon 9 mutations (Blanke 2008). This is also described in **Figure 2**, shown below.

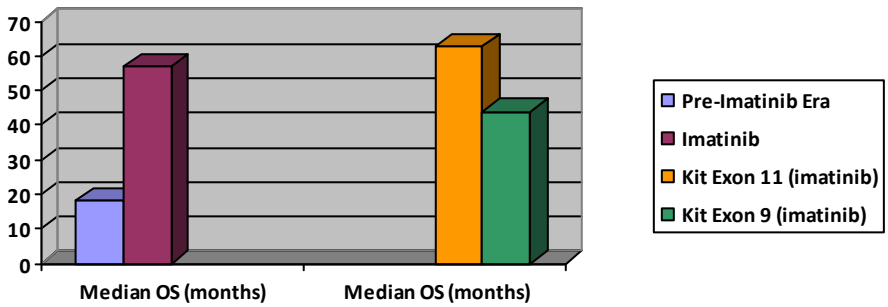

Fig. 2. Median overall survival in the pre-imatinib era compared to the long term survival data from the phase II study that led to the US FDA approval of imatinib in advanced GIST. Upon analysis of the long term survival data, it became clear that exon 9 mutations carry a worse prognosis than the more common exon 11 mutations (Blanke 2008) in imatinib-treated patients.

Registration trial	Treatment and comparison	Findings
Imatinib in unresectable or metastatic disease (Demetri GD, 2002)	400 mg or 600 mg imatinib p.o. daily in 147 patients. Comparison to historical controls SWOG criteria for response evaluation used, not RECIST	53.7% PR rate 27.9% SD rate 13.6% showed early resistance 0% CR rate Median PFS and OS identical on both arms Median survival 57 months for all patients 28% remained on therapy long-term Time to onset of response 3 months.
Sunitinib as second line therapy in patients intolerant/refractory to imatinib (Demetri GD, 2006)	Sunitinib 50 mg p.o. daily, for 4 weeks every 6 weeks. International study, 312 patients, randomized 2:1 in favor of sunitinib	27.3 weeks PFS on sunitinib; 6.4 weeks on placebo PR or SD for at least 6 months was observed for the three most common primary GIST genotypes: KIT exon 9 (58%), KIT exon 11 (34%), wild-type KIT/PDGFRA (56%) May have increased activity against exon 9 mutations.
Adjuvant imatinib after resection of GISTs ≥ 3 cm (DiMatteo, 2009)	Imatinib 400 mg p.o. daily for 1 year 713 patients randomized 1:1 to imatinib or placebo	Relapse free survival at 1 yr 98% with imatinib, and 83% with placebo

Abbreviations: CR, complete response, PR, partial response, SD, stable disease, PFS, progression-free survival, OS, overall survival, SWOG, Southwest Oncology Group, RECIST, Response Evaluation Criteria In Solid Tumors.

Table 1. Summary of the 3 major trials of targeted therapy in the treatment of GIST. Overview of treatment administered and relevant results.

7. Dose escalation of imatinib in advanced GIST

Like in CML, the use of higher doses of imatinib (800 mg vs 400 mg daily) upfront has not been found to be advantageous in terms of impacting overall survival, and 400 mg daily represents the standard initial dose for most patients. A meta-analysis performed in 2009 looked at two large randomized trials comparing two dosing regimens for advanced unresectable and metastatic GIST (MetaGIST, 2010). Two phase III studies (the EU-AUS and US-CDN studies) looked at standard dose imatinib (400mg once daily) and high dose imatinib (400mg twice daily). High dose therapy showed an initial improvement in progression free survival (PFS) at 2 years, which was no longer significant with long term followup. There are several possible contributing factors to this result. Nearly half of all

patients in both studies had to have a dose reduction by 6 months, raising the question of long term tolerability. It is also possible that the PFS improvement at 2 years was due to dose-dependent mechanisms of resistance within the first 2 years, with alternate mechanisms affecting late resistance. The only identified predictive risk factor was the presence of *KIT* exon 9 mutations. For exon 9 mutations, there was a 42% reduction in the risk of progression or death in the high-dose group, compared to the low dose group. A non-significant 31% reduction in the risk of death was also seen. Exon 9 mutation rates remained low (8.1% in US-CDN and 15.6% in EU-AUS), and as such, true differences were difficult to detect even in the context of a meta-analysis. As such, there continues to be debate over the status of exon 9 mutations and initial choice of therapy, and there is disagreement amongst expert opinions and guidelines from the United States and Europe. Currently, the US National Comprehensive Cancer Network (NCCN) recommends that patients with documented exon 9 mutations in *KIT* be considered for dose escalation to 400mg twice daily, as tolerated. The European Society for Medical Oncology (ESMO) considers higher dose imatinib to be standard of care in this setting. Both recommend dose escalation to 400mg twice daily at the time of progression, regardless of mutation status. Stabilization of disease or even response can be seen after progression on standard doses of imatinib.

8. Pharmacokinetic considerations of therapy

Interpatient variability in pharmacokinetic exposure to the drug may also influence outcome. In this regard, monitoring of plasma levels of imatinib has been proposed, although its clinical impact remains unclear, pending further evaluation. In a pharmacokinetic study, clinical outcomes were correlated with imatinib trough levels at steady state. The median time to progression was 11.3 months for patients in the lowest C(min) quartile (Q1, < 1,110 ng/mL) compared with more than 30 months for those in the second through fourth quartiles (P = .0029) (Demetri, 2009). Prior surgery plays a substantial role in the bioavailability of TKI therapy, as all compounds currently used in the treatment of GIST are taken orally. Imatinib has an acid-dependent solubility, and plasma concentrations are significantly lower in patients who have undergone gastrectomy as part of prior GIST resection surgery (Yoo, 2010). Additionally, genetic polymorphisms affecting cellular uptake of imatinib have been shown to be important in CML patients. The intracellular uptake and retention of imatinib is dependent on the active transporter, organic cation transporter 1, (OCT-1). CML patients with low levels of OCT-1 required higher doses of imatinib to achieve response than patients with high levels of OCT-1 (White, 2007). This pharmacokinetic variability has not been explored in GISTs at this time, and testing of OCT-1 expression is not routine for these patients. Collectively, the evidence suggests that individualized tailoring of therapy to achieve optimal drug levels may play a role in the future.

9. Duration of therapy and side effect profile

For advanced disease, treatment with imatinib is indicated indefinitely: interruption of therapy leads to rapid disease progression in most patients, even after years of responsive or stable disease (Le Cesne, 2010b). Common side effects (>20%) of imatinib include fluid

retention, fatigue, abdominal pain, skin rash, muscle cramps, nausea, vomiting, and diarrhea (Dagher, 2002). Edema is generally superficial and confined to the eyelids and extremities, but pleural effusion and ascites can be seen. Macrocytosis is frequently seen, as is a mild anemia with chronic use or at higher doses. Neutropenia, hypophosphatemia, gynecomastia, lung, liver and cardiac toxicity are occasionally reported, and rarely, tumor lysis syndrome may occur. Depression has been noted, and has rarely required discontinuation of the drug. Intratumoral hemorrhage of large tumors has been seen in responding patients, and hemoglobin should be monitored for patients with bulky disease as they start therapy.

10. Sunitinib as second line therapy

Sunitinib is another multitargeted TKI, inhibiting KIT, PDGFRA, PDGFRB, FLT3, vascular endothelial growth factor receptors (VEGFR) 1,2 and 3, RET and colony stimulating factor-1R (CSF-1R) tyrosine kinases. Sunitinib represents the standard of care in advanced renal cell carcinoma. Sunitinib is approved in the US at a dose of 50 mg daily for four out of every six weeks for imatinib-refractory or –intolerant advanced GISTs . This approval was based on an increasing number of reports indicating efficacy of sunitinib in these settings, which culminated in a large international phase III placebo-controlled trial. In this trial, 312 patients were randomized in a 2:1 ratio to receive sunitinib (n=207) or placebo (n=105) in a blinded fashion. Study medication was given orally once daily at a 50-mg starting dose in 6-week cycles with 4 weeks on and 2 weeks off treatment. The primary endpoint was time to tumor progression. The trial was unblinded early when a planned interim analysis showed significantly longer time to tumor progression in the sunitinib arm. Median time to tumor progression was 27.3 weeks (95% CI 16.0–32.1) in patients receiving sunitinib and 6.4 weeks (4.4–10.0) in those on placebo (hazard ratio 0.33; $p<0.0001$) (Demetri, 2006). The results of this pivotal study are also reviewed in table 1. While the approved dose of sunitinib for GIST in the United States is 50mg daily for 4 weeks followed by 2 weeks rest, continuous dosing at 37.5 mg daily appears to be similarly safe and effective (George, 2005). Common side effects of sunitinib include fatigue, diarrhea, anorexia, nausea, vomiting, abdominal pain, myelosuppression, hypothyroidism, and discoloration of skin and hair. Hypertension, cardiac and renal toxicity, elevations in serum amylase and lipase, and palmar-plantar erythrodysesthesia are less commonly seen. There may be a selective benefit to sunitinib versus imatinib, depending on the site of the *KIT* mutation. GISTs with the more common exon 11 *KIT* mutations are more sensitive to imatinib than exon 9 mutants. Conversely, sunitinib appears to benefit those with exon 9 mutations significantly more than those with exon 11 mutations. This was shown in a recent phase I/II study of patients who were resistant/intolerant to imatinib. Clinical benefit (PR or SD for at least 6 months) with sunitinib was observed for the three most common primary GIST genotypes: *KIT* exon 9 (58%), *KIT* exon 11 (34%), and wild-type *KIT/PDGFRA* (56%). Progression-free survival (PFS) was significantly longer for patients with primary *KIT* exon 9 mutations ($P = 0.0005$) or with a wild-type genotype ($P = 0.0356$) than for those with *KIT* exon 11 mutations (Heinrich, 2008). One confounder regarding sunitinib and exon 11 is that all published studies to date have evaluated sunitinib in the second line setting, after imatinib failure. It is known that secondary mutations will confer resistance to imatinib, and may appear years after imatinib therapy. These mutations are nonrandom and cluster in exons 13 and 14, part of the drug binding pocket of the receptor, as well as in exon 17, which encodes the kinase activation

loop. Secondary kinase mutations were significantly more common in GISTs with primary *KIT* exon 11 mutations than in those with exon 9 mutations (73% *v* 19%; P = 0.0003) (Heinrich, 2008). It is not known if sunitinib will have the same efficacy profile in therapy-naïve patients with GIST.

11. Adjuvant therapy

As in other malignancies, the success of imatinib in the setting of advanced disease led to its study in the adjuvant and neoadjuvant settings. After a phase II trial (ACOSOG Z9000) of one year of adjuvant imatinib in patients with high-risk completely resected GIST yielded encouraging findings, the pivotal phase III ACOSOG Z9001 trial was conducted. This trial, which was stopped early because of significantly fewer recurrences in the treatment arm, led to the approval in the US of adjuvant imatinib (400 mg daily) for patients with resected GISTs ≥ 3 cm in size, without indicating the optimal duration of therapy. 359 patients were randomized to imatinib and 354 to placebo. In this trial, imatinib significantly prolonged relapse free survival (RFS) compared with placebo (98% vs. 83% at 1 year; overall hazard ratio 0.35; one-sided P < 0.0001) (**Table I**, DiMatteo, 2009). Similar large phase III trials have been conducted in Europe, one with overall survival as the primary endpoint. Crucial to determining the need for, or optimal duration of, adjuvant imatinib is accurate risk-stratification, and ESMO guidelines state that adjuvant imatinib can be "proposed as an option" for patients at substantial risk for relapse, calling for shared decision-making in situations of uncertainty. An additional study of 105 patients in China looked at 3 years of adjuvant imatinib 400mg daily versus observation in patients with resected high-risk or intermediate-risk GIST. This duration of adjuvant imatinib treatment is 2 years longer than the published ACOSOG Z9001 study. Relapse free survival (RFS) at 1, 2 and 3 years was higher in the treatment group than in the control group (100% vs. 90% at 1 year; 96% vs. 57% at 2 years; 89% versus 48% at 3 years; P < 0.001, HR = .188). Subgroup analyses showed that adjuvant therapy significantly decreased the risk of recurrence in patients, whether at high risk or at intermediate risk, compared with control patients (3-year RFS 95% vs. 72% in intermediate risk; 85% versus 31% in high risk, P < 0.001). In addition, adjuvant imatinib treatment decreased the risk of death (P = .039, HR = .254) (Li, 2011). Apart from the risk factors mentioned above, tumor rupture and incomplete resection are independent risk factors that negatively impact disease-free survival.

12. Neoadjuvant therapy

Since surgery is the only potentially curative option for GIST, neoadjuvant imatinib has been investigated in an effort to improve surgical outcomes. At this time, there are no randomized clinical trials from which to draw conclusions. Data from several case reports, retrospective series and one phase II trial suggest a role for neoadjuvant imatinib. The RTOG 0132/ACRIN 6665 trial was a prospective phase II study evaluating safety and efficacy of neoadjuvant imatinib (600 mg/day) for patients with primary GIST or the pre-operative use of imatinib in patients with operable metastatic GIST. The trial continued post-operative imatinib for 2 years. Sixty-three patients were entered (52 analyzable), 30 patients with primary GIST (Group A) and 22 with recurrent, metastatic GIST (Group B). Responses (RECIST) in Group A were: 7% partial, 83% stable, 10% unknown, and in Group B were: 4.5% partial, 91% stable, 4.5% progression. Two-year progression-free survival was

83% in Group A, and 77% in Group B. Estimated 2-year overall survival in Group A was 93%, and 91% in Group B. Complications of surgery and imatinib toxicity were minimal (Eisenberg BL, 2009). One criticism of this study is that the duration of preoperative imatinib was relatively short (8-12 weeks), which is likely too soon for response to fully manifest. Long term followup of the original study using imatinib in advanced or metastatic disease showed that in 25% of the patients, an objective response was achieved only after 5.3 to 39 months of imatinib treatment (Blanke, 2008). While CT scans remain the standard imaging modality for assessment of response in this setting, PET scans may be helpful when an expeditious assessment of response is needed. In general, neoadjuvant imatinib is indicated for patients with marginally resectable tumors and for those who have potentially resectable disease but with the risk of significant surgical morbidity. Some advocate its use only in the context of clinical trials, and others reserve it for high-risk patients. A dose of 400 mg daily is most commonly used, although 800 mg/day is reasonable for patients with exon 9 mutations. Sunitinib is also being evaluated in the neoadjuvant setting in a current clinical trial. The duration of therapy varies from 3 to 12 months, and periodic imaging evaluations are needed. The optimal duration of neoadjuvant imatinib and timing of surgery (at first resectability versus once the response has reached a plateau) have to be individualized. For responding patients, at least a year of adjuvant imatinib after resection is recommended, with longer durations being considered by many. Additionally, imatinib has been used pre- and post-operatively with resection in patients with liver metastases. In one study, forty one patients with liver metastases were randomized to imatinib plus resection (6 months neoadjuvant imatinib, then resection, followed by adjuvant imatinib), versus imatinib alone. In the 36-month followup period, the combination group had 1- and 3-year survival rates of 100% and 89.5%, while the imatinib-only group had survival rates of 85% and 60% respectively ($P = 0.03$) (Xia, 2010) In the absence of clear randomized data, coupled with the long term tolerability of imatinib, it seems reasonable to pursue neoadjuvant and adjuvant imatinib in patients that are at high risk for surgical complications, or unresectable at presentation. Enrollment onto neoadjuvant clinical trials will be imperative to determining the optimum timing, duration, and response to neoadjuvant therapy.

13. Molecular considerations to targeted therapy

Agents within the same class of targeted therapies may have different properties that appear to play a role in response and side effect profiles. Even closely related compounds interact with their binding sites differently, and bind with different affinities to other RTKs. Imatinib works by competitively and reversibly binding to the ATP-binding pocket of KIT, resulting in stabilization of the inactive conformation of the kinase domain (Gajiwala, 2009). This specificity for the inactive conformation of KIT helps explain why certain mutations, such as the exon 17 activation loop (A-loop) mutation confer resistance to imatinib (Demetri GD, 2011). Additionally, mutations in the ATP pocket, such as exon 13 and 14 mutations lead to imatinib resistance. Sunitinib is a smaller molecule than imatinib, and mutations in the binding pocket do not confer the same resistance as they do with imatinib. The differences in binding properties enable sunitinib to overcome some, but not all, secondary mutations that arise on imatinib therapy. As sunitinib also binds to the ATP-binding pocket with affinity for the inactive conformation of the enzyme, mutations in the A-loop also confer drug resistance to sunitinib (Demetri GD, 2011). Dasatnib is another molecule with binding affinity towards KIT. Its chemical structure is different from imatinib and sunitinib in that it

is able to bind to the ATP-binding pocket regardless of the conformation of the kinase activation loop (Schittenhelm, 2006). Dasatinib is being studied in GIST in ongoing clinical trials. Molecular characterization of primary and secondary *KIT* mutations appear below in **Figure 3**.

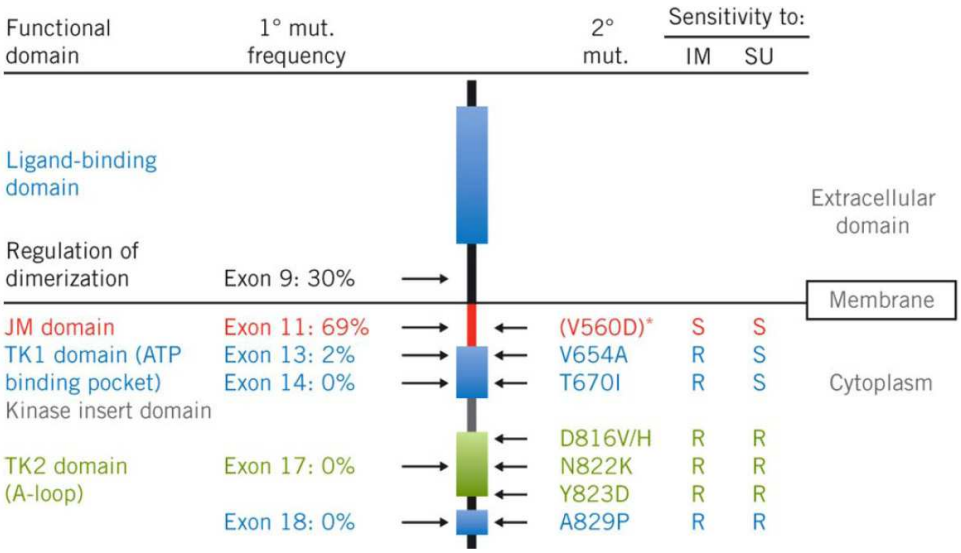

Fig. 3. Overview of the KIT protein, showing functional domains, and location of primary (1) and secondary (2) mutations (mut.) Frequencies of primary KIT mutations, specific secondary mutations, and resistance (R) or sensitivity (S) to imatinib (IM) or sunitinib (S) are as reported in the phase I/II trial of sunitinib in advanced GIST after imatinib failure (Heinrich, 2008). Reproduced, with permission, from Gajiwala, 2009. © 2009, National Academy of Sciences, USA.

14. New therapies in development

Several compounds are being investigated clinically in advanced GIST, as frontline therapy or after imatinib failure. In general, these compounds are directed at the RTKs KIT and PDGFRA. Oral masitinib was evaluated in 30 imatinib-naïve patients with advanced GIST (Le Cesne, 2010a) Masitinib has greater in-vitro activity and selectivity for the wild-type c-KIT receptor and the juxtamembrane domain mutation (exon 11) than imatinib. In a phase II study, the response rate (RR) at 2 months was 20% according to RECIST and 86% according to FDG-PET response criteria. Best responses were a CR in 1 of 30 patients, PR in 15 of 30 patients, SD in 13 of 30 patients, and PD occurred in 1 of 30 patients (disease control rate 96.7%). The OS rate at 2 and 3 years was high at 89.9%. There are plans to take masitinib forward in a phase III trial. Nilotinib is a second generation BCR/ABL TKI that is approved in the US for use in CML, both upfront and in patients resistant or intolerant to imatinib. Nilotinib has improved cellular uptake when compared to imatinib, and has been shown to have some preliminary activity in GIST in phase II studies. Thirty-five patients with intolerance or resistance to both imatinib and sunitinib were enrolled and treated with

nilotinib 400 mg twice daily. Disease control rate (CR+PR+SD) at week 24 was 29% (90% confidence interval, 16.4%-43.6%) (Sawaki, 2011). The median PFS was 113 days, and the median OS was 310 days. Nilotinib is entering a pivotal multicenter phase III study versus imatinib in front line therapy. Vatalanib (PTK787/ZK 222584) is another oral TKI that inhibits KIT, PDGFRs and VEGFRs. Forty-five patients whose metastatic GIST had progressed on imatinib were enrolled. Nineteen (42.2%) patients had also received prior sunitinib. Vatalanib 1250 mg was administered orally daily. Eighteen patients (40.0%) had clinical benefit including 2 confirmed PRs (duration, 9.6 and 39.4 months) and 16 (35.6%) with stable disease, median duration 12.5 months (Joensuu, 2011). Everolimus is a member of the class of compounds known as mammalian target of rapamycin (mTOR) inhibitors. The protein mTOR is part of the phosphatidyl-inositol-3-kinase (PI3K) pathway, activated downstream of KIT. Everolimus is being investigated in combination therapy with imatinib. A phase I/II study of the addition of everolimus to 600mg imatinib daily in patients with progressive disease showed the combination to be tolerable and safe, and efficacy data met the predetermined endpoint for further study (Schoffski, 2010). Finally, some PDGFRA mutations such as D842V confer relative resistance to imatinib. There is no known effective treatment for these PDGFRA-mutant tumors, but studies using crenolanib, a potent PDGFR inhibitor with preclinical activity against D842V and other PDGFRA mutants, are underway.

15. Conclusion

Understanding the molecular biology of genetic mutations in GISTs has dramatically altered the landscape of therapy. It has been transformed from a disease for which no therapies were effective and lifespan of patients with advanced disease was invariably short, to a disease in which there are effective therapies promising prolonged survival with tolerable side effects. There are over 10 rationally targeted agents in clinical trials at the time of this publication, targeting primary mutations, accessory pathways, as well as specific resistance mutations. As we acquire a deeper understanding of the primary and secondary mutations, oncologists may one day be able to profile an individual patient's GIST mutations, and select drug therapy based on optimum activity against that specific mutation. At the time of progression, the mutations can be re-characterized and the next line of therapy selected based on the new mutational status. Hopefully, in the not too distant future, GIST, like chronic phase CML, will end up becoming a disease where the vast majority of patients can expect to lead normal lives with minimal side effects from their daily oral treatment.

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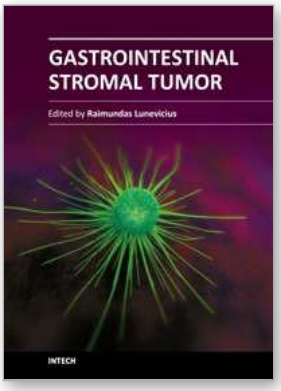

Gastrointestinal Stromal Tumor

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Almost 30 years have gone by since the postulation that GISTs derive from mesenchymal stem elements, and only 15 years have gone by since the definitive detection of origin of GISTs. Research in the last decade was more focused upon the justification of imatinib mezylate therapy in GISTs and clarification why a secondary resistance that occurred during the kinase inhibitors therapy. The era of therapy for GISTs, targeting the primary activating mutations in the KIT proto-oncogene; is being proclaimed as bringing the message of special importance to the pathologist role in multidisciplinary team that are responsible for treating patients with locally advanced or metastatic GIST. This is the first conclusive message forthcoming from this book. On the other hand, the book provides summarised and case-based knowledge on current management of gastrointestinal and extragastrointestinal stromal tumours. We hope that this book may be considered as a worthwhile timely addition to clinical science dissemination, medical education, further basic and clinical research.

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