Advances on Molecular Characterization and Targeted Therapies on GIST

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1 Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal gastrointestinal (GI) neoplasms, yet accounting for less than 1 % of all GI malignancies [1]. They are considered to originate from the interstitial cells of Cajal (ICC) or its progenitor cell [2]. These tumors are characterized by the presence of the CD117 (KIT) [3] and/or DOG-1 [4]. Around 3300–6000 new cases of GIST are diagnosed every year in the United States. The reported annual incidence varies by country, ranging from 6.8 per million in the United States to 19.6 in Hong Kong [5]. However, the real incidence is not known, in part due to lack of standardization for KIT and PDGFRA mutation analysis in some institutions and the fact that small GIST are often not included in cancer registries [6–8].

The highest incidence of GIST occurs between the fifth and sixth decades of life, and rarely occurs before the age of 20. A slight male predominance (53.5 % men and 46.5 % women) has been reported [9]. Around 60 % of GIST occur in the stomach, 25 % in the small intestine, and 10 % in the large bowel, rectum, appendix, and esophagus, and rarely in the extra-intestinal sites such as the gallbladder, omentum, and mesentery [10]. Some of these mesenchymal neoplasms do not cause symptoms and are discovered incidentally. More commonly, they are linked to nonspecific symptoms, except if they ulcerate, bleed, or grow large enough to produce pain or obstruction [11].

Tumors are staged based on the tumor size, number of mitoses, and presence of metastasis (to lymph nodes or other sites). Tumors smaller than 5 cm with fewer than five mitoses per 50 high-power microscopic fields (HPF) have lower risk of recurrence. Tumors larger than 10 cm with more than five mitoses per 50 HPF or ruptured GIST

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have a high risk of recurrence after complete resection [10]. Gastric GIST have a better prognosis than extragastric GIST [12]. The common metastatic sites for GIST include the liver and omentum, less frequently lung, regional lymph nodes, and bone [13].

There are several entities with increased incidence of GIST: The Carney–Stratakis syndrome (familial paraganglioma and GIST) and the Carney's triad (pulmonary chondroma, GIST, and paraganglioma) are affected with nonsporadic GIST. The patients are typically younger than their sporadic GIST counterparts [14]. Patients with neurofibromatosis type 1 (NF1) have an increased risk of developing GIST [15]. NF-associated GIST commonly arise on the small intestine, frequently presenting with a low mitotic activity and lacking *KIT* and *PDGFRA* mutations [16, 17].

Surgery remains the mainstay of therapy for patients with primary GIST with no evidence of metastasis, and this should be initial therapy if the tumor is technically resectable and associated with acceptable risk for morbidity [18]. Currently, the NCCN guidelines [18] recommend that risk stratification after surgical resection should be based on tumor mitotic rate, size, and location. The nomogram developed by Gold and colleagues accurately predicts RFS after surgery and might be useful for patient care, interpretation of trial results, and selection of patients for adjuvant therapy [19].

Imatinib mesylate (Gleevec, Novartis, Basel, Switzerland) revolutionized the treatment of patients with GIST. Imatinib has been proven to have substantial effect in patients with GIST in the adjuvant, neoadjuvant, and palliative setting. It constitutes the primary medical therapy for GIST [18]. More recently, newer generations of tyrosine kinase molecules are being used in specific settings on patients with advanced GIST [18].

2 Histopathology

Sarlomo-Rikali and associates discovered that GIST stained positive for CD117 almost universally [3]. Nearly 95 % of GIST stain for CD117. Other significant immunohistochemical markers include CD34 (70 %), smooth muscle actin (35 %), S-100 (10 %), and rarely desmin (5 %) [20]. DOG-1 (Discovered on GIST-1) has been shown to be highly expressed in GIST [21] and has a very high sensitivity and specificity [4]. A recent study showed that DOG-1 immunostaining was positive in 96.3 % of GIST. From all the cases stained with CD117 and DOG-1, 98.4 % were positive for at least one of these antibodies, suggesting a combination of CD117 and DOG1 immunostaining is sufficient to confirm the histological diagnosis [22]. Moreover, DOG-1 is expressed in 36 % of cases of KIT-negative GIST tumors, making it useful in correctly identifying the rare GIST subgroups that lack KIT mutations [4].

3 Pathophysiology and Molecular Markers

The KIT tyrosine kinase receptor, when activated by its native ligand, the stem cell factor (SCF), triggers multiple signal transduction molecules involved in

cellular proliferation, differentiation, maturation, survival, chemotaxis, and adhesion. The transmission of these various processes is mediated through the dimerization of KIT tyrosine kinase. Dimerization of the KIT receptor leads to phosphorylation and activation of several transduction pathways, including the phosphoinositide 3′ kinase (PI3K), JAK–STAT, Ras-ERK, and phospholipase C pathways [23].

Genetic mutations affecting *c-KIT* have been detected in 95 % of GIST [24]. Mutations in specific exons of the *KIT* genome lead to a gain of function of this tyrosine kinase receptor in GIST. KIT is constitutively active in the absence of stimulation by SCF or via homodimerization. This process ultimately induces oncogenesis [23]. Most mutations occur in the juxtamembrane region encoded by exon 11 (71 %) or extracellular region encoded by exon 9 (14 %) and less frequently in exon 13 (4 %) or exon 17 (4 %) that encode the tyrosine kinase domain [25].

Other mutations mainly affect platelet-derived growth factor receptor alpha (PDGFRα), present in around 5–8 % of GIST. A minority of GIST are c-KIT negative and PDGFRα-negative [24]. These so-called "wild-type" GIST are seen most commonly in children (around 90 % of the pediatric GIST cases) [26]. The BRAFV600E substitution is seen in about 13 % of wild-type GIST [27, 28]. This has led to a phase II clinical trial using dabrafenib (a newer generation BRAF inhibitor) [29]. It has been also reported that in naive GIST cell lines carrying activating mutations in KIT or PDGFRα, a concomitant activating mutation is present in KRAS (5 %) or BRAF (about 2 %) genes [30].

4 Tyrosine Kinase Inhibitor Therapy

Tyrosine kinase inhibitors (TKI) constitute the main medical treatment of patients with GIST. Before the year 2000 (pre-TKI era), the only available therapeutic option for patients with localized GIST was surgical resection. Unfortunately, even when excised in negative surgical margins, the recurrence rate for lesions larger than 3 cm was high [31]. The overall response rates for conventional systemic chemotherapy were very low (0–5 %), and the median survival was less than 2 years [32–34]. Furthermore, GIST are largely radioresistant, making radiation therapy ineffective [35]. It was this lack of effective treatment options that led investigators to seek alternative treatment strategies. Discovery of c-KIT overexpression sparked interest in TKI therapy for advanced GIST.

Imatinib (Gleevec) is an orally bioavailable 2-phenylpyrimidine derivative developed in the 1990s as therapy for chronic myelogenous leukemia (CML). Imatinib occupies the ATP-binding pocket of the ABL kinase domain inhibiting the oncogenic signaling. ABL shares considerable homology with the type III receptor tyrosine kinase family, which includes c-KIT [5]. Imatinib was first used as compassionate therapy in March 2000 in a patient with advanced GIST, and the patient reached partial response within few weeks [36]. These dramatic results led to a series of trials investigating the role of imatinib for patients with advanced disease.

4.1 Neoadjuvant TKI Therapy

There are situations where resection of a primary GIST might be aided with the downsizing of the tumor. For example, large GIST arising low in the rectum might require sphincter-sacrificing surgical procedures (i.e., abdominoperitoneal resection); however, if the tumor shrank and pulled away from the sphincter, local resection with sphincter preservation might be possible. In this way, neoadjuvant imatinib may provide several advantages: it will provide valuable in vivo evidence of the tumor's sensitivity to imatinib, potentially downsize the tumor, and "reduce" the surgical procedure necessary (or facilitate complete tumor extirpation). It may also work as conversion therapy for initially unresectable GIST. On the other hand, a potential downfall of the use of neoadjuvant imatinib may be that it precludes the accurate assessment of risk recurrence using any of the risk-classification models, as none of the current prognostic systems account for neoadjuvant therapy.

The largest retrospective study (to date) of neoadjuvant imatinib therapy published evaluated 126 patients who all received neoadjuvant imatinib for initially unresectable GIST; 17 patients subsequently had surgical resection. These patients received imatinib for a median of 10 months. The radiographic overall response rate was 76% (1 CR, 12 PR). Two patients were found to have no viable tumor at the time of surgical resection [37]. In a different study, neoadjuvant imatinib improved resectability and reduced surgical morbidity in patients with locally advanced or unresectable primary GIST. The median tumor size reduction was 34%, and the estimated PFS at 3 years was 77% [38]. Currently, the NCCN guidelines recommend considering preoperative imatinib on an individual basis for patients in whom surgical morbidity may be improved by reducing the size of the tumor [18].

4.2 Adjuvant TKI Therapy

Despite successful primary tumor resection, GIST have a high risk for recurrence. Stemming from the initial success of imatinib therapy for metastatic disease, several trials were designed to determine the efficacy of adjuvant imatinib in patients with primary GIST after complete surgical resection.

The ACOSOG Z-9001, an intergroup randomized, double-blind, placebo-controlled trial compared imatinib (at a dose of 400 mg daily for 1 year) versus placebo in 713 patients. The study reported a recurrence-free survival (RFS) of 98% (95% CI 96–100) in the imatinib group versus 83% (CI 78–88) in the placebo group (hazard ratio [HR] 0.35 [0.22–0.53], $p<0.0001$), but did not reveal an overall survival (OS) benefit [39]. Interestingly, the slopes of the disease-free survival curves become parallel after cessation of imatinib therapy. This suggests that imatinib might provide "growth suppression" of radiographically occult, micrometastatic disease. The similar OS between the study groups was likely an effect of the crossover design of the study that permitted patients assigned to the placebo group to get imatinib on tumor recurrence. This trial clearly showed, however, that the risk

of recurrent disease is directly linked to TKI therapy, and suggested that the duration of therapy might play an important role.

Accordingly, the SSG XVIII/AIO study, a randomized, open-label Phase III trial, compared the administration of imatinib (400 mg daily) for 1 year versus 3 years as adjuvant therapy. Four hundred KIT-positive, high-risk patients were recruited. The results clearly demonstrated that adjuvant imatinib given for 3 years improved RFS compared to that for 1 year only (hazard ratio [HR], 0.46; 95 % CI, 0.32–0.65; $p = 0.001$; 5-year RFS, 65.6 % vs. 47.9 %, respectively) [40]. Moreover, the 3 years of imatinib arm had a better overall survival (HR, 0.45; 95 % CI, 0.22–0.89; $p = 0.02$; 5-year survival, 92.0 % vs. 81.7 %) [40]. Based on these findings, 3 years of adjuvant therapy is currently the recommended duration of therapy for patients deemed at high risk for recurrence in the United States [18].

Currently, there are several ongoing trials that aim to clarify the role and duration of imatinib as an adjuvant treatment for GIST. The EORTC 62024 is a Phase III, randomized, open-label study, which aims to compare the effect of adjuvant imatinib mesylate (400 mg daily) for 2 years versus observation on the prognosis of patients with completely resected localized GIST at intermediate/high risk of relapse and to compare overall survival among patients in both arms [41]. Preliminary results of the first interim analysis were reported at the 2013 ASCO Annual Meeting. Five-year imatinib failure-free survival (IFS) was 87 % in the imatinib arm compared to 84 % in the control arm (HR 0.80, 95 % CI 0.51–1.26); 3-year RFS was 84 % versus 66 %; and 5-year overall survival was 100 % versus 99 % [42]. Finally, the PERSIST 5 trial is a Phase II, nonrandomized, open-label multicenter study of 5-year adjuvant imatinib in patients at significant risk for recurrence following complete resection of primary GIST. This study is ongoing but not recruiting patients at this time [43].

4.3 Adjuvant/Neoadjuvant Combined TKI Therapy

The RTOG S0132/ACRIN (American College of Radiology Imaging Network) 6665 trial enrolled patients with primary GIST (≥5 cm, group A) or resectable metastatic/recurrent GIST (≥2 cm, group B) who received neoadjuvant imatinib (600 mg/day) for approximately 2 months and maintenance postoperative imatinib for 2 years [44]. Thirty patients had locally advanced primaries and 22 had locally recurrent or metastatic disease. In the localized primary disease group, 7 % (2 patients) had an objective response to preoperative imatinib, but stable disease was achieved in 83 % (25 patients). In patients with recurrent or metastatic GIST, partial response and stable disease were observed in 4.5 % and 91 % of patients, respectively [44]. The most recent update at a median follow-up of 5.1 years demonstrated that the estimated 5-year progression-free survival was 57 % in group A versus 30 % in group B, and overall survival was 77 % in group A versus 68 % in group B. Median time to progression has not been reached for group A, and was 4.4 years for group B [45]. Long-term analysis suggested that a

high percentage of patients experienced disease progression after discontinuation of 2-year maintenance imatinib therapy after surgery. For that reason, they concluded that longer treatment duration should be studied in intermediate- to high-risk GIST patients [45]. These results added further evidence in support of longer treatment times. Similarly, the phase III BFR14 trial conducted by the French Sarcoma Group explored the effect of interrupting therapy after 1, 3, and 5 years of treatment with 400 mg/daily of imatinib in patients with advanced GIST. A subgroup analysis of patients with locally advanced primary GIST was associated with a 60 % partial response rate, and 36 % of patients underwent surgical resection after a median of 7.3 months of therapy. With a median follow-up of 53.5 months, there was a significant improvement in progression-free survival and overall survival for patients who underwent surgical resection versus those who did not (median not reached vs. 23.6 months, $p = 0.0318$ for PFS and median not reached vs. 42.2 months, $p = 0.0217$ for OS). In the group of patients who underwent resection followed by imatinib, the 3-year PFS and OS rates were 67 % and 89 %, respectively [46]. These data clearly demonstrate that adjuvant therapy with imatinib provides both disease-free and overall survival benefit to patients who have high-risk GIST.

4.4 TKI for Advanced/Metastatic Disease

Imatinib is the primary systemic therapy for patients with advanced/metastatic GIST [18]. The standard dose of imatinib was established in an EORTC phase I trial led by Van Oosterom and associates [47]. Utilizing a dose escalation schema, they concluded that a dose of 400 mg/day had the most favorable clinical benefit–side effect profile, including edema, nausea, diarrhea, malaise, and fatigue. Other rare side effects included myelosuppression, hemorrhage, and elevated transaminases, which required interruption or discontinuation in treatment [47]. Several phase II and III clinical trials were designed to assess the efficacy of imatinib in the metastatic setting. These studies reported an imatinib response ranging from 48 to 71 % and disease stabilization in 70–85 % of patients. The median progression-free survival ranges from 20 to 24 months [13, 48–50]. The B2222 trial reported an overall survival of 35 % at 9 years, and 38 % for those with complete response or partial response [51]. These data demonstrated the possibility of durable survival benefit for those patients who responded to imatinib.

Two large international studies randomized patients with metastatic GIST to standard dose or high-dose imatinib (400 versus 800 mg/daily, respectively) [13, 48]. The EORTC 62005 reported that after 760 days of follow-up, 56 % of the patients in the 400 mg daily dose had progression compared to 50 % in the 800 mg daily dose [13]. As one might expect, the lower dose cohort had fewer side effects. The North American Sarcoma Intergroup study, S0033, was an open-label phase III trial on patients with unresectable or metastatic GIST. Patients were randomized to receive the 400 mg daily dose (standard

dose) versus 400 mg twice daily (high dose). At a median follow-up of 4.5 years, the median progression-free survival was nearly identical between the two dosing regimens. Similarly, the median overall survival was essentially identical. Interestingly, after progression on standard dose imatinib, 33 % of patients who crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease [48]. These data were hypothesis-generating, including raising the possibility that some GIST require higher dosing to achieve therapeutic benefit.

One important concept regarding imatinib dosing is that different mutations in the *KIT* gene require different doses. The EORTC designed a phase III trial in which patients with GIST were randomized to receive imatinib at a dose of either 400 mg daily or 800 mg daily. The presence of KIT exon 9 mutations increased the relative risk of progression by 171 % and the relative risk of death by 190 % when compared with KIT exon 11 mutants [52]. Interestingly, patients whose tumors expressed an exon 9 KIT mutation did better with the higher dosing scheme [52]. It was concluded that tumor genotype is of major prognostic significance for patients treated with imatinib for advanced GIST. Interestingly, the relative risk of progression was also increased by 108 % and the relative risk of death by 76 % in patients without detectable KIT or PDGFRA mutations [52]. Typically, patients are started on 400 mg/day of imatinib, and after a short period, the dose is gradually escalated up to 800 mg/day. This seems to minimize some of the side effects when compared to starting out de novo with the 800 mg/day dosing.

A correlation study of the kinase genotype and clinical outcomes done along with the CALGB 150105 trial reported that patients with KIT exon 9 mutations treated with 800 mg daily dose of imatinib had better response rates compared to that with 400 mg daily dose (67 % vs. 17 %) [53]. Nevertheless, the survival outcomes for patients with exon 9-mutant, exon 11-mutant, or wild-type GIST were not affected by the imatinib dose. Furthermore, CD117-negative GIST patients had a similar time to tumor progression but inferior overall survival compared to CD117-positive patients. Those outcomes suggest that CD 117-negative GIST patients may also benefit from imatinib therapy [53]. The Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) reviewed the data of two doses of imatinib (400 mg daily versus twice daily) in 1640 patients with advanced GIST. Patients with wild-type, KIT exon 9 mutations, and patients with other mutations had worse progression-free survival and overall survival than patients with KIT exon 11 mutations [54]. In addition to proper dosing, interruption of therapy seems to impact outcome. Patients who continuously take their imatinib seem to have a more durable response, while patients whose therapy is interrupted develop progression sooner [55]. Reinstitution of therapy for patients who experience progression can result in control of the tumor in most patients. In one study, nearly one-half of patients who had achieved an initial response and subsequently progressed following discontinuation of imatinib were able to respond to restarting therapy [56]. Thus, interruption of imatinib causes rapid progression in most patients with advanced GIST and cannot be recommended unless there is significant toxicity.

4.5 Imatinib-Resistant GIST

For some patients, resistance to imatinib develops during therapy. Several mechanisms of resistance had been proposed, including inadequate imatinib plasma levels, specific types of mutations (BRAF mutation, PDGFRA D842V mutation, NF-1, SDH complex loss), accumulation of secondary mutations, KIT gene amplification, or loss of the wild-type allele. Some patients will develop clones that become resistant, while other tumor nodules remain sensitive. In practice, imatinib resistance is divided into primary and secondary.

Primary resistance (PR) PR is defined as development of progression within the first 6 months of imatinib therapy. Approximately 10–14 % of patients with GIST have primary resistance [24, 57]. Now, it is well known that primary resistance is driven by tumor biology and genotype [25, 52, 53]. It is particularly remarkable that strong imatinib resistance is seen in the presence of the PDGRFA D842V mutation [25, 58, 59]. NF-1, SDH, RAS, and BRAF mutations also predict primary resistance to imatinib [24]. For patients with these mutations, a different therapeutic strategy would be indicated, and the use of BRAF, MEK, and VEGFR inhibitors would be logical options.

Secondary resistance (SR) SR is defined as the development of resistance to imatinib while on therapy (more than 6 months). This resistance develops as a result of acquired mutations which tend to evolve within the first 2 years of treatment [13, 60]. Most mutations that lead to SR affect KIT and PDGFRA [61–64]. In patients with imatinib-naïve GIST, most mutations occur in the juxtamembrane (exon 11) or extracellular domain (exon 9). In patients with acquired resistance, the mutations are predominantly located in two regions of the intracellular kinase domain; one in the ATP-binding pocket (exons 13 and 14), which directly interferes with the drug binding, and the second one in the activation loop (exons 17 and 18), where mutations can stabilize KIT in the active conformation and hinder drug interaction [24].

Multiple authors have reported the presence of heterogeneity of resistance within the different lesions but also within the same tumor [63–66]. Liegl et al. studied KIT and PDGFRA mutations in 53 GIST metastases obtained from 14 patients who underwent surgical debulking after progression on imatinib or sunitinib. Primary KIT oncogenic mutations were found in 11/14 patients (79 %). Of these, 9/11 (83 %) had secondary drug-resistant KIT mutations, including six (67 %) with two to five different secondary mutations in separate metastases, and three (34 %) with two secondary KIT mutations in the same metastasis. FISH analyses revealed KIT amplicons in 2/10 metastases lacking secondary KIT mutations. This study demonstrates extensive intralesional and interlesional heterogeneity of resistance mutations and gene amplification in patients with clinically progressing GIST [65]. Other mechanisms of survival of imatinib-resistant GIST cells like PI3k/AKT pathway activation and AXL or IGF1R overexpression are being studied at this time. The mechanisms of development of additional genetic mutations is poorly understood.

4.6 TKI Therapy for Imatinib-Resistant Metastatic GIST

Once there is progression of disease on standard dosage imatinib, the initial approach is typically to maximize the dose of imatinib to 800 mg daily [18]. Dose escalation does provide some patients with meaningful response, with up to one-third experiencing disease stability with this approach. In addition, the median survival for patients who require dose escalation due to progression on the standard dosing regimen is approximately 19 months [67]. After progression on the maximum tolerated dose of imatinib, patients should be switched to another therapy, including sunitinib [18]. Sunitinib is a tyrosine kinase inhibitor that has both anti-angiogenic and antioncogenic properties, since it inhibits the vascular endothelial growth factor receptor and the KIT receptor, respectively. Sunitinib has been shown to provide clinical benefit in over one-half of patients with imatinib-resistant/intolerant GIST patients [68]. In a phase III randomized trial investigating, sunitinib at a 50 mg daily dose (4 weeks on and 2 weeks off per cycle) versus placebo in metastatic, imatinib-resistant GIST, patients receiving placebo had a much worse time to progression compared to those who received sunitinib (6.4 weeks vs. 27.3 weeks; $p < 0.0001$). There was a greater estimated overall survival, and the therapy was reasonably well tolerated [69]. Because of results like these, the FDA approved sunitinib for the treatment of GIST after disease progression on or intolerance to imatinib [18].

4.7 GIST Resistant to Imatinib and Sunitinib (GRIS)

Patients with GRIS may have a poor prognosis, and their treatment is challenging. Following established mechanisms of action, various TKIs have been studied in patients with GRIS, including sorafenib, nilotinib, dasatinib, and most recently regorafenib. Regorafenib is a multikinase inhibitor, with activity against KIT, PDGFR, and VEGFR, that was recently approved by the FDA for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib [18].

A multicenter phase II study in GRIS patients reported a clinical benefit rate of 79 % and a median progression-free survival of 10 months [70]. Most recently, a double-blind, phase III trial (GRID trial) randomized patients to regorafenib versus placebo (PL). The median progression-free survival was 4.8 months for REG versus 0.9 months for PL ($p < 0.0001$). In addition, disease control was achieved in half of the patients in the regorafenib arm [71]. These data established regorafenib as a viable option for patients with GRIS.

Sorafenib is a multityrosine and serine/threonine kinase inhibitor, with activity against RAF, PDGFR, VEGFR, and KIT. Several studies have established the potential benefit of sorafenib for patients with GRIS. The University of Chicago phase II consortium trial examined the use of sorafenib 400 mg twice daily in

GRIS patients. The study showed an overall disease control rate of 68 %. The median progression-free survival and overall survival were 5.2 months and 11.6 months, respectively. Interestingly, one-third of patients with primary sunitinib resistance had either a partial response or stable disease for greater than 6 months on sorafenib [72]. Others have shown that sorafenib is not only effective in patients with GRIS, but has a reasonable toxicity profile [73]. Toxicity has been reported in 56 % of the patients, and many will require a dose reduction [74, 75].

Nilotinib is a multikinase inhibitor with activity against KIT, BCR/ABL, PDGFRB, and DDR1/2. The clinical activity of nilotinib, given either as a single agent or in combination with imatinib in patients with refractory GIST, was established in a phase I clinical trial [76]. This led the way for a phase II study of nilotinib as third-line therapy for patients with GRIS, which reported disease control rate of 29 % at week 24 and a median progression-free survival of 3.5 months. The median overall survival was 310 days [77]. These data demonstrated that nilotinib has efficacy in patients with resistant GIST. A subsequent phase III trial provided further evidence on the efficacy of nilotinib in patients with advanced GIST following prior imatinib and sunitinib failure [78].

Dasatinib is a multikinase inhibitor that has activity against KIT, PDGFR, BCR/ABL, and SRC. It has demonstrated activity against the PDGFRA D842V mutation which confers the maximum resistance to imatinib, and it may be an effective treatment alternative for this group of patients [79]. A phase II study of dasatinib at a dose of 70 mg twice daily in patients with GRIS showed that 32 % of patients had a partial response, and 21 % patients were progression-free for over 6 months [80]. Therefore, dasatinib represents a viable treatment option for patients with this challenging mutation.

Several other tyrosine inhibitors are currently being evaluated. Pazopanib is a multityrosine kinase inhibitor of VEGFR, PDGFR, cytokine receptor, and interleukin-2. In a multicenter phase II study of patients with advanced GIST following failure of at least imatinib and sunitinib, pazopanib showed promising results with a 24-week nonprogression rate of 17 % and an overall survival of 10.7 months [81]. Masitinib mesylate is a highly selective TKI with comparable activity to imatinib against wild-type and mutant KIT (exons 9 and 11) [82, 83]. Initial phase I data [84] led to the design of a prospective, multicenter, randomized, open-label, phase II study, evaluating the safety and efficacy of masitinib versus sunitinib for the treatment of advanced imatinib-resistant GIST [85]. Interestingly, mastitinib seems to be better tolerated than sunitinib with fewer side effects. Results of this trial demonstrate a median overall survival that was significantly longer for patients receiving masitinib followed by postprogression addition of sunitinib when compared against patients treated directly with sunitinib as second-line therapy following progression on imatinib [85]. A phase III trial designed to determine the clinical use of masitinib in patients with imatinib-resistant GIST is currently ongoing [86]. These preliminary data are encouraging and suggest that mastitinib might play a role following progression on first-line imatinib.

5 Conclusions

Treatment of gastrointestinal stromal tumors represents one of the paradigms of modern oncology. The development of selective inhibitors based on specific mutational status provides many patients with promising treatment options. Multiple tyrosine kinase inhibitors exist and show various activities against GIST. Further research and drug development will no doubt result in more options for patients afflicted with GIST.

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