Review Article

Molecular target therapy for gastrointestinal stromal tumors

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Abstract: Gastrointestinal stromal tumors (GIST), the most common gastric mesenchymal tumor is unique due to the presence of a driver mutation called c-kit and the usage of imatinib as the targeted therapy. For resectable tumors, surgery is the preferred option and patients with high-risk GIST are considered for adjuvant imatinib for 3 years. The role of neoadjuvant imatinib is evolving. For the management of metastatic GIST, the FDA has approved imatinib, sunitinib and regorafenib as first, second and third line targeted therapy respectively. The increased prevalence of imatinib resistance has paved the way to the development of multiple other secondary and tertiary targeted agents. We present a brief review on the pathophysiology and resistance pathways and a comprehensive review of the various targeted agents which have been developed for the treatment of GIST.

Keywords: Gastrointestinal stromal tumors (GIST); imatinib; regorafenib; sunitinib; targeted therapy

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Introduction

Gastrointestinal stromal tumors (GIST) initially named by Mazur and Clark in 1983 (1) are the most common mesenchymal tumors of the GI tract with a specific mutation and a suitable targeted treatment. They occur most commonly in the stomach (60-70%) and small intestine (25-35%) and rarely in the colorectal region (5%), esophagus (<2%), appendix, omentum, mesentery or retroperitoneum (2) occurring most commonly in the 5th to 6th decade of life. Various risk stratification schemes have been identified for prognostication of GIST. As an addition to these factors, tumor genotyping is being studied extensively and in future may also be incorporated into the risk stratification schemes. Tumor genotyping involves the identification of the causative genetic alteration and tailored therapy catering to that particular genetic abnormality (3). Here we present a comprehensive review of targeted therapy used in the management of GIST.

Pathology

On histo-pathology, GISTs are made of fascicles of spindle cells with eosinophilic cytoplasm, nuclear palisading, inconspicuous nucleoli and extracellular collagen. They can be of three types: spindle (70%), epitheloid or mixture of both (2). On immunohistochemistry (IHC), along with diffuse CD117 positivity (about 95%), other markers which are useful diagnostically are BCL-2 (80%) and CD34 positivity (70%), variable expression of smooth muscle actins (20-30%) and S100 protein (10%) and desmin negativity (2-4% positive). DOG-1 (discovered on GIST) is a novel marker, which is a calcium dependent protein and is positive in GIST irrespective of the mutation status (4). Most of the tumors have low rate of mitoses. These tumor cells are admixed with lymphocytes and apoptotic debris giving a false impression of high mitotic index. Calculation of mitoses is one of the major tasks in calculation of the recurrence risk and the loophole is the difficulty in calculating mitotic count, as most pathologists tend to over count it due to the miscount of lymphocytes and apoptotic and karyorrhectic bodies as part of active mitotic figures (5). The dilemma lies in where exactly the mitotic count has to be assessed and how large the 50 high power fields (HPF) must be. While the area of each HPF has varied from

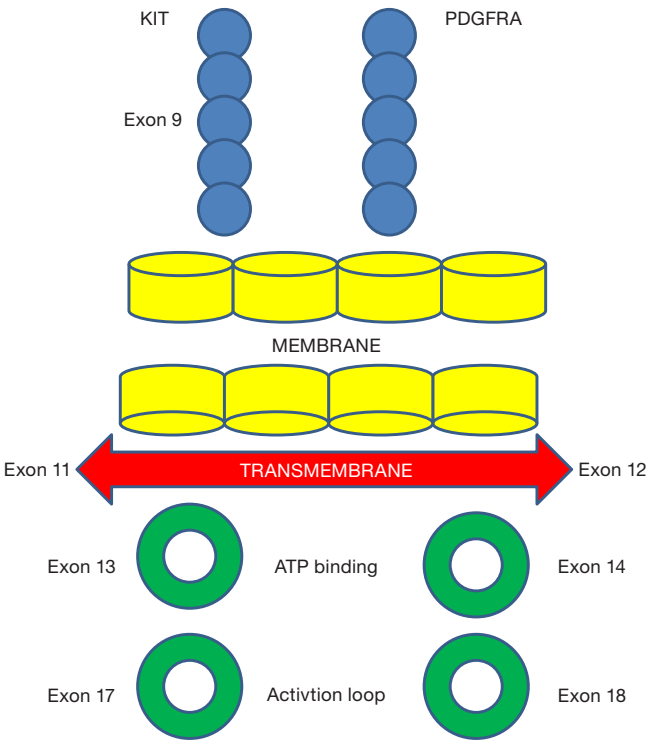

Figure 1 KIT and PDGFRA receptor complex with mutations. PDGFRA, platelet derived growth factor receptor alpha.

5 to 12 mm^2, the ESMO recommendation is an area of 10 mm^2. Moreover, whether the areas should be consecutive or randomly selected in highly cellular parts has not been standardized.

Molecular basis and mutations driving therapy

CD117 (*KIT*) mutation is the most common mutation seen in GIST (80-85%) (6). It was discovered by Hirota *et al.* in 1998 (7). It is encoded by the *KIT* proto-oncogene which is present on chromosome 4 (8). In physiologic conditions, the ligand for *KIT* receptor called the stem cell factor (SCF) (steel factor) binds at the receptor and then after homodimerisation results in a cascade of events causing cell survival and proliferation. Under malignant conditions, this cascade gets activated due to activating mutations and the same cycle is continued irrespective of ligand binding and results in tumorigenesis (9). The pathways activated are the Ras/Raf/MAPK pathway, JAK-STAT pathway, IGF pathway, PI3K/AKT and mTOR pathways (10,11). CD117 is expressed on the interstitial cells of Cajal which are responsible for GI peristalsis, thus hypothesized to be the cell of origin for GIST (7). Exon 11 *KIT* mutations are the most common (65-70%), which happens usually in the juxtamembrane domain (*Figure 1*). These could be point mutations, deletions or duplications and are more common in gastric GIST and show good response to imatinib, whereas exon 9 mutations (5-10%) usually are 2-codon 502-503 duplications in the extracellular domain (made up of five immunoglobulin like molecules) and these occur predominantly in intestinal versus gastric GISTs and are less responsive to imatinib. Other mutations could occur in the ATP binding domain of exon 13 and 14 or exon 17 at the activation loop of the kinase domain (12). In patients with *KIT* negative tumors (15%), 30-40% will be positive for platelet derived growth factor receptor alpha (*PDGFRA*), the gene for which is also situated on chromosome 4 and these tumors are usually of epitheloid variant and gastric in location (8,13). *PDGFRA* mutations could be in exon 18 (most common) (activation loop domain), 12 (juxtamembrane domain) or 14 (ATP binding domain) (11,13). A minority of the cases especially in pediatric age group will be wild type GISTs. *KIT* negative tumors have a better prognosis than *KIT* positive tumors (14). Patients with *KIT* mutation have a poor prognosis especially those with deletions affecting codons 557-558 (15,16). Presently studies are undergoing to study the genetic expression of GIST. Stomach and small bowel GISTs have varying genetic expression. High gene expression of vascular endothelial growth factor (VEGF), Macrophage colony stimulating factor, and *BCL2* was noticed in the wild-type group, and Mesothelin in exon 9 mutation group (17). AKT3 and Ezrin was expressed more in *KIT* exon 11 and 9 mutations and less in *PDGFRA* mutated GISTs whereas MEK and T Cell receptor signaling genes were found to be high in *PDGFRA* mutated tumors (18). In addition to the above mutations, loss of tumor suppressor genes present on chromosome 14 and 22q have also been seen (19). Other GISTs could be familial (mutation in exon 8, 11, 13 or 17) or associated with neurofibromatosis 1, Carney's triad or Carney-Stratakis syndrome (20).

Management of non-metastatic GIST

Neoadjuvant therapy and surgery

The success of imatinib in metastatic GIST led its entry into neo-adjuvant and adjuvant setting. Surgical resection with clear margins should be the main goal while treating GISTs with curative intent. While the median survival post complete resection is approximately 66 months, it gets reduced to 22 months if the disease is unresectable (9). Tumors more than 2 cm should be resected and lymph node dissection

Table 1 NIH, AFIP and Joensuu risk stratification system

Risk stratification (31-33)	Tumor size (cm)	Mitotic count (per HPF)	Tumor site	Tumor rupture
NIH-Fletcher				
Very low risk	<2	<5		
Low risk	2-5	<5		
Intermediate risk	<5	6-10		
	5-10	<5		
High risk	>5	>5		
	>10	Any		
	Any	>10		
AFIP				
Group 1	≤2	≤5		
Group 2	>2 to ≤5	≤5		
Group 3a	>5 to ≤10	≤5		
Group 3b	>10	≤5		
Group 4	≤2	>5		
Group 5	>2 to ≤5	>5		
Group 6a	>5 to ≤10	>5		
Group 6b	>10	>5		
Joensuu				
Very low	<2	≤5	Any site	
Low	2.1-5	≤5	Any site	
Intermediate	2.1-5	>5	Gastric	
	<5	6-10	Any	
	5.1-10	≤5	Gastric	
High	Any	Any	Any	Yes
	>10	Any	Any	
	Any	>10	Any	
	>5	>5	Any	
	≤5	>5	Non gastric	
	5.1-10	≤5	Non gastric	

NIH, National Institutes of Health consensus; AFIP, Armed Forces Institute of Pathology criteria; HPF, high power field.

is not recommended as metastases to nodes are rare (21). Imatinib when used in borderline resectable locally advanced cases can reduce the tumor bulk and make the tumor amenable for surgery with clear margins especially in critical sites like rectum (22,23). In a study of 46 patients, they found that all eleven patients with locally advanced disease could undergo complete surgical resection after a median of 11.9 months of neoadjuvant imatinib (24). The duration of neoadjuvant imatinib is not clearly defined. In a study they found that post neoadjuvant imatinib the 2-year recurrence-free survival (RFS) was 85% and 44% and overall survival (OS) was 97% and 73% for primary and recurrent/metastatic disease, respectively. Moreover on univariate analysis, the duration of neoadjuvant therapy of more than 365 days (P=0.02) was associated with a higher risk of recurrence (25). In a pooled database of ten EORTC STBSG sarcoma centers, patients with locally advanced GIST who received neo-adjuvant imatinib were studied. After a median 40 weeks of imatinib, the rate of R0 resection was 83% and the 5-year disease free survival (DFS) was 65% with median OS of 104 months (26). In a study done at Tata Memorial hospital in India, after a median duration of 8.5 months of neo-adjuvant imatinib, the response rate was 79% with a manageable post-operative complication rate of 14% and a 3-year OS of 100% (27).

Risk stratification and adjuvant therapy

In the absence of adjuvant therapy, 50% patients recurred, especially in the first 5 years (28). Patients with high risk of recurrence are recommended to take adjuvant imatinib after complete gross resection (28-30). There are a number of risk stratification systems to predict the recurrence of GIST after complete surgical resection. The important ones being (*Table 1*):

(I) The National Institutes of Health (NIH) consensus criteria (Fletcher's criteria);
(II) The Armed Forces Institute of Pathology (AFIP) criteria (Miettinen's criteria);
(III) Joensuu's modified NIH classification (J-NIHC) (the two modifications were):
  (i) Tumor rupture was added;
  (ii) Non-gastric tumors in the intermediate risk were converted to high risk;
(IV) The American Joint Committee on Cancer staging system (AJCCS);
(V) The Japanese modified NIH criteria.

The NIH, AFIP and Joensuu's criteria are the most commonly used. Bases on good to poor prognosis the site predilection is as follows: gastric, small intestine, colorectal, extra GI GISTs. Based on size, the 10-year recurrence rate for <1 cm (micro GIST), 5-10 cm and 10-15 cm tumors is 0%, 50% and 70% respectively. Based on mitosis, the 10-year recurrence rate for <5 and >5 mitoses/HPF is 25% and 70% respectively (34). According to the modified NIH criteria, the 10-year RFS for very low, low, intermediate and high risk is 95%, 90%, 85% and 35% respectively (34). Of 127 patients were analyzed at the MSKCC with localized primary GIST

who underwent complete gross surgical resection of disease. After a median follow-up of 4.7 years, RFS was 83%, 75%, and 63% at 1, 2, and 5 years, respectively. Factors predictive of increased recurrence were ≥5 mitoses/50 HPF, tumor size 10 cm, and patients with small intestine tumors did worse. While *KIT* exon 11 point mutations and insertions had a good prognosis, *KIT* exon 9 mutations or exon 11 deletions involving amino acid W557 and/or K558 had a bad prognosis and wild type GISTs had intermediate outcome (35). A nomogram to predict RFS based on tumor size, location and mitotic index (<5 or ≥5/HPF) after surgery in the absence of adjuvant imatinib was proposed by Gold *et al*. The concordance probability was 0.78 (standard error ±0.02). Moreover this nomogram was better than the NIH staging system and equivalent to the AFIP staging system for recurrence prediction (36). Yanagimoto *et al*. analyzed 712 GIST patients after surgery and compared the above systems. They found that the factors significant on multivariate analysis were size >5 cm, mitotic count >5/50 HPF, non-gastric location, and the presence of rupture and/or macroscopic invasion. They also found out that the J-NIHC and AJCCS were respectively the most sensitive and accurate tools to predict recurrence (37). Zhao *et al*. further classified the high risk group into very high risk group which included tumors having mitoses count >10/50 HPF and serosal invasion. Specifically in tumors with serosal invasion, despite adjuvant imatinib the recurrence rates were high, thus stressing the importance of neoadjuvant imatinib so that serosal invasion is reduced (38). In another study by the same authors, they found that Ki67 index >8% also was a poor prognostic factor (39).

In the ACOSOG Z9000 phase II trial, 107 high risk recurrence (tumor size >10 cm, tumor rupture, or <5 peritoneal metastases) patients received 1 year of imatinib 400 mg as adjuvant therapy and was compared with placebo. The 1- , 3- and 5-year RFS was 96%, 60% and 40% and OS was 99%, 97% and 83% respectively. While the median RFS was 4 years, the median OS had not been reached (40). In the subsequent phase III trial (ACOSOG Z9001) patients with tumor >3 cm were randomized to adjuvant imatinib versus placebo for 1 year. The RFS was 98% in the imatinib arm and 83% in the placebo arm [hazard ratio (HR), 0.35; 95% confidence interval (CI), 0.22-0.53; P<0.0001], especially better in patients with high (size ≥10 cm) and intermediate (≥6 to <10 cm) risk. However there was no difference in OS which could be as a result of crossover to imatinib arm on progression (41). In this study, 28% patients discontinued imatinib due to toxicity. Based on these results, adjuvant imatinib was granted accelerated FDA approval in the year 2008 which in 2012 was converted to full approval. In a recent publication, in the same study they showed that large tumor size, small bowel location and high mitotic rate had lower RFS irrespective of the tumor genotype. Moreover, adjuvant imatinib improved RFS in *KIT* exon 11 deletions but not in KIT exon 11 insertions or point mutations, *KIT* exon 9 mutations, *PDGFRA* mutation or wild type GIST (41).

In the subsequent phase III Scandinavian Sarcoma Group/Arbeitsgemeinschaft Internistische Onkologie trial XVIII (SSG XVIII/AIO) trial, patients at high risk for recurrence (with at least one of the following: longest tumor diameter >10 cm, mitotic count >10/50 HPF, tumor diameter >5 cm, and mitotic count >5 or tumor rupture) after surgical removal, were randomly assigned to either 1 or 3 years of adjuvant imatinib. The 5-year RFS and OS were 66% versus 48% (HR, 0.46; 95% CI, 0.32-0.65; P<0.0001) and 92% versus 82% (HR, 0.45; 95% CI, 0.22-0.89; P=0.02), respectively in the 3- and 1-year group (29). 13.6% of patients in the 3-year arm discontinued imatinib due to adverse events than 7.5% in the 1-year arm. In another study 900 patients with intermediate- or high-risk resected GIST were randomized to 2 years of adjuvant imatinib versus no adjuvant therapy. The 3- and 5-year RFS was 84% versus 66% (P<0.001) and 69% versus 65% (P<0.001) in the imatinib versus no adjuvant therapy arms, respectively (42). In the phase II PERSIST-5 trial (Post resection Evaluation of Recurrence-free Survival for gastrointestinal Stromal Tumors) the benefit of 5 years of adjuvant imatinib will be studied. The current recommendation is to give 3 years of adjuvant imatinib for tumors with high risk of recurrence after complete gross resection (30,43).

Management of metastatic GIST

Surgery in metastatic GIST

The role of surgery after imatinib pre-treatment in metastatic patients is controversial. Cheng *et al*. studied the significance of pathological complete response (pCR) post imatinib in metastatic GIST and found out that patients with pCR had better PFS and OS than those without pCR [2-year PFS and OS: 82.5% and 100% versus 35.6% and 49.4%, (P=0.014 and P=0.004) respectively]. They also found that patients with pCR had lesser secondary mutations (44). In another study, patients with recurrent or metastatic GIST who had stable disease after 6 months of imatinib were randomized to surgery followed by imatinib continuation versus surgery alone and found that the surgery group had better PFS (HR, 2.326;

95% CI, 1.034-5.236; P=0.0412) and OS (HR, 5.464; 95% CI, 1.460-20.408; P=0.0117) (45). In a study done in China, the 2-year PFS was 88.4% in the surgery arm and 57.7% in the imatinib alone arm (P=0.089) while the median OS was not reached in the surgery arm and was 49 months in patients with Imatinib-alone arm (P=0.024) (46). In spite of all these data, surgery in metastatic patients is not recommended as a guideline and may be decided on an individual patient's basis based on patient symptoms. The indications for surgery recommended by the NCCN in recurrent or metastatic GIST are (21):

(I) Disease that is stable or shrinking on TKI therapy when complete gross resection is possible;
(II) Isolated clones progressing on TKI therapy after initial response while other sites of disease remain stable;
(III) Emergencies like hemorrhage, perforation, obstruction or abscess.

First line TKI therapy for metastatic GIST

With the use of imatinib, the survival of advanced GIST can extend up to 5 years (47). Imatinib produces response rate of 67% in exon 11 *KIT* mutation and 40% in exon 9 mutation (48). Before the advent of imatinib, the OS of GIST patients varied from 10 to 20 months. The initial studies of imatinib in metastatic GIST were phase II trials which showed response rate of 82% with time to treatment progression (TTP) of 24 months and OS of 57 months (49,50). These benefits were later reconfirmed with phase III randomized trials (51,52). In the The EORTC Soft Tissue and Bone Sarcoma Group phase III randomised trial, 946 patients were randomised to receive 400 or 800 mg once daily imatinib. On progression on 400 mg, patients were allowed to crossover to the 800 mg arm. After a median follow-up of 2 years, the response rate in both groups was around 50% and OS at 1 and 2 years was 85% and 70% in the 400 mg and 800 mg groups respectively with many patients in the 800 mg arm requiring dose reductions (52). Even in the North American Sarcoma Intergroup study (S0033) 746 patients were randomised in a similar manner as the EORTC study. Even in this study the objective response rate (ORR), PFS and OS was similar in both the groups (53). Meta-analysis of these trials showed that the median OS was 4 years and both the doses were equivalent, however patients with exon 9 required 800 mg imatinib (54).

In metastatic patients, imatinib has to be continued until disease progression. In the French Sarcoma Group trial, 58 patients were randomised to imatinib continuation versus interruption after 1 year of treatment. Most of the patients in the interrupted group progressed, however majority of them responded to reintroduction of imatinib and no difference was seen in OS, resistance patterns or quality of life (55). The phase III Intergroup trial proved that *KIT* exon 11-mutant GIST had a better ORR of 71% and OS of 60 months, versus 45% (P=0.01) for both exon 9-mutant and *KIT*/*PDGFRA* wild-type tumors with OS of 39 and 49 months (P=0.049) (56).

Masitinib mesylate is another TKI with greater selectivity than imatinib especially in exon 11 mutation which has shown promising results in phase II trials when used as 1st line in metastatic GIST with a PFS of approximately 41 months and is currently being studied in phase III trials (57,58).

Response assessment to imatinib in GIST

RECIST which is used for response assessment in most solid tumors is not a very good criterion for assessing response to TKI in GIST, as due to necrosis and cystic degeneration, only calculation of tumor size may not be accurate. Choi *et al*. proposed different criteria (*Table 2*) in which along with size, tumor density is also taken into account (59). While routine CT scan is sufficient for assessing response, ^{18}FDG-PET can be used for (59):

(I) Staging and detecting metastases that may otherwise not be apparent;
(II) Detecting an otherwise unknown primary site;
(III) Monitoring response to TKI therapy especially if quick responses need to be assessed for planning early surgery (PET response post imatinib appears as early as 24 hours);
(IV) Detecting primary and secondary resistance to TKI;
(V) When the CT findings are inconclusive or inconsistent with clinical findings.

Second line therapy for metastatic GIST

Sunitinib is recommended as the second line agent in metastatic GIST patients who have progressed on imatinib or are intolerant to imatinib (60). Sunitinib is a TKI which acts against the stem cell-factor receptor (*KIT*), PDGFR—VEGF receptor, glial cell line-derived neurotrophic factor receptor [rearranged during transfection (RET)], colony-stimulating factor-1 receptor (CSF1R), and Fms-like tyrosine kinase-3 receptor (FLT3) (61). In a phase III trial, the PFS was 24 versus 6 months for patients on sunitinib versus placebo respectively (60). In another phase

Table 2 Assessing response on tyrosine kinase inhibitor therapy

Response	Choi criteria	RECIST criteria
Complete response (CR)	(I) Disappearance of all lesions; (II) No new lesions	Same
Partial response (PR)	(I) A decrease in size of 10% or more or a decrease in tumor density (HU) of 15% or more on CT; (II) No new lesions; (III) No obvious progression of non-measurable disease	At least a 30% decrease in the sum of diameter of target lesions
Stable disease (SD)	(I) Does not meet criteria for CR, PR, or progression; (II) No symptomatic deterioration attributed to tumor progression	Same as (I)
Progressive disease	(I) An increase in tumor size of disease 10% or more AND does not meet criteria of partial response by HU on CT; (II) New lesions; (III) New intra tumoral nodules or increase in the size of existing intra tumoral nodules	(I) At least a 20% increase in the sum of diameter of target lesions, along with an absolute increase of at least 5 mm; (II) New lesions

III trial, the PFS with sunitinib was 7, 9 and 13 months in patients who progressed after 1, 3 and 5 years of imatinib respectively (62). In a study by Demetri *et al*., once daily sunitinib 50 mg was given for 4 weeks with a 2-week break and was compared with placebo (patients on placebo arm could cross over to sunitinib arm on disease progression). Although there was no significant difference in OS due to crossover, TTP was 27 weeks in the sunitinib arm versus 6 weeks in the placebo arm. Patients in the placebo arm had a 3-fold greater risk of disease progression (HR, 0.339; 95% CI, 0.244-0.472; P≤0.001) (63). The side effects most commonly encountered with sunitinib are fatigue, anorexia, stomatitis, diarrhea, hand foot syndrome, thrombocytopenia, hypertension and hypothyroidism (64). When sunitinib is used in imatinib failure patients, it is more sensitive in patients with exon 9 mutation and wild type GISTs (65). The mechanisms proposed for sunitinib resistance are increased expression of interleukin-8, AMFR gene expression which is involved in angiogenesis and extracellular matrix metalloproteinase inducer (EMMPRIN), however most of these resistance mechanisms have been studied in renal cell carcinoma patients (66-68).

Third line therapy for metastatic GIST

Regorafenib which is structurally similar to sorafenib, is recommended once patients have progressed on imatinib and sunitinib. It is a pan-TKI which has multiple targets: *KIT*, RET, RAF1, BRAF, VEGFR1-3, TEK, PDGFR and fibroblast growth factor receptor (FGFR) (69,70). The dose recommended is 160 mg oral tablet once daily for 21 days, with cycle of 28 days each. In the initial multicentre phase II study, regorafenib as 3rd line agent showed a PFS of 10 months (71). In the subsequent phase III randomized study (GRID), 199 patients were randomized to third-line regorafenib versus placebo. Patients on progression in the placebo arm were allowed to cross over to the regorafenib arm. At 3 and 6 months, PFS was 60% versus 11% and 38% versus 0% in the regorafenib versus placebo arm respectively. The median PFS was 4.8 versus 0.9 months in the regorafenib versus placebo arms respectively (HR, 0.27, 95% CI, 0.19-0.39; P<0.0001), whereas the disease control rate was 53% versus 9% (P<0.0001). However as expected, due to crossover OS was not statistically different (72). Moreover the benefit of regorafenib was less if the patient had received less than 6 months of imatinib. Toxicity greater than grade 3 or more (HFS, mucositis, diarrhea, hypertension, fatigue) was seen in about 60%, with half the patients requiring dose reductions, however only 2% discontinued treatment due to toxicity. Based on the GRID study, the FDA in 2013 approved regorafenib as a third-line agent (progressed or intolerant to imatinib and sunitinib) in metastatic GIST.

Another option for patients in third-line setting is to rechallenge the patient with imatinib after progression on imatinib and sunitinib, however the patients should have

Table 3 Mutations and response to TKI

Gene	Exon mutation	Imatinib response	Sunitinib response	Regorafenib response
KIT	9	Yes, 800 mg preferred	Yes, marked	Yes
KIT	11	Yes, marked, Val559Ile resistant	Yes	Yes
KIT	13	Yes	Yes	Yes
KIT	17	Yes, Asn822Lys resistant	Minimal	Yes
PDGFR	12, 14	Yes	Yes	Yes
PDGFR	18 D842V	No	No	No
Wild type		Yes	Yes	Yes

TKI, tyrosine-kinase inhibitor; *PDGFR*, platelet derived growth factor receptor.

Table 4 Key phase III randomized trials with tyrosine kinase inhibitors in patients with GIST

Name of study	Setting	N	Randomized arms	PFS/RFS	OS	Response rate
ACOSOG Z9001 (41)	Adjuvant	713	1-year imatinib *vs.* placebo	1-year RFS 98% *vs.* 83% (P<0.0001)	HR =0.816; P=0.438	Not available
SSG XVIII/AIO (29)	Adjuvant	400	1- *vs.* 3-year imatinib	5-year RFS 66% *vs.* 48% (P<0.0001)	5-year OS 92% *vs.* 82% (P=0.02)	Not available
EORTC (52)	1st line metastatic	946	400 *vs.* 800 mg imatinib	2-year PFS 56% *vs.* 50% (P=0.026)	2-year OS 69% *vs.* 74%	50% *vs.* 54%
North American Sarcoma Intergroup study (S0033) (53)	1st line metastatic	746	400 *vs.* 800 mg imatinib	2-year PFS 50% *vs.* 53%	2-year OS 73% *vs.* 78%	43% *vs.* 41%
Demetri *et al*. (63)	2nd line metastatic	243	Sunitinib *vs.* placebo	Median 27.3 *vs.* 6.4 weeks (P<0.0001)	Median 72.7 *vs.* 64.9 weeks (P=0.306)	Not available
GRID (72)	3rd line metastatic	199	Regorafenib *vs.* placebo	Median 4.8 *vs.* 0.9 months P<0.0001)	Same (HR =0.77; P=0.199)	76% *vs.* 35%

GIST, gastrointestinal stromal tumors; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio.

initially shown some response to imatinib. This was studied in a randomized manner in the phase III RIGHT study, in which 81 patients were randomized to imatinib 400 mg daily or placebo as 3rd line agent. The disease control rate with imatinib was 32% and the PFS was 1.8 versus 0.9 months in the imatinib versus placebo arms respectively, however there was no OS benefit (73).

Table 3 shows the response of various TKIs based on the mutation. *Table 4* summarizes the key phase III trials.

Mechanism/drivers of resistance to molecular therapy

In metastatic patients, after a few years of imatinib, the tumors become resistant. However most of the times this resistance is partial, i.e., only few clones become resistant and grow, while few other clones are still sensitive. Imatinib resistance could be either primary or secondary. Primary imatinib resistant tumors progress within the initial few months of therapy whereas secondary resistance happens later due to the development of new secondary mutations, which prevent the binding of imatinib to the *KIT* receptor (74,75). Some of the mechanisms proposed for Imatinib resistance are (76):

(I) Development of secondary mutations in *KIT* and *PDGFRA* which are resistant to imatinib (77);
(II) Amplification and over expression of the *KIT* genome (irrespective of mutation);
(III) Activation of alternate receptor tyrosine kinases;
(IV) Functional resistance—activation of other sites in the *KIT* apparatus (other than usual juxtamembrane site).

Primary resistance is seen in mutations in the activating loop of *PDGFRA* such as D842V in which imatinib is unable to bind to the ATP-binding site of the tyrosine kinase receptor (79,80) and in 15% of *KIT* exon

9 mutations. Secondary mutations usually affect *KIT* exons 13 to 17 (11). In tumors with mutations in exons 13 and 14 which corresponds to the ATP-binding region of the kinase domain, competitive inhibition of imatinib is impaired, where as in exons 17 and 18 mutations the activation loop is affected. Hence in the former more potent TKIs like sunitinib may be beneficial whereas the latter are equally resistant to most TKIs (80).

D842V mutations are usually also resistant to 2nd and 3rd line agents like sunitinib and regorafenib (65,71,79,81) while exon 9 mutations may benefit with higher dose (800 mg) imatinib.

In an EORTC study, factors predictive of early and late resistance were studied. While the presence of lung metastases and absence of liver metastases predicted early resistance, late resistance was predicted by high baseline granulocyte count, a non-stomach primary tumor, large primary size, and low initial imatinib dose (76). Imatinib causes cell death by apoptosis, however some cells escape this due to quiescence, during which the cells are sent to resting phase and hence they escape death by imatinib. This process of quiescence is further enhanced by DREAM complex, hence in imatinib resistant cases, targeting this DREAM complex is also an active part of research in the recent times (82).

In phase II studies sunitinib as third-line therapy had a response rate of 10% with PFS of 5 months (80,83). Another TKI which has got significant benefit in chronic myeloid leukemia called nilotinib failed to demonstrate any benefit in GIST both as 1st line and 3rd line agent in phase III trial (84,85). Ponatinib in another TKI which was initially studied in CML is now being probed in GIST also (86). Heat shock protein (HSP) prevents the proteosomal degradation of *KIT*, hence the new area of interest in the management of GIST is HSP90 inhibitors (87), especially in imatinib resistant cases. Presently the HSP90 inhibitors which are under clinical trials are STA-9090, AT-13387 and AUY922 (88-90). In imatinib resistant clones the PI3K/AKT pathway plays an important role in cell survival and hence targeting this pathway with PI3K inhibitors looks promising (91,92). The MAPK pathway stabilizes ETS translocation variant 1 (ETV_1), which is a transcription factor responsible for tumorigenesis. The transcription factor ETV_1 involved in the MAPK pathway is also expressed on GIST cells, which has led to the study of MEK 162 which is a MEK inhibitor along with imatinib in GIST (93).

Studies have shown that in wild type GISTs with imatinib resistance, there is deficiency in succinate dehydrogenase (SDH) activity which is most often the result of up regulation of IGF1 receptor (10). Hence in wild type GIST the IGF1 receptor inhibitor linsitinib is being studied in phase II trials currently. Other targets which are being studied in imatinib resistance are the downstream signaling pathway molecules like m TOR inhibitors (everolimus and temsirolimus), AKT inhibitor (perifosine), CDK inhibitor (flavopiridol) (11), IGF1 and BRAF inhibitors. Crenolanib is an oral benzimidazole which is a selective and potent inhibitor of *PDGFRA* and *PDGFRB*. It is found to be 135 fold more potent than imatinib in *PDGFRA* D842V mutated GISTs (94). Recently, an anti-*KIT* monoclonal antibody called SR1 has been identified which is active in both imatinib sensitive and resistant cell lines. SR1 reduces cell surface *KIT* expression and also enhances macrophagic phagocytosis of cancer cells causing immunologic cell mediated tumor clearance (95). The development of so many molecules is the proof that imatinib resistance is an active field in current medical research and like the recent approval of regorafenib we are hopeful to have many approvals in the near future.

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