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Targeted therapy of gastrointestinal stromal tumours

Ashish Jakhetiya, Pankaj Kumar Garg, Gaurav Prakash, Jyoti Sharma, Rambha Pandey, Durgatosh Pandey

Ashish Jakhetiya, Pankaj Kumar Garg, Jyoti Sharma, Durgatosh Pandey, Department of Surgical Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

Pankaj Kumar Garg, Department of Surgery, University College of Medical Sciences and Guru Teg Bahadur Hospital, University of Delhi, Delhi 110095, India

Gaurav Prakash, Clinical Hematology and Bone Marrow Transplant Unit, Department of Internal Medicine, Post-Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Rambha Pandey, Department of Radiation Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

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Correspondence to: Dr. Pankaj Kumar Garg, Associate Professor, Department of Surgery, University College of Medical Sciences and Guru Teg Bahadur Hospital, University of Delhi, Dilshad Garden, Delhi 110095, India. dr.pankajgarg@gmail.com
Telephone: +91-1122-592536
Fax: +91-1122-590495

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Abstract

Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms originating in the gastrointestinal tract, usually in the stomach or the small intestine, and rarely elsewhere in the abdomen. The malignant potential of GISTs is variable ranging from small lesions with a benign behaviour to fatal sarcomas. The majority of the tumours stain positively for the CD-117 (KIT) and discovered on GIST-1 (DOG-1 or anoctamin 1) expression, and they are characterized by the presence of a driver kinase-activating mutation in either KIT or platelet-derived growth factor receptor α. Although surgery is the primary modality of treatment, almost half of the patients have disease recurrence following surgery, which highlights the need for an effective adjuvant therapy. Traditionally, GISTs are considered chemotherapy and radiotherapy resistant. With the advent of targeted therapy (tyrosine kinase inhibitors), there has been a paradigm shift in the management of GISTs in the last decade. We present a comprehensive review of targeted therapy in the management of GISTs.

Key words: Gastrointestinal tumors; Molecular targeted therapy; Protein kinase inhibitors; Imatinib; Survival

Core tip: Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumours of the gastrointestinal tract. They are characterized by the presence of a driver kinase-activating mutation in either CD-117 or platelet-derived growth factor receptor α. Development of tyrosine kinase inhibitors has led to a paradigm shift in the management of GISTs. Surgery is the primary

modality of treatment in localized non-metastatic GISTs. Adjuvant Imatinib for three years is a preferred option for high-risk patients to lessen disease recurrence. The role of neoadjuvant Imatinib is evolving. Imatinib, Sunitinib, and Regorafinib are recommended as first, second and third-line targeted therapies, respectively, for the management of metastatic GISTs.

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INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and hypothesised to arise from the intestinal cells of Cajal[1]. GISTs constitute 1%-3% of all malignant gastrointestinal tumours, with an annual incidence rate of 10 to 15 cases per million[2]. Commonly, they arise from the stomach (60%-70%) and small intestine (25%-35%); other rare intestinal sites are the colorectum, oesophagus and appendix. Rarely, they can also involve extra-intestinal sites including the omentum, retroperitoneum, and mesentery (extra-intestinal GISTs)[3]. Histologically, GISTs can be of three types: Spindle cell type (70%), epithelioid, and mixed subtype[3]. They are diagnosed based on clinical and morphological features which are supported by immuno-histochemistry studies. CD-117 (KIT) and discovered on GIST-1 (DOG-1 or anoctamin 1) are the most sensitive and specific markers; other diagnostic markers include CD-34 (70% positivity), smooth muscle actin (20%-30% positivity), S-100 (10% positivity), and negativity for desmin (2%-4% of GISTs may be positive for desmin). About 5% of GISTs are negative for KIT expression, however many of them express DOG-1[3-6]. Complete resection (R0) is the primary treatment in the management of localized GISTs. Traditionally, GISTs are considered chemo-resistant and radio-resistant tumors[7]. Half of the patients have disease relapse in the first five years of surgery, and 5-year actuarial survival rate after surgery was reported as 54%[4]. This highlights the need for effective adjuvant therapy. Imatinib, a tyrosine-kinase inhibitor (TKI) developed in 1998 for chronic myeloid leukaemia (CML), galvanized a lot of enthusiasm in the management of GISTs due to its direct inhibition of KIT and platelet-derived growth factor receptor α (PDGFRA) mutation related tyrosine kinase activity[7]. The last 15 years witnessed remarkable progress in the field of TKIs resulting in significant improvement in the treatment outcomes in locally advanced and metastatic GISTs. The present article reviews the current status of targeted therapy of GISTs.

RATIONALE OF TARGETED THERAPY

Around 75%-80% of GISTs have KIT mutations, mainly affecting juxta-membrane domain coded by exon 11. Deletions are the most common; however insertions, substitutions and combinations can be seen. Rarely, mutations can also affect extracellular domain (exons 8 and 9) or kinase Ⅰ and Ⅱ domains (exons 13 and 17)[8-10]. Approximately 20%-25% of GISTs do not have KIT mutations; around 10% of these cases have PDGFRA mutations. The remaining (10%-15%) who do not have either KIT or PDGFRA mutations are labelled as wild-type GISTs; this group forms a heterogeneous group which have mutations acting on downstream of receptor kinases[11-13]. Ultimately mutations of KIT and PDGFRA promote cell signalling through the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) pathways[9,10,14]. As structural similarities were detected between BCR-ABL kinase and KIT kinase, Imatinib was used in a metastatic GIST patient and it led to a dramatic response. This success led to the beginning of multiple clinical trials to establish the role of Imatinib and other TKIs in GISTs[7,12].

ROLE OF TARGETED THERAPY IN METASTATIC GISTS

Although there has never been a randomized controlled trial (RCT) to compare targeted therapy with chemotherapy in the management of metastatic GISTs, various studies have highlighted the potential role of targeted therapy in improving survival.

Imatinib mesylate

Imatinib, a small molecule TKI with activity against BCR-ABL, KIT and PDGFRA related kinases, was the first Food and Drug Administration approved agent in metastatic GISTs. In an open label phase Ⅱ trial to assess efficacy and safety of Imatinib in 147 patients with advanced GISTs, Demetri *et al*[13] in 2002 reported that Imatinib resulted in partial response in 53.7% and stable disease in 27.9% of patients. Therapy was well tolerated, although mild to moderate edema, diarrhea, and fatigue were common, and gastrointestinal or intra-abdominal hemorrhage occurred in approximately 5% of patients. Long-term results of this trial, published in 2008, further confirmed that nearly 50% of patients with advanced GISTs who were treated with Imatinib survived for more than 5 years. After a follow-up of up to 71 mo, there was complete response in 1.4% and partial response in 68.1%; disease remained stable in 15.6% and progressed in 11.6%. This translated into median progression free survival (PFS) of 24 mo and median overall survival (OS) of 57 mo[15]. These results were soon validated by two phase Ⅲ multi-centric RCTs which were designed to address the optimal daily dose of Imatinib. A multi-centric RCT was conducted by

EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group to address dose dependency of response and PFS with Imatinib for metastatic GISTs[16]. They randomized 946 patients into two groups based on daily dose of Imatinib, 400 mg either once or twice a day. At median follow-up of 760 d, higher dose Imatinib (400 mg twice a day) led to better PFS (56% *vs* 50%, HR = 0.82, 95%CI: 0.69-0.98, *P* = 0.026). They concluded that a dose of 400 mg twice a day leads to significantly longer PFS, as compared to once a day dosing, although both dosing achieve similar response induction. Moreover, higher dosing also resulted in a significantly higher number of treatment interruptions (64% *vs* 40%) or dose reductions (60% *vs* 16%). Relatively different results were noted by another phase Ⅲ RCT, Southwest Oncology Group S0033 trial[17]. Although the authors confirmed the effectiveness of Imatinib as a primary systemic therapy in metastatic GISTs, they concluded that higher dose (800 mg/d) does not provide any advantage over conventional dose (400 mg/d) therapy. They also reported a higher frequency of drug related toxicities among patients who received 800 mg/d Imatinib (grade 3-5 toxicities 63% *vs* 43%). The Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) conducted a meta-analysis exploring the data of the previously published two large, randomized, cooperative-group studies which had compared two doses of Imatinib (400 mg daily *vs* twice daily) in 1640 patients with advanced GISTs[18]. They reported a small (HR = 0.89; 95%CI: 0.79-1.00) but significant (*P* = 0.04) PFS advantage for the high-dose arm; however, no significant difference was observed in OS (HR = 1.00, *P* = 0.97) between the two groups. Cox regression analysis showed that higher dose therapy would potentially delay the first occurrence of disease progression and increase objective response rate in only those patients who harbor KIT exon 9 mutations. Based on these results, 400 mg daily is established as standard first line therapy; however, due consideration for higher dose (800 mg/d) may be given in patients who have KIT exon 9 mutation or have progressed on 400 mg/d of Imatinib. The subgroup analysis of these two trials also highlighted that those patients who have exon 11 mutations would respond better to Imatinib than those who have exon 9 or wild-type allele[16-19]. Although almost all mutant subtypes are likely to have improved PFS and OS when treated with Imatinib compared to chemotherapy (historical controls), D842V mutations in PDGFRA confer resistance to Imatinib therapy; no clinical benefit has been demonstrated with Imatinib in tumours having this mutation[18,20,21]. How long Imatinib is to be given in metastatic GISTs is the next natural question. French Sarcoma Group designed a phase Ⅲ RCT to compare continuous (CONT) compared with interrupted (INT) Imatinib beyond 1 year of treatment[22]. They randomized 58 advanced GIST patients who had either response or stable disease after one year of Imatinib therapy into two groups - 32 patients (INT arm) stopped while 26 patients (CONT arm) continued to receive Imatinib therapy. There was a significantly higher frequency of disease progression in INT arm - 26 of 32 (81%) patients had documented disease progression patients as compared to 8 of 26 (31%) patients in the CONT group (*P* = 0.0001). Moreover, 24 of 26 patients with documented disease progression in the INT arm responded when Imatinib was reintroduced to them. This led to the conclusion that Imatinib is to be continued in advanced GISTs till evidence of disease progression or intolerance.

Other targeted agents

Sunitinib is a TKI, which inhibits KIT, PDGFRA, vascular endothelial growth factor receptors (VEGFR) 1-3 and FLT3 receptor kinase[23]. Apart from having an inhibitory effect on oncogenic kinases, it also has antiangiogenic properties. In an initial phase Ⅰ/Ⅱ study, Sunitinib has shown promising clinical activity for Imatinib resistant patients[24]. A phase Ⅲ trial randomized 312 Imatinib resistant metastatic GIST patients to receive either Sunitinib or placebo; best supportive care was given in both the arms[25]. Time to tumour progression (TTP) was four times longer in Sunitinib arm as compared to placebo (27.3 wk *vs* 6.4 wk, HR = 0.33, 95%CI: 0.23-0.47, *P* < 0.0001); similarly PFS was significantly better in Sunitinib arm (24.1 wk *vs* 6 wk, HR = 0.33, 95%CI: 0.24-0.47; *P* < 0.0001). Although relatively low but confirmed objective response rate was better in Sunitinib arm (7% *vs* 0%, *P* = 0.006); 16% of patients were progression free at 6 mo in Sunitinib arm *vs* 1% in placebo. Despite cross-over, OS was better in Sunitinib arm than placebo (HR = 0.49, 95%CI: 0.29-0.83; *P* = 0.007). Serious treatment related adverse events were 20% in Sunitinib arm and 5% in placebo arm and only 9% discontinued treatment in Sunitinib arm due to adverse events. So, Sunitinib improved TTP, PFS and OS in patients with Imatinib resistance with acceptable toxicity profile. Presently, Sunitinib is recommended as second line therapy for patients who are intolerant or have progressive disease on Imatinib. Recommended dosing schedule is 50 mg daily orally for four weeks followed by a break for 2 wk; or a continuous regimen with daily dose of 37.5 mg can also be used[25,26].

Regorafinib is an oral multikinase inhibitor which inhibits various protein kinases, including those involved in angiogenesis (VEGFR 1-3, PDGFRB, FGFR1) and oncogenesis (KIT, RET, BRAF)[27]. In a multicenter phase Ⅱ trial, Regorafinib at a dose of 160 mg daily for 3 wk in a 4 wk cycle showed a clinical benefit rate of 79% (95%CI: 61%-91%). Median PFS was 10.0 mo[28]. On the basis of these results, a multicentric phase Ⅲ trial, GRID, was planned to evaluate the efficacy and safety of Regorafinib in metastatic GIST patients who had progressed after initial Imatinib and Sunitinib therapy. A total of 199 patients were randomized to receive Regorafinib or placebo along with best supportive care in both the arms. Disease control rate was significantly better in Regorafinib arm than in placebo arm (52.6%

vs 9.1%, *P* < 0.0001). Median PFS was 4.8 mo (interquartile range = 1.4-9.2) in Regorafinib arm and 0.9 mo (0.9-1.8) in placebo arm (HR = 0.27, 95%CI: 0.19-0.39, *P* < 0.0001). Eighty-five percent of patients crossed over from placebo to Regorafinib group, so OS was not different (HR = 0.77). Regorafinib related grade Ⅲ or more toxicity was present in 61% of patients[29]. Thereafter, Regorafinib was approved as a third line standard of care in metastatic GIST patient who have progressed or intolerant to Imatinib and Sunitinib.

Masitinib is another highly selective TKI with significant activity against GISTs. In a recent RCT it was compared with Sunitinib in advanced GIST patients after failure of Imatinib. Trial showed encouraging results in favour of Masitinib with better safety profile[30]. Another phase Ⅲ RCT (NCT01694277) is recruiting patients to evaluate the safety and efficacy of Masitinib in comparison to Sunitinib in patients with GISTs after progression with Imatinib.

ROLE OF TARGETED THERAPY IN NON-METASTATIC GISTS

Surgery is the standard of care for localized GISTs; complete excision (R0 resection), without rupturing the pseudocapsule, is the aim of surgery. Regional lymphadenectomy is usually not a part of radical surgery as lymph node metastasis is rarely present in GISTs[31,32]. A high frequency of post-surgery disease recurrences mandates identification of high-risk group which can be exposed to adjuvant therapy. Various risk stratification systems are available to predict post-surgery disease recurrence - National Institute of Health (NIH) consensus criteria, modified NIH criteria, Armed Forces Institute of Pathology criteria, Memorial Sloan Kettering Cancer Centre prognostication criteria and prognostic contour maps[21]. Main factors which have been identified for predicting post-surgery recurrence are mitotic rate, tumour size, and location of the tumor[33]. Imatinib is the only recommended adjuvant targeted therapy which has been evaluated in clinical trials.

In the ACOSOG Z9000 trial, 106 patients with a high risk of recurrence (defined as tumor size > 10 cm, intra-peritoneal tumor rupture and up to four peritoneal implants) underwent curative resection and received adjuvant Imatinib for one year. After median follow-up of 7.7 years, the 1, 3 and 5-year OS rates were 99%, 97% and 83%, respectively, which compared favourably with a historical 5-year OS rate of 35%[4].

In ACOSOG Z9001, a phase Ⅲ RCT, 713 patients were randomized to adjuvant Imatinib for one year *vs* placebo based on tumour size more than 3 cm. The 1-year recurrence free survival (RFS) rate was 98% in Imatinib arm in comparison to 83% in placebo arm (HR = 0.33; 95%CI: 0.20-0.53; *P* < 0.0001). Retrospective analysis of the trial suggested that adjuvant therapy was more effective in high-risk patients (tumor size > 10 cm and high mitotic rate). There was no difference in OS (HR = 0.66, 95%CI: 0.22-2.03, *P* = 0.47) due to cross-over design of the trial. Grade 3 or 4 events occurred in 30% of patients in Imatinib arm[34]. Recently published long term results after median follow-up of 74 mo showed no significant difference in OS. They found that high mitotic rate, large tumour size and small bowel location are associated with lower RFS irrespective of tumour genotype. Imatinib therapy improved RFS in patients with KIT exon 11 deletions but not in those with exon 11 insertions or point mutations, KIT exon 9 mutations or wild type GISTs. As 400 mg/d of Imatinib therapy was prescribed in exon-9 mutation patients, this can be argued that 800 mg/d daily dose could have improved treatment outcomes based on the experience from trials conducted in metastatic GISTs. Additional studies are needed to better define the management of wild type tumours in both adjuvant and metastatic settings[35].

In subsequent SSG XVIII/AIO phase Ⅲ RCT, 400 patients were randomized based on high risk features (at least one of the following: Tumour size > 10 cm, mitotic rate > 10/50 high power field (HPF), tumor size > 5 cm and mitotic rate > 5/50 HPF, tumour rupture before or during surgery) to either 1 or 3 years of adjuvant Imatinib[36]. Patients in 3-year arm had longer 5-year RFS compared to 1-year arm (65.6% *vs* 47.9%, HR = 0.46, 95%CI: 0.32-0.65, *P* < 0.001). OS was also longer in 3-year arm compared to 1-year arm (92% *vs* 81.7%, HR = 0.45, 95%CI: 0.22-0.89, *P* = 0.02). However, grade 3 or 4 toxicities were also higher in 3-year arm (32.8% *vs* 20.1%) and more patients discontinued treatment in 3-year arm (25.8% *vs* 12.6%) compared to 1-year arm. Based on the results of these two trials, three-year adjuvant Imatinib therapy is presently the standard of care in high-risk patients. Recently, a clinical trial (the PERSIST-5 trial, NCT00867113; ClinicalTrials.gov, 2009) examining the role of 5 years of adjuvant Imatinib in high-risk patients completed accrual; however, final results will be available after 2018.

Neoadjuvant setting is another area of interest in the management of locally advanced GISTs which are not operable upfront. In the absence of phase Ⅲ trials, role of neoadjuvant therapy remains investigational. Two phase Ⅱ trials have demonstrated efficacy and safety of neoadjuvant Imatinib in locally advanced GISTs[37,38]. The dosing and duration of targeted therapy in neoadjuvant setting are currently based on the experience gathered through trials conducted in metastatic GISTs. As phase Ⅲ EORTC 62005 trial designed for metastatic GISTs showed that there was no difference in overall response rate between 400 mg *vs* 800 mg group, this indicates that 400 mg daily dose for neoadjuvant therapy would be appropriate to downstage the tumour. As the reported median time to best response was 4 mo, this should be taken as length of neoadjuvant treatment, and it can be extended up to 6 mo[16]. Another study suggested that neoadjuvant TKI can be given for 9 to 12 mo; however, it should not be extended beyond 12 mo because of the risk of resistance[39]. In a pooled database

Table 1 Published randomized controlled trials of role of targeted therapy in gastrointestinal tumours

Study	Research question	Sample size	Study arms	Response rates	PFS/RFS	OS	Toxicity (Grades 3-5)	Conclusion
SWOG S0033[14]	Imatinib as first line in metastatic GISTs	746	400 mg daily *vs* 400 mg twice daily	ORR 45% (CR 5%, PR 40%) *vs* 45% (CR 3%, PR 42%)	2 yr PFS 41% *vs* 46% (P = 0.13)	2 yr OS 76% *vs* 72% (HR = 0.98)	43% *vs* 63%	400 mg daily is initial dose and consider dose escalation with disease progression
EORTC 62005[13]	Imatinib as first line in metastatic GISTs	946	400 mg daily *vs* 400 mg twice daily	51% *vs* 54%	2 yr PFS 56% *vs* 50% (HR = 0.82, P = 0.026)	2 yr OS 69% *vs* 74%	32% *vs* 50%, P < 0.0001	Better PFS in 400 mg twice daily with higher toxicity
Demetri *et al*[25]	Sunitinib as second line in metastatic GISTs	312	Sunitinib *vs* placebo	7% *vs* 0% (SD 58% *vs* 48%)	Median TTP 27.3 wk *vs* 6.4 wk (HR = 0.33, P < 0.0001)	Better in Sunitinib arm (HR = 0.49, P = 0.007)	20% *vs* 5%	Sunitinib is approved as a second line therapy in metastatic GISTs
GRID[29]	Regorafinib as third line in metastatic GISTs	199	Regorafinib *vs* placebo	4.5% *vs* 1.5% (SD 71.4% *vs* 33.3%)	Median PFS 4.8 mo *vs* 0.9 mo (HR = 0.27, P < 0.0001)	No difference, HR = 0.77	61% *vs* 14%	Regorafinib is approved third line therapy in metastatic GISTs
ACOSOG Z9001[35]	Imatinib as adjuvant	713	1 yr (400 mg) *vs* placebo	Not available	1 yr RFS 98% *vs* 83% (HR = 0.33, P < 0.0001)	1 yr OS 99.2% *vs* 99.7% (HR = 0.66, P = 0.47)	30.9% in Imatinib arm	1 yr adjuvant Imatinib is effective and safe
SSG XVIII/AIO[36]	Imatinib as adjuvant	400	1 yr *vs* 3 yr	Not available	5 yr RFS 47.9% *vs* 65.6% (HR = 0.46, P < 0.001)	5 yr OS 81.7% *vs* 92% (HR = 0.45, P = 0.02)	20.1% *vs* 32.8%	3 yr adjuvant Imatinib improved RFS and OS

SWOG: Southwest Oncology Group; GISTs: Gastrointestinal stromal tumours; ORR: Overall response rates; CR: Complete response; PR: Partial response; SD: Stable disease; PFS: Progression free survival; RFS: Recurrence free survival; TTP: Time to tumour progression; OS: Overall survival; HR: Hazard ratio.

Table 2 Current role of targeted therapy in gastrointestinal stromal tumours

Agent	Use	Dose	Duration
Imatinib	First line in metastatic GISTs[13-15]	400 mg once daily (oral)	Till progression or intolerance
	Progression on 400 mg[13-15]	400 mg twice daily (oral)	Till progression or intolerance
	Exon 9 mutation[13-15]	400 mg twice daily (oral)	Till progression or intolerance
	Adjuvant in high risk cases[37]	400 mg daily (oral)	3 yr
	Neoadjuvant setting[29,39,40]	400 mg daily (oral)	6-12 mo
Sunitinib	Second line in metastatic setting[21,24]	50 mg once daily for 4 wk every 6 wk (oral) or 37.5 mg once daily continuously (oral)	Till disease progression or intolerance
Regorafinib	Third line in metastatic setting[26]	160 mg once daily for 3 wk every 4 wk (oral)	Till disease progression or intolerance

GISTs: Gastrointestinal stromal tumours.

of ten EORTC STBSG centers, 161 patients with locally advanced, non-metastatic GISTs were identified who received neoadjuvant Imatinib. R0 resection was achieved in 83% and 5-year DFS rate was 65% with median OS of 104 mo[40]. The National Comprehensive Cancer Network guidelines recommend neoadjuvant Imatinib therapy in locally advanced GISTs to achieve R0 resection and to minimize postoperative morbidity. Imatinib can be stopped just before surgery and again restarted as soon as patients resume oral intake[41].

Table 1 displays the published RCTs in GISTs. Table 2 displays the current role of targeted therapy in GISTs based on available evidence.

SIDE EFFECTS OF TARGETED THERAPY

Most of the side effects of Imatinib are mild and well tolerated. Anaemia (70%-80%) and leukopenia (35%-45%) are common haematological side effects. Non-haematological toxicities include periorbital edema (60%-75%), diarrhoea (45%-55%) and fatigue (50%). Other side effects (20%-40%) are nausea, muscle cramps, leg edema, anorexia and rashes. Most patients develop tolerance for these side effects on continuous use. Therefore, patient's education about occurrence of these common side effects and advice against interrupting treatment due to these side effects is of paramount value before starting Imatinib mesylate. Previous trials have reported a higher frequency of Grade 3 or more toxicities in high dose 800 mg/d (50%-60%) compared to conventional 400 mg/d Imatinib therapy (50%-60% *vs* 30%-40%)[18-20,41]. Common side-effects seen with Sunitinib therapy include fatigue (34%), diarrhoea (29%) and skin discolouration (25%); other less-common side effects are hematological toxicity (anaemia and leukopenia), hand-foot syndrome, hypertension,

and hypothyroidism[25]. Toxicity profile of Regorafinib includes hand-foot skin reactions (56%), hypertension (49%) and diarrhoea (40%)[29].

DRUG RESISTANCE

In GIST patients on Imatinib, resistance can be primary or secondary. Primary (intrinsic) resistance is seen in approximately 15% patients and is due to mutations such as D842V in PDGFRA and KIT exon 9, where Imatinib is not able to bind on ATP binding site of tyrosine kinase receptor[12,25]. Secondary (acquired) resistance usually develops after 18-24 mo of treatment. A number of mechanisms have been put forward for secondary (acquired) resistance in GISTs: Occurrence of a second mutation in KIT receptor, other gene mutations, *KIT* genomic amplification and activation of an alternative receptor tyrosine kinase protein in the absence of *KIT* expression, increased serum acid glycoprotein levels and increased multidrug resistance gene expression, lower bioavailability of Imatinib during chronic therapy possibly due to up-regulation of hepatic enzymes responsible for drug clearance, and impaired drug delivery due to formation of fibrous stroma. More than 80% of patients on treatment ultimately develop secondary resistance[16,42]. Based on the results of previous trials, the dose of Imatinib can be increased from 400 mg to 800 mg to overcome problem of resistance; however, median time of benefit with this approach is short (11.6 wk)[16]. Like Imatinib, Sunitinib also binds to ATP binding domain of KIT and PDGFRA, but both these agents have different binding domains. Moreover, Sunitinib also has anti-angiogenesis activities and is now approved as a second-line targeted therapy in Imatinib resistant cases[25]. However, subsequent drug resistance to Sunitinib evolves within one year due to secondary mutations. Regorafinib is approved as a third line targeted therapy in this setting[28].

FUTURE DIRECTIONS

Although three lines of targeted therapy are present, failure to respond to Regorafinib leaves us with no further standard options. Usual strategy in this sitting is to re-challenge with previously used therapy. Further studies are needed to address this problem of TKI resistance. Various new targeted agents are under evaluation for Imatinib resistant GISTs. Masitinib, a multi-kinase inhibitor, is under evaluation as a second-line therapy in comparison to Sunitinib. Initial results are promising and a phase Ⅲ RCT is recruiting patients[30]. Ponatinib is another multi-kinase inhibitor which was studied in CML, and now its role is being evaluated for GISTs[43-45]. Crenolanib is an inhibitor of Imatinib resistant PDGFRA kinases including D842V in GIST patients; a phase Ⅱ trial has been initiated to treat this population[46]. Inhibitors of downstream pathway kinases (PI3K and MAPK) are under evaluation[47,48]. Heat shock protein (HSP) protects KIT oncoproteins from degradation and agents targeting HSP 90 are under investigation for Imatinib resistant GISTs[49]. Many new targeted agents are under evaluation to overcome the Imatinib resistance; further research will clear the air regarding their clinical application.

CONCLUSION

Application of Imatinib revolutionized the management of GISTs, and soon after its introduction, it became the standard of care in metastatic GISTs due to its promising activity in improving PFS and OS. Use of Imatinib in adjuvant setting leads to decreased postoperative recurrences and improved survival, though presently, it is only recommended for high-risk cases. Role of Imatinib in neoadjuvant settings is increasingly being explored to escalate resection rates in locally advanced GISTs. Drug resistance is a major concern with TKIs. Intense molecular research is underway to identify other pathways of drug resistance and to develop newer targeted agents.

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