

REVIEW

Contemporary Management of Metastatic Gastrointestinal Stromal Tumors: Systemic and Locoregional Approaches

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ABSTRACT

The treatment of metastatic gastrointestinal stromal tumors (GISTs) changed dramatically with the introduction of imatinib into the therapeutic lexicon in 2001. Over the past 15 years, tyrosine kinase inhibitors in the adjuvant and metastatic settings have remained the standard of care for this disease, though alternate classes of agents and new therapeutic targets are being actively explored in clinical trials. Although data are limited, the use of surgical and non-surgical locoregional techniques for the treatment of GIST metastases has increased and given reports of promising and durable responses. Herein we provide an overview of the contemporary therapeutic landscape of metastatic GIST.

Keywords: Gastrointestinal stromal tumors; Genotype; Locoregional therapy; Metastases; Therapeutic targets; Tyrosine kinase inhibitors

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are digestive tract sarcomas originating from the interstitial cells of Cajal [1]. Most GISTs develop in the stomach and small intestine and frequently metastasize to the liver and peritoneum. Lymph node and lung metastases are rare [2].

Activating mutations of the *KIT* oncogene are the pathogenic hallmark of GISTs and are present in 75–85% of tumors [1–3]. Approximately 65% of *KIT* mutations involve the juxtamembrane domain of the *KIT* receptor encoded by exon 11, and 7–10% involve exon 9, which encodes the extracellular domain [3]. Ten percent of GISTs harbor mutations in the platelet-derived growth factor receptor alpha (*PDGFRA*) gene, which occur mutually exclusive of *KIT* mutations, and another 10–15% are *KIT*/*PDGFRA* wild-type [3]. Up to 50% of these previously termed wild-type GISTs demonstrate defects in succinate dehydrogenase (SDH), which is associated with Carney–Stratakis syndrome, one of the few heritable GIST syndromes associated with

pediatric GISTs [4]. Mutations in *PIK3CA* and *NF1* (neurofibromatosis type 1) have also been identified very infrequently [3].

The connection between *KIT* mutations and GISTs coincided with the clinical development of what was then called STI571, an oral small molecular inhibitor of Abl, KIT, and PDGFRs, which showed compelling activity in chronic myelogenous leukemia [5, 6]. In 2001, Joensuu et al. [7] described the dramatic response of a patient with rapidly progressive, chemorefractory GIST to STI571. Subsequent clinical trials confirmed the antineoplastic activity of STI571, now called imatinib, in metastatic GIST, leading to its approval by the FDA in 2001 (Fig. 1).

In the 15 years that have since passed, the therapeutic repertory for metastatic GIST has expanded significantly and includes additional targeted agents as well as new locoregional techniques. This review will discuss the current therapeutic landscape for metastatic GISTs.

SYSTEMIC THERAPY FOR METASTATIC GIST

Imatinib

In phase I, II, and III studies, imatinib induced objective responses in 45–55% of patients, 3–5% of whom had a complete response [8–11]. The median time to response was ~3–4 months, though some responses were observed up to 2 years later [11]. Median progression-free survival (PFS) and overall survival (OS) were 18–24 months and 50–60 months, respectively [10–12]. Clinical outcomes were similar across different doses ranging from 400 mg QD to 400 mg BID.

Tumor genotype influences sensitivity to imatinib. *KIT* exon 11 mutations are associated with significantly better response and survival outcomes compared to exon 9 mutated and wild-type GISTs [13–16]. Because high dose imatinib (400 mg BID) has been

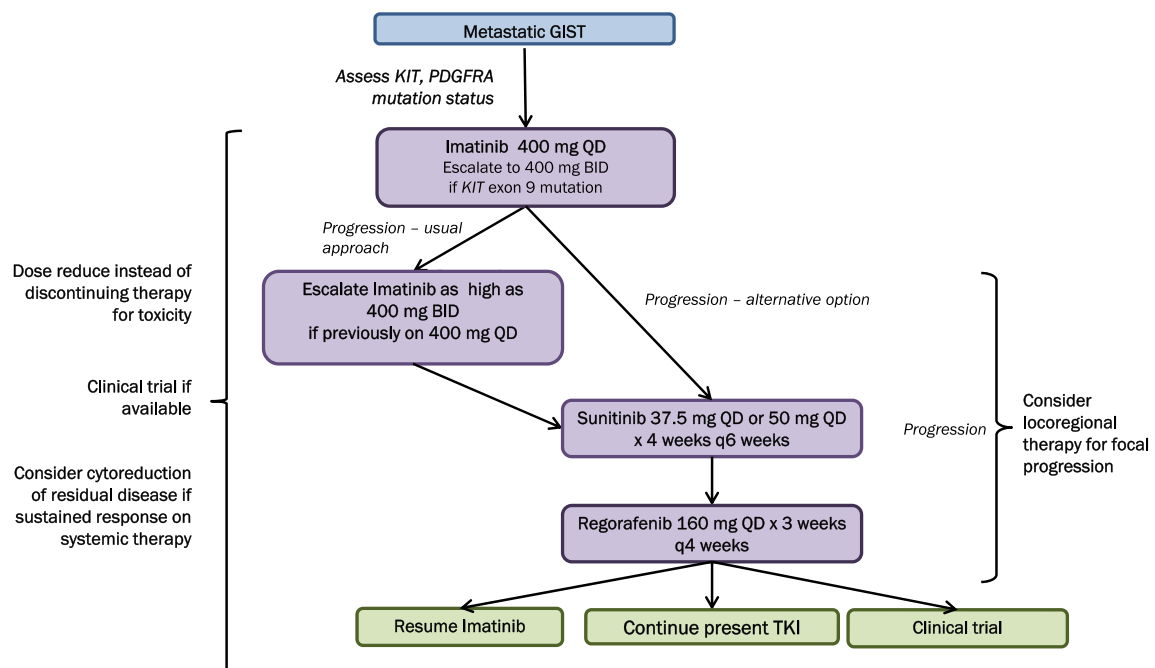


Fig. 1 Suggested treatment algorithm for metastatic gastrointestinal stromal tumor

shown to increase the ORR and PFS in patients with exon 9 mutations [13, 16], patients with this genotype should be closely monitored for progression and dose-escalated as tolerated [17]. *PDGFRA* mutations are associated with variable sensitivity to imatinib with the D842V mutation resistant and other mutations generally sensitive to imatinib [18].

Secondary progression on imatinib is usually the result of acquired secondary *KIT* mutations in exons 13, 14, 17, and 18, which hinder drug-receptor interactions [3, 19]. *KIT* amplification, loss of *KIT* protein expression, and *PDGFRA* D842V mutations also confer resistance [3, 19]. Imatinib dose escalation may “rescue” some patients, around 30% of whom regain disease control [10, 20]. Even patients who progress on multiple agents may benefit from a retreat of imatinib given that some tumors retain imatinib-sensitive clones [17, 21].

Several unique aspects concerning the clinical use of imatinib deserve mention. First, among patients experiencing toxicity, it is recommended to dose reduce rather than discontinue therapy [17]. Rapid progression occurs in >80% of patients within a year of stopping imatinib and is associated with a poor prognosis [22]. Second, there is no established role for on-therapy monitoring of plasma drug levels. Although one study linked imatinib trough levels <1100 ng/mL with poorer outcomes, there was significant interpatient variability and therapeutic compliance was not monitored [17, 23]. Third, the sensitivity of conventional response criteria in solid tumors (RECIST) to detect radiological change on imatinib is limited. While most imatinib-sensitive GISTs demonstrate shrinkage, some tumors may enlarge while becoming more hypodense on CT [24]. By conventional RECIST, such tumors would be

labelled as progressing when they are in fact responding. Likewise, conventional RECIST may fail to detect “resistant clonal nodules”, an early sign of progression in which a new enhancing focus appears within pre-existing tumor mass that is otherwise stable in size [25]. Recognition that a significant decrease in metabolic activity on PET scan predicts subsequent response on CT or MRI led to the development of the “Choi criteria” in which a 10% decrease in tumor size or 15% decrease in tumor density on CT correlates with a favorable response on PET [26]. The Choi criteria outperform conventional RECIST with respect to sensitivity in identifying PET responders (97% vs 52%), and in predicting disease control and survival outcomes on imatinib [24, 26].

Sunitinib

Sunitinib targets *KIT*, *PDGFR*, vascular endothelial growth factor receptor (*VEGFR*), *Fms*-like tyrosine kinase 3 (*FLT3*), and *RET* [27]. Based on preclinical and phase I/II studies showing promising activity in imatinib-refractory GIST [28, 29], a phase III trial was launched. The primary endpoint, time to progression (TTP) was significantly longer with sunitinib versus placebo (27.3 vs 6.4 weeks, HR 0.33, $p < 0.0001$) [27]. Objective responses were uncommon but favored sunitinib (7% vs 0%, $p = 0.006$). Median OS was significantly improved in this study that allowed cross-over from placebo to drug (HR 0.49, $p = 0.007$). The most common toxicities were fatigue, gastrointestinal, skin rash or discoloration, anorexia, and stomatitis, which were mostly grade 1–2. Comparable outcomes have been reported with sunitinib given on a continuous (37.5 mg QD) or intermittent schedule (50 mg QD for 4 weeks every 6 weeks) [27, 30].

Patients with *KIT/PDGFR*A wild-type or *KIT* exon 9 mutated GISTs fared better on sunitinib than those with exon 11 mutations [31]. Secondary *KIT* exon 13 or 14 mutations were also associated with better outcomes than exon 17 or 18 mutations [31]. Sunitinib was FDA-approved for imatinib-resistant GIST in 2006.

Regorafenib

Regorafenib inhibits KIT, VEGFR, PDGFR, fibroblast growth factor receptor 1 (FGFR1), TIE-2, RET, RAF, and MAP kinases [32]. In a phase II trial in patients with GIST resistant to both imatinib and sunitinib, median PFS was 10 months and 75% of patients had disease control lasting ≥ 16 weeks [32]. The main side effects were mostly grade 1–2 hand foot skin reaction, hypertension, fatigue, and diarrhea. PFS appeared superior in patients with *KIT* exon 11 mutations compared to exon 9 mutations.

The phase III GRID trial randomized patients with imatinib and sunitinib-resistant GIST to regorafenib (160 mg QD for 3 weeks of a 4-week cycle) or placebo [33]. The primary endpoint, median PFS, significantly favored regorafenib (4.8 vs 0.9 months, HR 0.27, $p < 0.0001$). The ORR and stable disease rate with regorafenib were 4.5% and 71%, respectively. There was no difference in median OS (HR 0.77, $p = 0.199$). Outcomes were similar in patients with *KIT* exon 9 and 11 mutations. Toxicities mirrored those reported in the phase II trial and responded to dose reductions. In 2013, regorafenib was FDA-approved for the treatment of metastatic GIST refractory to imatinib and sunitinib.

Nilotinib

Nilotinib is a more potent inhibitor of BCR-Abl than imatinib, and also inhibits KIT, PDGFR,

and discoidin domain receptor (DDR) tyrosine kinases [34]. Nilotinib was evaluated in GIST resistant to imatinib and sunitinib in phase II and III studies [35–37]. Median PFS and OS were 12–16 weeks and 34–47 weeks, respectively. The ORR was $\leq 10\%$, but 37–66% of patients had stable disease. In the phase III trial randomizing patients to nilotinib or best supportive care \pm imatinib or sunitinib, PFS was significantly longer with nilotinib by local assessment (119 vs 70 days, HR 0.58, $p = 0.0007$). So-called “clinical benefit rates” (CBR; complete response + partial response + stable disease) were similar between arms (53% vs 45%, $p = 0.28$), and median OS was longer with nilotinib (332 vs 280 days, HR 0.79, $p = 0.29$). A post hoc analysis restricted to the 80% patients with clearly documented progression on imatinib and sunitinib only yielded a significant prolongation in OS by >4 months ($p = 0.02$) with nilotinib [37].

A phase III trial randomizing treatment naïve patients to imatinib versus nilotinib was terminated early due to a higher occurrence of progression and death events in the nilotinib arm [34]. Mutational subgroup analysis revealed differential responses to nilotinib: 2-year PFS was superior with imatinib in patients with *KIT* exon 9 mutations, but was similar between arms in the exon 11 mutation subgroup (67.5% and 70%). This finding, along with the non-overlapping toxicity profile, has led some to propose nilotinib as an alternative in patients with *KIT* exon 11 mutations who are intolerant to imatinib [38]. Nevertheless, nilotinib is not FDA-approved for GIST, and there are no plans for further clinical development in this disease.

Sorafenib

Sorafenib inhibits VEGFR, PDGFR, KIT, RAF, and MAP kinases. The activity of sorafenib in

multi-TKI (imatinib, sunitinib, nilotinib) resistant GIST was evaluated in phase II studies and in a retrospective series [39–42]. Partial response rates ranged from 10 to 24% and 16–60% of patients experienced stable disease. Median PFS and OS were 4.9–7.2 months and 9.7–15.2 months, respectively.

The most common toxicities were HFSR, rash, abdominal pain, hypertension, and diarrhea, which were mostly grade 1/2 [39, 41, 42]. In one study, patients who required a dose reduction for HFSR tended to have a longer PFS than those who did not (8.0 vs 4.7 months, $p = 0.07$) [41].

Masitinib

Masitinib is a potent and selective KIT inhibitor that also targets PDGFRs, FGFR3, and intracellular Lyn kinase [43]. A phase II study of first-line masitinib reported a 5-year OS of 61.5% and median PFS was 41.3 months [44]. In patients with imatinib-resistant GIST, masitinib was associated with a better toxicity profile and significantly longer OS than sunitinib [45]. Randomized phase III studies of masitinib in first and second-line are ongoing (NCT00812240, NCT01694277).

Vatalinib

Vatalinib inhibits KIT, PDGFR, and VEGFR. In phase II studies of patients with imatinib ± sunitinib-resistant GIST, the disease control rate was 40–67% and median TTP was 4.5–8.5 months [46, 47]. The most common grade 1/2 side effects were hypertension, nausea, dizziness, proteinuria, diarrhea, pyrexia, and abdominal pain. Grade 3/4 hypertension, abdominal pain, asthenia, transaminases, hypercalcemia, and headache occurred in 2–7% of patients.

Dasatinib

Dasatinib inhibits BCR-Abl, KIT, PDGFR, and Src family kinases. In a phase II study of first-line dasatinib, median PFS was 13.6 months and 4-year survival was 74%. Nearly 75% of patients had metabolic responses on PET scan [48].

Dasatinib was also assessed in imatinib and sunitinib-resistant GIST in a phase II study [49]. Nearly a third of patients had a partial response by Choi criteria, and median PFS and OS were 2 and 19 months, respectively. In patients with wild-type GIST, median PFS was 8.2 months. Grade 3/4 myelosuppression, pain, constitutional, gastrointestinal, and respiratory toxicities were reported in 30% of patients.

Linsitinib

Linsitinib inhibits insulin-like growth factor receptor-1, which is highly expressed in wild-type GISTs demonstrating a loss of SDH, and also weakly inhibits insulin receptor signaling [50]. In a phase II study restricted to patients with wild-type GIST, 35% of patients had a partial or stable metabolic responses on PET. Nine-month PFS and OS were 52% and 80%, respectively [50]. The most common toxicities were nausea, vomiting, fatigue, and liver enzymes.

Dovitinib

Dovitinib targets VEGFR 1-3, FGFR 1-3, KIT, PDGFR-beta, and fetal liver tyrosine kinase receptor 3 [51]. In a phase II study conducted in imatinib and sunitinib-refractory GIST, 13% had metabolic partial responses and 50% had stable disease on PET scan [51]. Median PFS was 3.6 months and median OS was 9.7 months. Diarrhea, nausea, asthenia, anemia, and

increased alanine aminotransferase occurred in 50–63% of patients and were mostly grade 1/2 in severity. Grade 3/4 asthenia, myelosuppression and dyslipidemia occurred in 10–20% of patients.

Ponatinib

Ponatinib is a pan-BCR-Abl inhibitor that is also active against KIT mutant isoforms associated with TKI resistance [52]. Initial results from a phase II study in patients with TKI refractory GIST reported higher CBR, ORR, PFS, and OS in patients with a *KIT* exon 11 mutation than those without a mutation [53]. Rash, fatigue, myalgia, dry skin, headache, abdominal pain, and constipation occurred in 34–54% of patients. One patient died of pneumonia possibly related to ponatinib.

Pazopanib

Pazopanib inhibits KIT, VEGFR, and PDGFR and has been evaluated in two phase II trials of TKI-resistant GIST [54, 55]. In a randomized study of pazopanib ± best supportive care, 4-month PFS was significantly better with pazopanib (47.7% vs 19.5%, HR 0.56, $p = 0.02$) but there was no difference in survival [55, 56]. There were no objective responses but 84% had stable disease compared to 71% on best supportive care only. Serious toxicities were more frequent with pazopanib (52.5% vs 14.6%) and included gastrointestinal disorders, decreased global health status, and pulmonary embolism. Absence of prior gastrectomy was independently associated with improved PFS [56]. A patient with SDH-deficient wild-type GIST had prolonged disease control [54]. Results from the single-arm phase II PAGIST trial of pazopanib in imatinib and sunitinib-resistant GIST (NCT 01524848) are pending.

Binimetinib

The ETV1 transcription factor mediates GIST oncogenesis, maintenance, and survival, and is part of a positive feedback loop with KIT [57]. Inhibition of MAPK signaling using the MEK inhibitor binimetinib destabilizes KIT and synergizes with imatinib. In a phase Ib study of binimetinib and imatinib, the CBR was 65% and ORR was 41% by Choi criteria [58]. Median PFS was 8 weeks. Two patients had stable disease lasting over a year; one was SDH deficient and the other had a *KIT* exon 11 mutation. Grade ≥ 3 fatigue, edema, rash, HFSR, gastrointestinal toxicities, electrolyte disturbances, and increased liver enzymes occurred in 17–28% of patients, and 89% had asymptomatic grade 3/4 elevations of CPK. A phase II trial is ongoing (NCT01991379).

PI3K/Akt/mTOR Inhibitors

mTOR activation is a mechanism of secondary resistance to imatinib and occurs in 70% of *PDGFRA*-mutated and “wild-type” GISTs [59, 60]. Based on preclinical data showing synergy [61], everolimus was combined with imatinib in several phase II studies [62, 63]. Median PFS and OS were 1.9 and 14.9 months, respectively, in second line, and 3.5 and 10.7 months, respectively, in third-line [61]. Thirty to 40% of patients had stable disease [62, 63].

Preclinical data suggest suppression of PI3K or Akt may yield greater therapeutic benefit [64]. In a phase II trial, the Akt inhibitor perifosine plus imatinib yielded a CBR of 36% in patients with imatinib-resistant disease, especially those with wild-type tumors. Median PFS and OS were 2.2 and 18.3 months, respectively [65]. Several clinical trials of PI3K inhibitors in GIST are underway (NCT01468688, NCT01735968) [64].

Heat Shock Protein 90 Inhibitors

Heat shock protein 90 (HSP90) is a chaperone molecule that protects protein integrity, including mediators of oncogenesis, growth, and maintenance [66]. Preclinical studies have shown that the antineoplastic effects of HSP90 inhibition in GIST cell lines are mediated by KIT degradation [67].

The HSP90 inhibitor retaspimycin has been evaluated in several clinical trials. In a phase I study, ORR was 3% by RECIST and 38% on PET [68]. Median PFS and TTP were 10.6 and 12 weeks, respectively. One patient with imatinib and sunitinib-resistant disease remained on retaspimycin for 5 years. The most common toxicities were fatigue, nausea, headache, diarrhea, and vomiting. Grade 1–2 arrhythmias and QTc prolongation occurred in 2–20% of patients. A phase III study of retaspimycin versus placebo in TKI-resistant GIST was terminated early due to four drug-related deaths [69].

Other HSP90 inhibitors such as BIIB021, AT13387, and ganetespib have shown good tolerability and disease-stabilizing activity in GISTs [70–72].

Immunotherapy

The GIST microenvironment contains regulatory, cytotoxic, proinflammatory, and anti-inflammatory cells, which appear to create a net immunosuppressive effect [73, 74]. GIST infiltrating lymphocytes demonstrate upregulation of the programmed-death receptor-1 (PD-1) and ligand (PD-L1), which dampen immune responses [75]. Imatinib increases the ratio of cytotoxic to regulatory T cells and enhances cross-talk between dendritic and natural killer cells [76, 77], providing a

rationale for evaluating immunotherapy combined with TKIs in metastatic GIST.

In a phase Ib trial of dasatinib and the anti-CTLA4 inhibitor ipilimumab, four out of eight GIST patients had durable disease control [78]. PD-1/PD-L1 axis inhibition demonstrated an additive antiproliferative effect on murine GISTs when combined with imatinib [75]. In a cohort of eight patients, imatinib and pegylated interferon-alpha 2b yielded an ORR of 100% and OS was 100% after a median follow-up of 3.6 years [79].

A summary of these agents and their associated outcomes is provided in Table 1.

LOCOREGIONAL THERAPY FOR METASTATIC DISEASE

Although TKIs are the therapeutic mainstay for metastatic GIST, locoregional approaches can play a complementary role by extending the progression-free interval in patients responding to TKIs, and controlling focal areas of progression due to expansion of resistant clones.

Surgery

Cytoreductive surgery may prevent or delay the onset of resistance and progression in patients on systemic therapy by eliminating viable cells and treatment-resistant clones. Patients with responding disease who undergo complete cytoreduction have the best outcomes; 2-year OS and PFS are 90–100% and 60–70%, respectively [80–82]. Median survival times exceeding 8 years have been reported, even in patients with liver and peritoneal metastases [83].

Selected patients with limited progression, gastric GISTs, smaller tumor size and number,

Table 1 Approved and unapproved TKIs for metastatic GISTs and associated outcomes

Drug	Targets	Trial phase and setting	Response	PFS/TTP	OS
Imatinib [15–18]	BCR-Abl, KIT, PDGFRs	Phase III; first-line	ORR 45–55% SD 20–30%	18–24 months	50–60 months 5-year OS 55% ^a
Sunitinib [27, 28]	KIT, PDGFR, VEGFR, FLT3, CSF-1R, RET	Phase II/III; second-line	ORR 7–13% SD 40–58%	3.9–4.9 months	15.3 months
Regorafenib [31, 32]	KIT, VEGFR, FGFR1, PDGFRA, TIE-2, RET, BRAF, MAPK	Phase II/III; third-line	ORR 4.5–12% SD 66–71%	4.8–10 months	1-year OS ~70%
Nilotinib [34–37]	BCR-Abl, KIT, DDR, PDGFR, CSF-1R	Phase III; first-line Phase II/III; third-line	ORR: 42% ORR ≤ 10% SD 37–66%	25.9 months 3–4 months	2-year OS 82% 8.5–11.8 months
Sorafenib [38–41]	VEGFR, PDGFR, KIT, RAF, MAPK	Phase II, retrospective; second- or third-line	ORR 10–24% SD 16–57%	4.9–7.2 months	9.7–15.2 months
Masitinib [43, 44]	KIT, PDGFR, LYN, FGFR3	Phase II; first-line Phase II; second-line		41.3 months 3.7 months	5-year OS 61.5% 29.8 months
Vatalinib [45, 46]	KIT, PDGFR, VEGFR	Phase II; second-line Phase II; third-line	ORR 8–13% SD 38.5–53% ORR 0% SD 32%	5.8–8.5 months 3.2 months	
Dasatinib [47, 48]	BCR-Abl, KIT, PDGFR, SRC family kinases	Phase II; first-line Phase II; third-line	ORR 74% (FDG-PET) ORR 32% (Choi)	13.6 months 2 months	4-year OS 74% 19 months
Linsitinib [49]	IGF-1R	Phase II; first-line	ORR/SD 35% (PET)	9-month PFS 52%	9-month OS 80%
Dovitinib [51]	VEGFR, FGFRs, KIT, PDGFR-beta, FLT3	Phase II; third-line	ORR 13% (FDG-PET) SD 50% (FDG-PET)	3.6 months	9.7 months

Table 1 continued

Drug	Targets	Trial phase and setting	Response	PFS/TTP	OS
Ponatinib [53]	BCR-Abl, KIT	Phase II; TKI refractory	CBR 55%, ORR 8% (exon 11 MT)	7 months, 6-month PFS	6-month OS 80%
			CBR 22%, ORR 0% (no exon 11 MT)	60% 4 months, 6-month PFS	6-month OS 71%
Pazopanib [54–56]	KIT, VEGFR, PDGFR		ORR 0%, SD 84%	4-month PFS 48%	
Binimetinib + imatinib [58]	MEK1-2 inhibitor	Phase 1b + imatinib; second- or third-line	ORR 41% (Choi) CBR 65%	8 weeks	
Everolimus + imatinib [61–63]	mTOR	Phase II; second-line, third-line	SD 30–40%	1.9 months 3.5 months 10.7 months	14.9 months 10.7 months
Perifosine + imatinib [64]	Akt	Phase II; second-line	CBR of 36%	2.2 months	18.3 months
Retaspimycin [68]	HSP90	Phase I; TKI refractory	ORR 38% (FDG-PET)	10.6 weeks	12 weeks

CBR clinical benefit rate, *FDG-PET* Fludeoxyglucose-positron emission tomography, *GIST* gastrointestinal stromal tumor, *MT* mutation, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *SD* stable disease, *TKI* tyrosine kinase inhibitors, *TTP* time to progression

^a In patients who responded to imatinib not overall population

and completely cytoreducible disease may also benefit from surgery [84]. Those with generalized disease do not benefit from cytoreduction [82, 83]. Imatinib should be resumed post-operatively to reduce the risk of recurrence or progression.

Radiotherapy (RT)

Though long considered radioresistant, GIST metastases can be effectively palliated by RT [85–87]. In a prospective study of 25 patients with TKI-refractory GIST, 80% had stability of target lesions lasting a median of 16 months and median OS was 19 months [87]. Median TTP of target lesions was significantly longer in patients who did not continue TKIs during RT than in those who did (23 vs 11 months, $p = 0.014$). One patient developed grade 4 biliary tract necrosis while taking sorafenib during RT.

Hepatic Artery Embolization (HAE)

HAE involves the selective catheterization and delivery of microspheres through a tumor-feeding artery, inducing ischemia and apoptosis. Transarterial chemoembolization (TACE) is HAE performed with chemotherapy. Response rates using modified RECIST guidelines, which only measure arterially enhancing disease instead of the entire tumor diameter, are 45–54% [88, 89]. Median liver PFS and OS times range from 3.4 to 8.2 months and 9.7–23.8 months, respectively. The absence of extrahepatic metastases, multiple versus single embolizations, fewer liver metastases, and disease control following embolizations are independently associated with improved survival on multivariate analyses [88, 90, 91].

The main side effect of HAE/TACE is post-embolization syndrome consisting of

abdominal pain, fatigue, fever, nausea and vomiting. Moderate to severe complications including liver failure, abscess, respiratory failure, pulmonary embolism, cholecystitis and hemorrhage occur in 5–14% of patients [88, 90, 91]. When used, the authors recommend bland HAE rather than TACE given the lack of sensitivity to standard chemotherapy agents, even at very high concentrations.

Radiofrequency Ablation (RFA)

RFA induces coagulative necrosis of tumors using thermal energy.

In small retrospective series, complete ablation was achieved in >90% of treated tumors, and 3- and 5-year local tumor progression rates were 0% and 12.5%, respectively [92–94]. As with cytoreductive surgery, patients who undergo RFA for residual disease after maximal response to imatinib experienced the best outcomes [92].

Radioembolization

Radioembolization with yttrium-90 selectively delivers high dose radiation to target lesions while sparing the normal hepatic parenchyma. In a small retrospective series of nine evaluable patients with progressive GIST on ≥ 2 prior TKIs, 33% had a complete response, 56% had a partial response and 11% had stable disease [95]. Median hepatic PFS was 16 months and OS was nearly 30 months. Toxicities primarily consisted of increased liver enzymes which were mostly grade 1, although one patient developed a chronic gastric ulcer and required surgery.

Outcomes associated with various locoregional therapies are summarized in Table 2.

Table 2 Locoregional therapies for GIST metastases

Therapy	Response rates	PFS/TTP	OS
Surgery [63–67]	–	2-year PFS 60–70% ^a 1-year PFS 70% ^b 7.7 months ^b 3 months ^c	2-year OS 90–100% ^a 2-year OS 75% ^b 29.8 months ^b 5.6 months ^c
HAE/TACE [71–74]	ORR 8–54.5% (RECIST 1.1) 45–54% (mRECIST)	3.4–8.2 months	9.7–23.8 months
RFA [75–77]	Complete ablation 92–100%	2-year PFS 29% ^d 2-year PFS 75% ^c	–
External beam radiation [70]	ORR 8%, SD 80%	16 months (treated lesions)	19 months
Radioembolization [78]	ORR 89%, SD 11%	16 months	29.8 months

GIST gastrointestinal stromal tumor, *HAE* hepatic artery embolization, *mRECIST* modified RECIST, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *RFA* radiofrequency ablation, *SD* standard deviation, *TACE* transarterial chemoembolization, *TKI* tyrosine kinase inhibitor, *TTP* time to progression

^a No progression, ^b limited disease progression, ^c generalized disease progression, ^d TKI not resumed after RFA, ^e TKI resumed after RFA

FUTURE DIRECTIONS AND CONCLUSIONS

Patients with metastatic GIST have more treatment options than ever before. Since the introduction of imatinib in 2001, a panoply of newer generation TKIs and agents targeting intracellular signaling cascades, stress response mediators, epigenetic modifiers, and the immune system have entered the picture. In addition, the judicious use of locoregional therapies can extend the benefit of TKIs that are otherwise working for the bulk of disease in a given patient. Growing knowledge of the molecular pathophysiology of GISTs guides the rational design of combination strategies and later-line therapies based on known mechanisms of resistance.

Areas of future research include the ongoing assessment of therapeutic targets beyond the current spectrum of receptor tyrosine kinases and the development of agents to improve the

outcomes of molecular subpopulations. The identification of biomarkers beyond *KIT* and *PDGFRA* mutations to facilitate patient selection and improve the cost-effectiveness of treatment is another priority. Prospective studies are also needed to delineate the optimal timing and use of locoregional strategies, and to ascertain their impact on outcomes in different disease contexts.

In summary, the outcomes of patients with metastatic GIST are optimized through a contemporary framework that combines systemic and locoregional therapies, established standards of care, and investigational approaches.

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