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LEADING ARTICLE

Emerging Agents for the Treatment of Advanced, Imatinib-Resistant Gastrointestinal Stromal Tumors: Current Status and Future Directions

Sebastian Bauer[1,2] · **Heikki Joensuu**[3]

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Abstract Imatinib is strongly positioned as the recommended first-line agent for most patients with advanced gastrointestinal stromal tumor (GIST) due to its good efficacy and tolerability. Imatinib-resistant advanced GIST continues to pose a therapeutic challenge, likely due to the frequent presence of multiple mutations that confer drug resistance. Sunitinib and regorafenib are approved as second- and third-line agents, respectively, for patients whose GIST does not respond to imatinib or who do not tolerate imatinib, and their use is supported by large randomized trials. ATP-mimetic tyrosine kinase inhibitors provide clinical benefit even in heavily pretreated GIST suggesting that oncogenic dependency on KIT frequently persists. Several potentially useful tyrosine kinase inhibitors with distinct inhibitory profiles against both KIT ATP-binding domain and activation loop mutations have not yet been fully evaluated. Agents that have been found promising in preclinical models and early clinical trials include small molecule KIT and PDGFRA mutation-specific inhibitors, heat shock protein inhibitors, histone deacetylase inhibitors, allosteric KIT inhibitors, KIT and PDGFRA signaling pathway inhibitors, and immunological approaches including antibody-drug conjugates. Concomitant or sequential administration of tyrosine kinase inhibitors with KIT signaling pathway inhibitors require further evaluation, as well as rotation of tyrosine kinase inhibitors as a means to suppress drug-resistant cell clones.

Key Points

Mutated KIT kinases that confer drug resistance emerge frequently in patients with advanced GIST treated with imatinib.

Besides ATP-mimetic tyrosine kinase inhibitors many other agents with a different mechanism of action are efficacious in the treatment of patients with advanced GIST.

Concomitant or sequential administration of agents with different mechanisms of action may become a novel approach to treat advanced GIST.

1 Introduction

Gastrointestinal stromal tumor (GIST) is one of the most common types of sarcoma [1]. Small (<1 cm) GISTs ("micro-GISTs") are highly prevalent (~20 %) in the general population aged over 50 years [2, 3], but these lesions have little or no malignant potential. Excluding micro-GISTs, the annual incidence of GIST is about 1/100,000. Approximately 40 % of patients will eventually have metastases after macroscopically complete surgery [4]. The median overall survival for patients with

✉ Heikki Joensuu
heikki.joensuu@hus.fi

[1] Sarcoma Center, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany

[2] German Cancer Consortium (DKTK), 69120 Heidelberg, Germany

[3] Department of Oncology, Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, 00029 Helsinki, Finland

metastatic GIST was 12–18 months before the introduction of imatinib [5].

Approximately 90 % of metastatic GISTs harbor an activating mutation in the genes that encode KIT or platelet-derived growth factor-α (PDGFRA) receptor tyrosine kinases [6, 7]. Mutations are usually located in *KIT* exon 11 (~70 %), *KIT* exon 9 (~10 %), or *PDGFRA* exons 12 or 18 (~10 %). Mutations in other exons are infrequent in patients who have not been treated with tyrosine kinase inhibitors (TKIs) [8], and 5–10 % of GISTs do not harbor *KIT* or *PDGFRA* mutation (frequently referred to as "wild-type GISTs").

Conventional chemotherapy agents have little activity against GIST. During the past 15 years TKIs have transformed the treatment landscape in an unprecedented way. Several TKIs yield durable responses in patients with advanced GIST, and adjuvant imatinib improves recurrence-free survival [9, 10] and likely overall survival [10] when administered to GIST patients after surgery. Although the treatment of GIST with TKIs is one of the most compelling success stories in the recent history of medicine, a major challenge is the eventual emergence of drug resistance in advanced GIST. We review here the experimental agents studied to treat imatinib-resistant advanced GIST.

2 Approved Agents

2.1 Imatinib

Imatinib has been considered the standard first-line agent since its approval in 2002. It is an inhibitor of a few kinases including KIT, PDGFRA, ABL, Fms-like tyrosine kinase-3 (FLT3), and colony stimulating factor-1 receptor (CSF1R), and yields durable responses or stabilized disease (SD) in approximately 85 % of the patients [11, 12].

Two randomized phase III trials that compared an imatinib daily dose of 400 to 800 mg identified the 400-mg dose as the standard dose for patients with a *KIT* exon 11 mutation [13, 14]. In a retrospective subgroup analysis, patients with a *KIT* exon 9 mutation had longer progression-free survival (PFS) on the 800-mg dose as compared with the 400-mg dose [15]. *PDGFRA* substitution mutations at codon D842 (usually D842V) lead to imatinib-resistant mutant kinases [16]. Mutational testing for *KIT* and *PDGFRA* is therefore considered mandatory in the treatment planning [17].

Most patients with advanced GIST are not cured with imatinib. The median PFS is 2–3 years [18], but a minority remain progression-free for ≥10 years after starting imatinib [19]. Patients are treated with continuous imatinib as discontinuation in responding patients is usually associated with rapid progression [20]. In one trial patients whose GIST had progressed on at least imatinib and sunitinib were randomly assigned to either imatinib re-challenge or placebo. The median PFS was 1.8 months on imatinib and 0.9 months on placebo [21]. Despite survival not improving, these findings suggest a modest benefit from imatinib, even as "last-line" therapy.

2.2 Sunitinib

Like imatinib, sunitinib binds to the ATP-binding pocket of the KIT and PDGFRA kinases. Sunitinib has different binding characteristics from imatinib and it also efficiently inhibits the vascular endothelial growth factor receptor (VEGFR) and RET tyrosine kinases.

Sunitinib was approved in 2006 for patients whose GIST has progressed on imatinib or who do not tolerate imatinib based on the results of a placebo-controlled trial [22]. In this study with 312 patients sunitinib was administered at a dose of 50 mg/day for 4 weeks followed by a break of 2 weeks before the next cycle. The median PFS was 6.3 and 1.5 months in the sunitinib and placebo groups, respectively [hazard ratio (HR) 0.33, $p < 0.0001$), the partial response (PR) rates were 7 and 0 %, and the rates of stabilized disease (SD) 58 and 48 %. Cross-over to the sunitinib group was allowed, but despite this, overall survival was superior in the sunitinib group. The most frequent adverse effects were anemia, neutropenia, fatigue, diarrhea, skin discoloration, nausea, and anorexia. Sunitinib treatment is also frequently associated with hand-foot syndrome and occasionally hypothyreosis [23]. Administration at a continuous daily dose of 37.5 mg is considered an alternative dosing schedule [24]. Despite these convincing results, the clinical benefits of second-line sunitinib remain moderate as compared with the substantial benefits obtained with imatinib in a first-line setting.

2.3 Regorafenib

Regorafenib is an oral TKI that inhibits multiple kinases involved in oncogenesis (KIT, PDGFRA, RET, RAF1, BRAF), angiogenesis (VEGFR1-3, TIE2), and the tumor microenvironment (fibroblast growth factor receptor, FGFR). Regorafenib was approved in 2013 for the treatment of GIST patients who no longer respond to imatinib and sunitinib based on a placebo-controlled, randomized phase III trial (GRID) [25]. In GRID, 199 such patients were allocated to regorafenib 160 mg/day or matching placebo (3 weeks on/1 week off) until disease progression. The median PFS was 4.8 months on regorafenib and 0.9 months on placebo (HR 0.27, $p < 0.0001$). Six (4.5 %) and one (1.5 %) of the patients assigned to regorafenib and

placebo had PR, respectively, and 71.4 and 33.3 % had SD. Drug-related grade 3 adverse events were frequent in the regorafenib group as compared to placebo (58 vs. 8 %), with hand-foot skin reaction, hypertension, and diarrhea being most often recorded.

Sunitinib and regorafenib have a less favorable side effect profile compared to imatinib, which is likely associated with their broader kinase inhibition spectrum. Hand-foot syndrome tends to occur earlier with regorafenib than with sunitinib and is generally more severe. Regorafenib has significant liver toxicity, and liver function tests are recommended before initiation of regorafenib and at least every 2 weeks during the first 2 months on therapy [26]. The benefit of VEGFR inhibition remains undefined in GIST.

3 Imatinib Resistance

Secondary *KIT* mutations are the dominant mechanism for imatinib resistance [27, 28]. They occur frequently either in the kinase ATP-binding domain (encoded by exons 13 and 14) or in the activation loop (a-loop, encoded by exon 17), and typically affect the key amino acids that interact with imatinib binding to the kinase. Mutations in the a-loop shift the equilibrium towards the active kinase conformation, while imatinib and sunitinib bind to the inactive conformation [29].

In a mutagenesis screen of cells driven by mutant KIT proteins, sunitinib effectively suppressed cells with *KIT* exon 13 (V654A) or exon 14 resistance mutations (T670I), but not exon 17 mutant kinases [30]. These results are compatible with findings from a clinical trial in which sunitinib had substantial activity against GISTs with secondary *KIT* exon 13 mutations [31]. In contrast, regorafenib shows higher potency for *KIT* exon 17 mutations, but is less potent for the ATP-binding domain affecting mutations. Imatinib-resistant disease frequently harbors several resistance mutations, sometimes even within a single metastasis [28, 32, 33].

The rare alternative mechanisms that may cause imatinib resistance include *KIT* amplification and loss of tumor KIT expression [27]. Alternative signaling pathways may supplant KIT as the oncogenic driver, but have not been confirmed in patients. Notably, dysregulation of the phosphatidylinositide 3-kinases (PI3K)/AKT pathway by *PI3K*-mutations or aberrations that cause loss of the phosphatase and tensin homolog (PTEN) function, or mutations of *BRAF*, *KRAS*, or *HRAS* that activate the RAS/RAF/MEK pathway, have been detected in single cases, but their overall role in drug resistance is unclear [34, 35].

4 Investigational Agents

Many investigational agents are potent KIT and PDGFRA inhibitors, and therefore potentially active against GIST.

4.1 ATP Mimetics

ATP mimetics are orally administered small molecule agents that bind to the target kinase ATP-binding pocket and compete with ATP for binding (Table 1).

4.1.1 Nilotinib

Nilotinib has been evaluated in randomized trials [36, 37] and cohort studies [38, 39]. In a randomized study carried out in a first-line setting, 644 patients who had received no systemic antineoplastic therapy or who had GIST recurrence $\geq$6 months after discontinuing adjuvant imatinib received either nilotinib 400 mg twice daily or imatinib 400 mg once daily [37]. Accrual was stopped early after crossing the futility boundary, and both PFS and overall survival significantly favored imatinib. Somewhat unexpectedly, patients treated with imatinib had better PFS in the subgroup with *KIT* exon 9 mutation, but not among patients with exon 11 mutation.

Nilotinib was compared to best supportive care (BSC) or with the physician's choice in a randomized trial with 248 patients who had progressed on imatinib and sunitinib [36]. Most control group patients received either imatinib or sunitinib in addition to BSC. No PFS difference emerged at a blinded central radiology review between the groups.

The development of nilotinib in the treatment of GIST was halted based on these results, but since nilotinib is well tolerated, it could have a niche in the treatment of patients who do not tolerate imatinib and whose GIST harbors *KIT* exon 11 mutation.

4.1.2 Masitinib

Masitinib is approved for the treatment of mastocytosis in dogs. In a phase II trial where 30 imatinib-naïve patients received masitinib 7.5 mg/kg/day, one patient had complete response (CR), 15 had PR, 13 SD, and one disease progression as the best response, and the median PFS was 41.3 months [40]. These efficacy results resemble those obtained with imatinib. The most frequent grade 3/4 toxicities were skin rash (10 %) and neutropenia (7 %).

In a small randomized, open-label trial 23 patients who had progressed on imatinib were assigned to 12 mg/kg/day of masitinib and 21 comparable patients to sunitinib [41]. The median PFS was relatively short in the masitinib group (3.7 months), but overall survival favored masitinib to

Table 1 Experimental agents studied in advanced gastrointestinal stromal tumors (GIST)

Drug	Key molecular targets	Manufacturer	Setting tested	Phase	Common dose	Frequent adverse effects
Nilotinib (Tasigna®)	KIT, PDGFRs, BCR-ABL	Novartis	First line, third line	III	400 mg bid	Nausea/vomiting, fatigue, skin rash
Masitinib (Masivet®)	KIT, PDGFR, FGFR3, Lyn, FAK	AB science	First line, second line	II, III, ongoing	First line, 7.5 mg/kg; second line, 125 mg/kg	Mild asthenia, diarrhea, nausea, edema, muscle spasms, rash, neutropenia
Sorafenib (Nexavar®)	KIT, VEGFRs, PDGFR, RAF	Bayer	≥Third line	Retro-spective cohorts	400 mg bid	Rash, hand-foot syndrome, diarrhea, hypertension
Dovitinib	KIT, PDGFR, VEGFR 1-3, FGFRs 1-3, FLT3	Novartis	Second line, third line	II	500 mg od (5 days on/2 days off)	Hypertension, fatigue, vomiting, asthenia, neutropenia, thrombocytopenia, hypertriglyceridemia
Pazopanib (Votrient®)	KIT, PDGFRα, VEGFR 1-3	GlaxoSmithKline	Second line, third line, >third line	II	800 mg od	Diarrhea, fatigue, elevated serum liver enzyme levels, mild hand-foot-syndrome.
Ponatinib (Iclusig®)	BCR-ABL, KIT (including exon 17 mutants)	Ariad	Third line, second line	II	45 mg od	Rash, fatigue, myalgia, dry skin, headache, abdominal pain, constipation, arterial thrombosis
Cabozantinib (Cometriq®)	RET, MET, VEGFR 1-3, KIT, TRKβ, FLT-3, AXL, TIE-2	Exelixis	Second line	II	140 mg od	Fatigue, diarrhea, nausea, weight loss, hypertension, hand-foot syndrome, taste alterations
Vandetanib (Caprelsa®)	VEGFRs, EGFR, RET	Novartis	Any line, ongoing	II	300 mg od	Diarrhea, hypertension, acne, asthenia, QTc prolongation, rash
Famitinib	KIT, PDGFRs, VEGFR 2 and 3, RET FLT1, FLT3	Jiangsu Hengrui Medicine	Second line	II	25 mg od	Hypertension, hand-foot syndrome, mucositis, fatigue, neuropathy
Vatalanib	KIT, VEGFR, PDGFR	Bayer Schering, Novartis	Second line	II	1250 mg od	Dizziness, nausea, hypertension
Dasatinib (Sprycel®)	KIT, PDGFRs, BCR-ABL, SRC	Bristol-Myers Squibb	First line ≥ third line	II	100 mg od	Fluid retention, pleural effusion, diarrhea
BLU285	KIT D816V, PDGFR D842 -mutants	Blueprint Medicines	–		NA	NA
Crenolanib	PDGFRA (including D842), FLT3	AROG	All lines	II	NA	Nausea, vomiting, serum liver transaminase level elevation
Ganetespib (STA-9090)	HSP90	Synta	≥First line	II	200 mg/m^2 iv weekly (3 weeks on, 1 week off)	Diarrhea, fatigue, nausea, vomiting, increased alkaline phosphatase, headache, insomnia, abdominal pain
BIIB021	HSP90	Biogen Idec	Third line	II	600 mg po twice weekly, or 400 mg thrice weekly	Dizziness, syncope, elevation of alkaline phosphatase

Table 1 continued

Drug	Key molecular targets	Manufacturer	Setting tested	Phase	Common dose	Frequent adverse effects
AT13387	HSP90	Astex	≥First line	II	N.A.	Diarrhea, nausea, vomiting, fatigue
AUY922	HSP90	Novartis	≥Third line	II	70 mg/m^2 iv weekly	Diarrhea, nausea, fatigue, night blindness
Panopinostat	Histone deacetylase inhibitor	Novartis	≥Third line	I	20 mg orally thrice weekly during 3 out of 4 weeks in combination with imatinib 400 mg od	Thrombocytopenia, anemia, fatigue, creatinine elevation, nausea, diarrhea
Binimetinib/ MEK162 plus imatinib	MEK	Novartis	First line	Ib/II	Escalating doses of MEK162, imatinib 400 mg/d	NA
BYL719 plus imatinib	PI3K	Novartis	Third line	Ib/II	Escalating doses of BYL719, imatinib 400 mg/d	NA
LOP628	KIT antibody conjugated with maytansine	Novartis	KIT-positive solid tumors	I	NA	NA
Dasatinib plus ipilimumab	KIT/Src-inhibitor plus an anti-CTL4 antibody	BMS	All lines	I	Dasatinib 70 mg od, ipilimumab 10 mg/kg 3-weekly x4 iv, then 12-weekly	GI-hemorrhage (DLT), ALT-elevation, fatigue, nausea, pleural effusion
Palbociclib (PD-0332991)	CDK4/6	Pfizer	Third line	II	125 mg od (3 weeks on, 1 week off)	NA
BGJ398 plus imatinib	FGFRs	Novartis	First line	I/II	Escalating doses of BGJ (3 weeks on/1 week off) plus imatinib 400 mg/d	NA
BBI503	Unknown (cancer stem cell inhibitor)	Boston Biomedical	>Third line	II	300 mg od	NA

BCR-ABL break point cluster region-Abelson, *bid.* twice daily, *CDK* cyclin-dependent kinase, *EGFR* epidermal growth factor receptor, *FAK* focal adhesion kinase, *FGFR* fibroblast growth factor receptor, *FLT1* Fms-like tyrosine kinase 1, *FLT3* Fms-like tyrosine kinase 3, *HSP90* heat-shock protein 90, iv intravenously, *Lyn* Lck/Yes novel tyrosine kinase, *NA* not available, *od* once daily, *PI3K* phosphoinositide 3-kinase, *PDGFR* platelet-derived growth factor, *po* orally, *TRKB* tropomyosin receptor kinase B, *VEGFR* vascular endothelial growth factor receptor

sunitinib after allowing post-progression administration of sunitinib in the masitinib group. Masitinib was better tolerated. These results warrant confirmation in the ongoing phase III trials (NCT00812240 and NCT01694277).

4.1.3 Sorafenib

Sorafenib resembles regorafenib in structure and in the kinome inhibition spectrum. Sorafenib is approved for the treatment for unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and differentiated thyroid cancer. In vitro, sorafenib inhibits imatinib-resistant kinases with mutations in the KIT ATP-binding pocket and in the activation loop, with the exception of kinases resulting from substitutions at *KIT* codon D816 or *PDGFRA* codon 842 [42].

In a retrospective cohort study with 117 evaluable patients whose GIST had progressed on imatinib and sunitinib, and who were treated with sorafenib 400 mg twice daily, 12 (10 %) patients responded and 70 (60 %) had SD. The median PFS was 6.4 months [43]. Sorafenib was moderately well tolerated, with skin rash, hand-foot syndrome, and diarrhea being the most frequent adverse effects.

In another retrospective study, six (19 %) patients responded and 14 (44 %) had SD in a cohort of 32 patients whose GIST had progressed on imatinib, sunitinib, and nilotinib [44]. These and further data [45] suggest that the efficacy of sorafenib might be comparable to that of regorafenib in the treatment GIST resistant to imatinib and sunitinib.

4.1.4 Dovitinib

The Korean GIST group conducted a study that evaluated dovitinib among 30 patients whose disease had progressed at least on imatinib and sunitinib, and found a disease control rate of 13 % at 24 weeks after treatment initiation and a median PFS of 3.6 months [46].

In another study in 38 patients who had progressed on imatinib or who were intolerant to imatinib, two (5 %) patients had PR with dovitinib and 16 (42 %) SD. The median PFS was 4.6 months [47]. The most frequent grade 3 side effects were hypertension (18 %), fatigue (12 %), vomiting (10 %), and elevated blood triglyceride and γ-glutamyltransferase levels. Dovitinib may not be superior to sunitinib or regorafenib, but careful data evaluation might identify subgroups of patients who benefit from dovitinib.

4.1.5 Pazopanib

Pazopanib is approved for the treatment of renal cell cancer and soft tissue sarcomas. The IC_{50} value for inhibition of wild-type KIT was 74 nM in in vitro kinase assays [48], but little is known about its activity on KIT drug resistance mutations.

In a phase II study 12 (48 %) out of the 25 patients whose GIST had progressed on at least imatinib and sunitinib had SD and the median PFS was 1.9 months [49].

The randomized phase II PAZOGIST trial compared pazopanib plus BSC with BSC alone among 81 patients whose GIST was resistant to imatinib and sunitinib, or who did not tolerate these agents [50]. The 4-month PFS rate favored pazopanib plus BSC over BSC alone (45 vs. 18 %, respectively; $p = 0.03$). Of the 76 patients who were treated with pazopanib (including 36 patients who crossed over from BSC to pazopanib after progression), 72 % had ≥grade 3 adverse events (37 % had hypertension). These data do not suggest a higher activity as compared with regorafenib, but the toxicity profile of pazopanib could be more favorable.

4.1.6 Ponatinib

Ponatinib is highly active in heavily pre-treated patients for Philadelphia-positive leukemia, and exhibits a pan-BCR-ABL inhibitory profile in vitro with no single mutation conferring ponatinib resistance [51]. Ponatinib is one of the few ATP-competitive KIT-inhibitors that has been tested against a large panel of mutant KIT variants [30]. In a mutagenesis screen 40 nmol/L of ponatinib suppressed the growth of all *KIT* secondary mutants except V654A, which was suppressed at 80 nmol/L. Ponatinib shows high activity against *KIT* exon 17 mutants, and unlike the approved KIT inhibitors, it is active against the *KIT* exon 17 D816 mutant kinases [30].

The preliminary results from a non-randomized phase II trial that evaluated ponatinib at a dose of 45 mg/day in heavily treated GIST patients (74 % had ≥4 prior agents) the clinical benefit rate (CR, PR, or SD ≥16 weeks) was 55 % in patients with primary *KIT* exon 11 mutation, but responses were also observed with the 30-mg dose [30, 52]. The most common side effects were skin rash (54 %), fatigue (46 %), myalgia (46 %), dry skin (40 %), and headache (40 %). Ponatinib is only infrequently associated with hand-foot syndrome or mucositis. No serious thromboembolic events were observed during the short follow-up, but 11.8 % of the patients with BCR–ABL-driven leukemia had serious arterial thrombotic events that accumulated over a period of 24 months.

The risk of thromboembolic events may be dose-dependent, and the ponatinib blood maximum concentrations with the 15 mg/day dose and the trough concentrations with the 30 mg/day dose exceeded the 40 nM/L concentration that is required to suppress most imatinib-resistant KIT clones [53]. A phase II trial (POETIG) will evaluate ponatinib at a dose of 30 mg/day in patients whose GIST is resistant to imatinib.

4.1.7 Other Tyrosine Kinase Inhibitors

In a phase I study evaluating cabozantinib, four pretreated Japanese patients had SD lasting for 6–20 months [54]. The CABO-GIST study (NCT02216578) aims to evaluate cabozantinib in a larger patient cohort.

Vandetanib is approved for the treatment medullary thyroid cancer [55]. It is being investigated in a phase II trial in pediatric and adult patients with GIST who lack *KIT* and *PDGFRA* mutations (NCT02015065).

Famitinib induced PR in one of the two patients with treatment-naïve GIST included in a phase I study [56], and is being investigated as second-line treatment of advanced GIST (NCT02336724). Side effects included hypertension, hand-foot syndrome, mucositis, fatigue, and neuropathy.

In a phase II trial with 45 patients whose GIST was resistant to imatinib or to both imatinib and sunitinib, two (4 %) patients treated with vatalanib had confirmed PR and further 16 (36 %) had SD lasting for ≥6 months (median 12.5 months) [57]. Vatalanib was well tolerated, with hypertension (29 %), nausea (29 %), and dizziness (24 %) being the most common side effects (usually grade 1 or 2). Vatalanib is not being tested further in clinical trials.

Dasatinib is a potent inhibitor of BCR-ABL and the SRC-family kinases, and it also inhibits KIT and the PDGFRs [58]. Dasatinib is approved for the treatment of chronic myeloid leukemia. In a phase II study where TKI-naïve GIST patients were treated with dasatinib 70 mg twice daily, 31 (74 %) of the 42 eligible patients had metabolic response in fluorodeoxyglucose (FDG)-PET performed 4 weeks after dasatinib initiation [59]. The median PFS of 13.6 months achieved appears short in this setting. Adverse effects were most frequently gastrointestinal or pulmonary (grade 3, 48 %; grade 4, 5 %). Similarly, in another series where all patients had imatinib-resistant GIST and most also sunitinib-resistant disease, the median PFS was only 2.0 months [60].

4.1.8 Mutation-Specific Inhibitor

BLU285 is a mutation-specific inhibitor of *KIT* D816V and *PDGFRA* D842V mutated kinases that are resistant to most TKIs. Preclinical data suggest a favorable toxicity profile, but clinical trials are pending [61]. BLU285 has a very narrow inhibition profile, and might therefore become a candidate for combination trials.

4.1.9 PDGFRA-Targeted Agents

Crenolanib is an oral small-molecule inhibitor of FLT3 and the PDGFRs (including D842V-mutated kinase) [62]. Metastatic PDGFRA-mutant GIST is exceedingly rare, and in a phase II trial with seven patients, one had an objective response and three had SD [63]. In a trial that accrued leukemia patients, the most common side effects were fatigue, nausea, and vomiting [64]. A clinical trial investigating olaratumab, an anti-PDGFRA antibody, was terminated prematurely due to lack of efficacy.

4.2 Other Targeted Agents

4.2.1 Heat Shock Protein 90 (HSP90) Inhibitors

HSP90 chaperone protein stabilizes and enhances conformational maturation of many proteins [65] including KIT and PDGFRA. As ATP hydrolysis is required, HSP90 becomes pharmacologically targetable [66]. HSP90 inhibition eventually results in proteasomal degradation of the client proteins. One of the first HSP90-inhibitors, the geldanamycin analogue 17-AAG, inhibited KIT regardless of the type of imatinib-resistance mutation [67]. The HSP90 co-chaperone cdc37 ranked the highest in a genome-wide functional screen on two KIT-mutant cell lines, suggesting that the chaperones are relevant in maintaining KIT signaling [68].

Retaspimycin (IPI-504), a 17-AAG derivative, had promising efficacy in a phase I trial [69], but a subsequent randomized phase III trial performed in a third-line setting was terminated early due to higher mortality in the retaspimycin group.

Ganetespib was generally well tolerated in a cohort of 23 GIST patients, but no responses were obtained and the 12 (52 %) SDs achieved were usually short [70]. BIIB021 was also well tolerated, but had limited clinical activity [71].

AT13387 showed promising preclinical activity in GIST [72], and seven GIST patients were treated in the first-in-human phase I trial. One patient had PR lasting for 10 months, and three had SD for up to 8 months [73]. This prompted initiation of a phase II trial in GIST (NCT01294202), but the results are pending. Similarly, a small molecule inhibitor, AUY922, had activity in preclinical GIST models, but the results from a phase II trial conducted in a patient population with imatinib- and sunitinib-resistant GIST are not yet available (NCT01404650).

4.2.2 Histone Deacetylase Inhibitors (HDACIs)

Acetylation of the lysine residues of the core histone proteins leads to a relaxed chromatin structure enabling transcription [74]. HDACIs have selectivity for cell cycle inhibitory genes [75]. In addition, many non-histone proteins important for oncogenesis are targets for acetylation and deacetylation (e.g. p53) [76].

HDACI treatment results in transcriptional downregulation and proteasomal degradation of KIT, and additive

effects are found in combination with imatinib both in vitro and in vivo [77, 78]. This prompted a phase I trial with panobinostat, a third-generation pan-HDACI, in combination with imatinib 400 mg/day in a heavily pretreated GIST patient population. The maximum tolerated dose in the combination was 20 mg panobinostat given orally three times weekly during three out of every four weeks, which was only moderately well tolerated with substantial hematological toxicity (thrombocytopenia) [79]. One out of the 11 evaluable patients showed metabolic PR, seven were metabolically stable for ≥3 weeks, and three progressed. The longest treatment duration was 17 weeks. The panobinostat administration schedule may need further refinement, and other combinations warrant evaluation.

4.2.3 Allosteric KIT Inhibitors

In addition to the ATP-binding pocket KIT has another pocket, an interior pocket located between the N- and C-lobes of the kinase. There are two pendant ligands that compete for occupancy of this "switch pocket" [80, 81]. Mutation or deletion of the inhibitory switch ligand renders KIT constitutively active. Novel KIT inhibitors that target the switch pocket were recently developed (DP-2976, DP-3636, and DP-4444). They are highly potent against several imatinib and sunitinib-resistant GIST cell lines [80, 82]. It is unclear whether these compounds are candidates for clinical trials, but the rationale for their use is strong. While the ATP-binding pockets are highly conserved throughout the kinome, the allosteric sites have greater structural diversity, and compounds targeting these sites may inhibit kinase activity with a high selectivity [80].

4.3 Inhibition of Signaling Pathways

The oncogenic KIT signaling is mainly relayed via the PI3K/mammalian target of rapamycin (mTOR) and the RAS/RAF/MEK/MAPK pathways in GISTs with or without secondary resistance mutations, and inhibition of both PI3K and MEK results in strong proapoptotic and antiproliferative effects in vitro and in vivo [83–85]. Besides KIT, molecular aberrations in other key proteins may activate these pathways, such as aberrations in PTEN, PI3K, RAF, RAS, or NF1 [35, 86–88].

The combination of everolimus, an mTOR inhibitor, and imatinib was one of the first combinations of targeted agents studied in GIST [89]. When patients refractory to imatinib or to imatinib and sunitinib were treated with everolimus and imatinib 600–800 mg/day, the combination was well tolerated, with diarrhea, nausea, fatigue, and anemia as the most common adverse events. The progression-free rate was 37 % 4 months after treatment initiation and one patient had PR, but the median PFS of 3.5 months achieved was relatively short. No follow-up trial was initiated, but this combination might qualify for testing with a PI3K inhibitor in imatinib-resistant disease.

Ongoing trials are investigating the combination of imatinib plus a MEK inhibitor (MEK162/binimetinib) as first-line treatment (NCT01991379), and imatinib plus a PI3K inhibitor (BYL719) as third-line treatment (NCT01735968). In a phase Ib/II trial in a heavily pretreated patient population, nine out of the 15 evaluable patients treated with binimetinib plus imatinib had stable disease at 8 weeks on treatment, and five (33 %) had a partial response according to the Choi criteria [90].

4.4 Immunological Approaches

LOP628 is a conjugate consisting of an anti-KIT humanized IgG1/κ antibody linked with a maytansine payload. As this approach is based on KIT expression and not on the type of *KIT* mutation, it might have efficacy not only against GISTs refractory to TKIs but also for patients with wild-type GIST.

In a study investigating the combination of dasatinib and ipilimumab (NCT01643278), an antibody targeting the immune checkpoint protein cytotoxic T-lymphocyte-associated protein-4 (CTLA4), one out of the eight patients treated had durable SD for 59+ weeks [91]. Few data are available about the expression of other checkpoint proteins such as PDL1, PDL2, or LAG3 in GIST. The study evaluating pembrolizumab, an antibody that targets the programmed cell death 1 (PD-1) receptor, in advanced sarcomas (NCT02406781) is not yet recruiting patients. Some studies suggest a role for the natural killer cells in the immune control of GIST [92, 93].

4.5 Other Targets

CDKN2A loss is a common genetic aberration in metastatic GIST [94], and several studies show an association between low tumor $p16^{ink4}$ (the gene product of *CDKN2A*) and frequent response to cyclin-dependent kinase (CDK) 4/6 inhibitors [95]. Based on such observations, one study is investigating palbociclib (a CDK 4/6 inhibitor) in patients whose GIST is refractory to imatinib and sunitinib (NCT01907607).

FGFRs may mediate resistance to imatinib in GIST [96, 97]. A current trial evaluates a pan-FGFR inhibitor BGJ398 in combination with imatinib in untreated advanced GIST (NCT02257541), but no results are yet available.

Inhibition of the mouse double minute 2 homolog (MDM2) enhanced the pro-apoptotic effects of KIT inhibitors in GIST cell lines [98]. MDM2 inhibitors are

currently being tested in phase I trials, but not at present in GIST. A trial with BBI503, an orally administered multi-kinase inhibitor with putative activity against cancer stem cells, is being planned as the treatment for advanced GIST (NCT02232620).

5 Future Prospects

A large tumor load is a negative prognostic factor for overall survival [99]. Minimizing the tumor load by metastasis surgery might postpone emergence of drug-resistant mutations [100], but this hypothesis remains unproven. Plasma DNA sequencing might help in screening for pre-existing or emerging resistant subclones.

Alternation of TKIs with different kinome inhibitory profiles may be feasible and might suppress resistant clones. It is important to investigate drug combinations that include a mutation-specific inhibitor or an agent that inhibits a KIT-depending signaling cascade, and the novel immune function-modifying agents also warrant investigation.

6 Conclusions

Imatinib is strongly positioned as the recommended first-line agent for most patients with advanced GISTs because of its good efficacy and tolerability. Use of sunitinib and regorafenib as second- and the third-line agents, respectively, is supported by large randomized trials. There are, however, several agents that are potentially useful but have not yet been fully evaluated, such as sorafenib, masitinib, and ponatinib, and the novel approaches described warrant further study. In the authors' opinion, potentially effective novel agents may be investigated relatively early in patient populations with imatinib-refractory GIST, prior to treatment with sunitinib or regorafenib, as sunitinib and regorafenib are only moderately well tolerated and responses to them may remain relatively short lived.

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