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Resistance in gastrointestinal stromal tumors

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Summary The approval of imatinib for the treatment of patients with gastrointestinal stromal tumor has (GIST) revolutionized the treatment in the adjuvant setting and metastatic disease. Imatinib is an inhibitor of the receptor tyrosine kinases KIT and platelet-derived growth factor receptor (PDGFR), which are constitutively activated in most cases of GIST. Even though substantial survival improvements have been observed with imatinib, primary or secondary resistance to imatinib represents a major challenge in the treatment of GIST. This short review focusses on treatment strategies to overcome resistance and provides an overview of promising new agents currently evaluated for imatinib-refractory disease.

Keywords GIST · Resistance · Imatinib · KIT · PDGFRα

Introduction

Gastrointestinal stromal tumors (GIST) are a distinct subgroup of mesenchymal neoplasms. Although it is a very rare tumor entity with an annual incidence of approximately 1:100,000, it represents the most common non-epithelial type of cancer in the gastrointestinal tract [1, 2]. The only curative treatment for GIST is radical surgery at the right time. Adjuvant therapy is indicated in cases with a high risk of recurrence following the risk classification of Miettinen and Lasota [3]. The liver is the most common metastatic

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site in patients with GIST, approximately 10% of patients present with synchronous liver metastases at the time of diagnosis [4]. For a long time, survival in metastatic disease remained poor due to the low efficacy of chemo- and radiotherapy in GIST. However, treatment of metastatic GIST has changed substantially during the past two decades. The identification of the nearly unique expression of the CD117 antigen in GIST, which is a subunit of the KIT receptor encoded by the KIT proto-oncogene, led to a deeper understanding of the pathophysiology of GIST [5, 6]. Activated KIT mutations induce activation of downstream pathways (i.e., JAK/STAT or RAS/MAP) with induction of tumorigenesis and proliferation [7]. It is estimated that approximately 80% of all GISTs harbor a mutation in KIT [8].

Imatinib, a tyrosine kinase inhibitor (TKI), has dramatically changed the treatment of chronic myeloid leukemia (CML). Imatinib blocks the activated abl kinase, which is responsible for proliferation in CML [9]. It was only a matter of time before it was noticed that abl, KIT, and platelet-derived growth factor receptor-alpha (PDGFRα) show a similar chemical structure and therefore provide a biologic rationale to evaluate imatinib in patients with GIST [10]. In the first clinical trial conducted by Demetri and colleagues, imatinib was tested on 147 patients with nonresectable or metastatic GIST. In this study, radiographic response within 6 months was observed in 54% of patients [11]. Long-term results confirmed the efficacy of imatinib and yielded a 5-year overall survival (OS) of nearly 50% (median OS: 57 months) and a median progression-free survival (PFS) of 24 months [12]. A further analysis revealed that outcome in GIST patients undergoing treatment with imatinib depends on specific KIT mutations. It was observed that exon 11 alterations are associated with better OS and PFS compared with exon 9 mutations or wild-type (WT) KIT

[13]. Today, guidelines suggest treatment with imatinib in advanced GIST patients harboring a sensitive KIT mutation (i.e., exon 11, exon 9; [14]). Owing to an inferior outcome in patients with exon 9 mutations, an increased dose of imatinib (800 mg daily) is suggested in this subset of patients. The rationale for increased dosing in GIST with exon 9 mutations is based on a meta-analysis comparing different doses of imatinib in GIST. According to this analysis, imatinib 800 mg was associated with improved PFS compared with conventional dosing (400 mg daily) in patients with exon 9 mutation [15].

Primary and secondary resistance to imatinib

Although imatinib is the mainstay of therapy in metastatic GIST, there are subgroups of patients showing primary resistance to imatinib. In approximately 5–7% of GISTs, no KIT alterations but instead PDGFRα alterations are detected. The PDGFRα D824V mutation is the most common alteration associated with primary imatinib resistance. According to a study evaluating outcome in GIST patients harboring PDGFRα mutations, no patient with PDGFRα D824V showed response to imatinib [16]. Another subgroup of GISTs, which only occasionally occurs in adults, is characterized by the lack of KIT and PDGFRα mutations. This distinct molecular entity is therefore classified as WT-GIST. Most of these tumors show mutations in the SDHX (succinyl dehydrogenase) gene. In an observational study of WT-GIST, response was only seen in one of 49 patients treated with imatinib [17].

The most common acquired resistance mechanisms are induced by secondary KIT mutations. These secondary mutations are usually located in the ATP-binding domains of KIT and PDGFRα, thereby hindering the binding of imatinib to the target structure [18].

Strategies to overcome resistance

In patients with disease progression on imatinib treatment, dose escalation might be considered. In a subgroup analysis of a randomized dose-finding study, stable disease (SD) was observed in 27% of patients who crossed over from the 400 mg to the 800 mg imatinib treatment arm because of progressive disease (PD). Partial response (PR) was seen in 2% of patients [19]. In an American dose-finding study, comparable results were observed with SD and objective response (ORR) in 28 and 3%, respectively [20].

To date, two other agents have been approved for patients with GIST who have disease progression on imatinib first-line therapy: sunitinib and regorafenib. Sunitinib is an oral multikinase inhibitor targeting several kinases, including PDGFRα, VEGFR, as well as KIT. Sunitinib is suggested as standard second-line therapy [14]. A pivotal phase III trial met its primary endpoint by showing prolonged PFS (6.3 vs. 1.5 months) and increased time-to-progression (TTP; 27 vs. 6 weeks) in patients treated with sunitinib compared with placebo. A prolongation of OS was not observed owing to the pre-specified cross-over study design [21]. Interestingly, clinical activity of sunitinib in GIST seems to depend on the mutational status. A phase I/II trial with patients resistant or intolerant to imatinib and subsequent treatment with sunitinib revealed that PFS rates in the KIT exon 9 mutations and WT-GIST groups were significantly longer than in patients harboring primary exon 11 mutations [22]. Comparable mechanisms as in secondary imatinib-refractory disease are suspected to induce sunitinib resistance [23].

For GIST patients showing a PD on imatinib as well as sunitinib, regorafenib is a further treatment option. This oral multikinase inhibitor targets KIT, PDGFR, FGRFR, BRAF, RET, VEGF1-3, and TIE2 [24]. In a phase II trial investigating regorafenib after imatinib and sunitinib disease progression, a clinical benefit rate (CBR) of 79% and a median PFS of 10.0 months were observed [25]. The subsequent phase III GRID trial, evaluating regorafenib versus placebo, revealed a prolongation of PFS of approximately 4 months in the regorafenib arm (4.8 vs. 0.9 months, $p < 0.001$).

Other oral TKIs have also been evaluated for GIST patients. Sorafenib, a multikinase inhibitor targeting KIT, VEGFR, and PDGFR, was evaluated in a small phase II trial in patients with imatinib or imatinib/sunitinib-refractory disease. In this trial, a disease control rate (DCR) of 68% and a median PFS of 5.2 months were reported [26]. Ponatinib was tested in patients with GIST refractory to approved agents. Patients were stratified according to the presence or absence of exon 11 mutations. The CBR of >16 weeks in patients without exon 11 mutation was 55% whereas in patients with primary exon 11 mutations the CBR was 22% [27]. In a phase III trial, nilotinib, a second-generation TKI, was investigated in GIST patients after imatinib and sunitinib failure. The median PFS, assessed by local investigators, was significantly longer in the nilotinib arm compared with patients receiving best supportive care (119 vs. 70 days, $p = 0.0007$). However, according to central radiologic review, no PFS benefit was observed [28]. The PAZOGIST trial evaluated the activity of pazopanib in GIST after imatinib/sunitinib progression. The 4-month PFS was significantly improved in patients receiving pazopanib compared with best supportive care (45% vs. 18%, $p = 0.029$; [29]). Dasatinib has shown promising activity in GIST including patients with WT-GIST and PDGFRα mutations. According to a single-arm trial, in imatinib-refractory patients undergoing treatment with dasatinib, a 6-month PFS rate of 29% and ORR of 25% was observed [30].

Potential new drugs

Besides the aforementioned TKIs, other agents are currently being investigated for metastatic GIST. In vitro studies indicate promising activity of crenolanib, a receptor tyrosine kinase inhibitor, in GIST harboring a PDGFRα D824V mutation [31]. Crenolanib is currently evaluated in a phase III trial in GIST patients with this particular gene alteration (NCT-02847429). A phase II trial revealed that olaratumab, a monoclonal antibody targeting PDGFRα, only shows modest activity in GIST. However, in patients harboring a PDGFRα D824V mutation, olaratumab treatment might lead to a longer DCR [32]. Only recently, the first results of checkpoint inhibition in metastatic GIST were published. In a phase II trial, the CBRs in patients receiving nivolumab (anti-PD-1 antibody) or nivolumab/ipilimumab (anti-CTLA-4 antibody) were 43 and 40%, respectively. Another study, investigating pembrolizumab (anti-PD-L1 antibody) in combination with epacadostat (IDO-inhibitor), is currently recruiting. Study completion is planned in 2019.

Avapritinib, a highly selective inhibitor of mutated KIT and PDGFRα, has shown significant activity in GIST. In the phase I NAVIGATOR trial in pretreated GIST, avapritinib demonstrated encouraging activity with an ORR of 84% (CR 9%, PR 75%). The CBR at 4 months was 96% [33]. The ongoing phase III VOYAGER study is currently evaluating avapritinib vs. regorafenib in pretreated GIST patients (NCT-03465722). DCC-2618, a KIT/PDGFRα switch-control inhibitor, represents another potent agent. According to the first results of a phase I trial, an ORR of 14% and a DCR at 3 months of 70% were achieved in GIST patients undergoing treatment with DCC-2618 [34]. Based on these results, a phase III trial will evaluate the agent in the fourth-line setting (NCT03353753). Furthermore, the oral multikinase inhibitor cabozantinib is currently tested within an EORTC phase II trial (NCT-02216578) in patients with disease progression on imatinib and sunitinib therapies.

Conclusion

The advances in oncologic research and the understanding of fundamental molecular cancer pathways have led to highly effective targeted treatments in patients with GIST in the past 10 years. The mechanisms of TKI resistance represent a major treatment challenge. Currently, several new potentially active agents are being evaluated in different clinical trials to overcome these resistances. The results of these studies are awaited in the next few years. It remains to be seen which therapies will enrich the treatment arsenal in GIST.

Take-home message

Imatinib is a mainstay of therapy for GIST. Resistance to imatinib remains a major challenge. Second- and third-line agents are in clinical use and several further agents are currently evaluated in clinical trials to overcome imatinib resistance and to improve survival.

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