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Therapeutic Strategies after Imatinib Resistance in Gastrointestinal Stromal Tumors

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Abstract: Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor commonly found in the gastrointestinal tract and its pathogenesis is mainly associated with c-KIT and PDGFRA gene mutations. Surgery is the standard treatment for limited GIST, while imatinib (IM) is the first-line treatment for patients with advanced or unresectable GIST. However, imatinib resistance (both primary and secondary resistance) remains a major challenge in the treatment of GIST. To address this challenge, the second-line drug sunitinib, the third-line drug regorafenib, and the fourth-line drug Ripretinib, as well as avapritinib targeting the PDGFRA D842V mutation, have been introduced into the clinic. In addition, therapeutic agents for wild-type GIST, such as SDH-deficient, NTRK-fusion and BRAF V600E mutant, have shown initial efficacy. Next-generation TKIs and other therapeutic strategies (e.g., heat shock protein inhibitors, mTOR inhibitors, immunotherapy) are still being explored, bringing new hope to patients with advanced drug-resistant GIST. In the future, the in-depth study of drug resistance mechanisms, the development of personalized treatment regimens, and the exploration of combination therapies will hopefully further improve the survival and quality of life of GIST patients.

Keywords: Gastrointestinal Stromal Tumor (GIST); Imatinib (IM); Drug Resistance; Tyrosine Kinase Inhibitor (TKI).

1. Introduction

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor derived from Cajal cells[1], with an incidence rate of approximately (10-15)/million people[2], of which the incidence rate in some areas of China (Hong Kong[3], Shanghai[4]) may be as high as 19-22 per million people per year. It occurs most commonly in the stomach (55.6%), followed by the small intestine (31.8%), colon (6.0%), various other sites (5.5%), and esophagus (0.7%)[2].

The most common oncogenic driver genes in GISTs are c-KIT and PDGFRA mutations, of which c-KIT accounts for about 75%-80%, including mutations in exon 11 (67%), exon 9 (10%), exon 13 (1%), and exon 17 (1%)[5–7], and the latter accounts for about 5%-10%, mainly including mutations in exon 18, exon 12 (i.e., V561D) and exon 14 (i.e., N659K) mutations, with exon 18 mutations further categorized as D842V or non-D842V[8], and approximately 10% of GISTs lack c-KIT or PDGFRA mutations and are referred to as wild-type GISTs[9], the most common of which is succinate dehydrogenase (SDH) deficiency (8%)[10,11], and other subtypes are less common, including NF-1, BRAF, RAS, NTRK mutations, and other unknown subtypes[12–15].

The current standard treatment for limited gastrointestinal mesenchymal stromal tumors is complete surgical resection[16], and for patients with unresectable, metastatic, or recurrent advanced GIST, imatinib mesylate (IM) is the first-line therapeutic agent consistently recommended by both Chinese and foreign guidelines. Imatinib mesylate (IM) is a selective tyrosine kinase inhibitor (TKI) developed to target the c-KIT/PDGFRA mutation, and a large number of studies have shown that IM can significantly improve the 5-year survival rate of patients with advanced GIST[17,18]. However, in the course of clinical use, some patients develop resistance to imatinib, resulting in decreased therapeutic efficacy or even failure[19].

Consequently, an exhaustive examination of the mechanisms associated with imatinib resistance in GIST is imperative to enhance patient survival outcomes. In this article, we will review the mechanisms of drug resistance in gastrointestinal mesenchymal stromal tumors and the coping strategies after the occurrence of drug resistance.

2. Mechanisms of Resistance to Imatinib in Gastrointestinal Mesenchymal Tumors

2.1. Primary Resistance:

Imatinib resistance can be categorized into primary and secondary resistance based on when resistance occurs. Primary resistance refers to disease progression in GIST patients within 6 months of imatinib treatment, and its incidence is approximately 15%[20]. Primary resistance was found to be closely related to the genotype of GIST, which was mainly found in wild-type GIST, KIT exon 9 mutation and PDGFRA exon 18 D842v mutation[21]. Among them, KIT exon 9 mutation hinders imatinib binding through spatial conformation changes[22], while PDGFRA exon 18 D842V mutation is located in the activation loop and interferes with the interaction between imatinib and PDGFRA binding site[8].

2.2. Secondary Resistance:

Secondary resistance refers to GIST patients who initially receive imatinib with significant efficacy, but the tumor progresses after 6 months, and statistically, secondary resistance occurs in nearly 50% of patients within 2 years[23]. Secondary mutations in KIT and PDGFRA are the main reason for the emergence of secondary resistance, and such mutations most commonly occur in the ATP-binding pocket of the tyrosine kinase domain (exons 13 and 14) and in the activation loop of the tyrosine kinase domain (exons 17 and 18)[24], leading to reactivation of downstream signaling pathways (e.g, PI3K/AKT/mTOR) that drive further tumor growth. In addition, imatinib-resistant GIST cells exhibit

significant metabolic reprogramming features, including significant enhancement of the enhanced oxidative phosphorylation (OXPHOS) and glycolytic pathways[25,26], a phenomenon that opens the possibility of therapeutic strategies targeting energy metabolism. Non-coding RNAs such as lncRNAs and miRNAs also play important regulatory roles in the molecular mechanisms of imatinib resistance. For example, HOTAIR (HOX antisense intergenic RNA) promotes drug resistance by activating the autophagy mechanism[27], and miR-125a-5p enhances drug resistance by down-regulating specific protein expression[28].

3. Treatment Strategies after Imatinib Resistance

3.1. Tyrosine Kinase Inhibitors (TKI)

3.1.1. First-line Agent – imatinib

A clinical trial[29] showed no statistically significant difference in objective remission rate (ORR), progression-free survival (PFS), or overall survival (OS) in patients receiving high-dose imatinib (800 mg/d) compared with standard dose (400 mg/d), and that patients receiving the high dose were more likely to experience grade 3 or higher toxicity. However, after progression on standard-dose imatinib therapy, 33% of patients switched to a high-dose imatinib regimen and achieved objective remission or disease stabilization[29]. And their follow-up analysis showed that for patients harboring the KIT exon 9 mutation, median progression-free survival (mPFS) was significantly longer in the high-dose imatinib group than in the standard-dose group (19 months vs. 6 months)[30]. In addition, a meta-analysis[31] involving 1640 patients showed that high-dose imatinib significantly prolonged progression-free survival (PFS) and improved objective remission rates (47% vs. 21%) in patients harboring the KIT exon 9 mutation compared with the standard dose (400 mg). Therefore, the recommended starting dose of imatinib for patients with KIT exon 9 mutations is 800 mg/d.

3.1.2. Second-line Drug - Sunitinib

Sunitinib was approved by the U.S. Food and Drug Administration (FDA) in 2006 for the treatment of patients who are resistant or intolerant to imatinib and is currently the only approved drug for second-line therapy[32]. Compared to imatinib, it has a broader target activity, inhibiting the activity of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit (RET), and fms-related receptor tyrosine kinase 3 (Flt3)[33]. In a phase III clinical trial involving 312 patients with GIST, sunitinib significantly prolonged median time to progression (mTTP) (27.3 weeks vs. 6.4 weeks) and progression-free survival (24 weeks vs. 6 weeks)[34]. Another study involving a total of 1124 imatinib-resistant GIST patients from 34 countries showed a median time to progression of 8.3 months and a median overall survival of 16.6 months[35]. Common adverse effects of sunitinib include fatigue, diarrhea, hand-foot syndrome, skin changes, hypertension, and hematopoiesis[34–36], and in a small number of patients, hypothyroidism and adverse cardiac events (e.g., reduced ejection fraction and left ventricular dysfunction) were also observed, but grade 3 or higher adverse events were rare (<1%)[36]. Further studies found that PFS and OS were significantly longer in patients harboring the KIT exon 9 mutation than in those harboring the KIT exon 11 mutation (PFS: 19.4 months vs. 5.1 months; OS: 26.9 months vs. 12.3 months). In addition, patients with secondary KIT exon 13/14 mutations had longer PFS and OS (PFS: 7.8 months vs. 2.3 months; OS: 13.0 months vs. 4.0 months) and higher rates of clinical benefit compared to patients with exon 17/18 mutations.[37].

3.1.3. Third-line Drug - regorafenib

Regorafenib was approved by the U.S. Food and Drug Administration (FDA) in 2013 and is currently the only tyrosine kinase inhibitor (TKI) approved for the third-line treatment of patients with advanced GIST. It inhibits the activity of KIT, PDGFRA, VEGFR, and BRAF[38].Demetri et al. conducted a multicenter, randomized, placebo-controlled phase III clinical trial involving a total of 199 patients with metastatic or unresectable GIST after failure of imatinib and sunitinib treatment and demonstrated that oral regorafenib significantly prolonged progression-free survival (PFS) compared to placebo in patients with GIST (4.8 months vs. 0.9 months). The recommended starting dose of regorafenib, 160 mg/day, was generally well tolerated using a 3-week on, 1-week off dosing regimen. The most common grade 3 or higher drug-related adverse events in the Regorafenib arm were hypertension, hand-foot syndrome and diarrhea[39]. In addition, some molecular analyses have shown that Regorafenib is more active than Sunitinib against KIT exon 17 activation loop mutations, but weaker than Sunitinib against KIT exon 13 V654A ATP-binding pocket mutations, because Regorafenib mainly inhibits mutations in the activation loop, whereas Sunitinib inhibits mutations in the ATP-binding pocket. Thus, Regorafenib and Sunitinib have complementary activities, and rapid alternation of Sunitinib and Regorafenib inhibits the growth of polyclonal imatinib-resistant GISTs more effectively than a single agent. [40].

3.1.4. Fourth-line Medication

Ripretinib was approved by the U.S. Food and Drug Administration (FDA) in May 2020 for the fourth-line treatment of advanced GIST[41]. As an oral type II kinase inhibitor, Ripretinib has been shown to broadly inhibit activating loop mutations in KIT and PDGFRA, aiming to cover the full spectrum of their mutations, thus becoming a new option to overcome the heterogeneity of resistance mechanisms and a new hope for patients with advanced GIST[42]. The INVICTUS study was a double-blind, placebo-controlled, phase III trial in patients with multidrug-resistant GIST that enrolled 129 patients with advanced GIST who had failed treatment with Imatinib, Sunitinib, and Regorafenib. After a median follow-up of 6.3 months, the median progression-free survival (mPFS) in the Ripretinib group was significantly better than that in the placebo group (6.3 months vs. 1 month)[43], and there was a significant prolongation of median overall survival (OS) (15 months vs. 6.6 months).The INTRIGUE study was a double-blind, randomized phase III trial that enrolled 453 patients who had failed Imatinib and compared the efficacy of Ripretinib with Sunitinib. In the overall population, there was no significant difference in median PFS between the two groups (8 months vs. 8.3 months)[44], but an exploratory circulating tumor DNA (ctDNA) analysis of the study found that the efficacy of Ripretinib may be related to the mutation site. Patients harboring the KIT exon 11+ 17/18 (excluding 9/13/14) mutation treated with Ripretinib had superior progression-free survival (PFS), objective remission rate (ORR) and overall survival (OS) to those treated with Sunitinib, while patients harboring the exon 11+ 13/14 (excluding 9/17/18) mutation treated with sunitinib had superior PFS, ORR and

OS to those treated with Ripretinib [45]. Ripretinib was generally well tolerated, with common adverse reactions including fatigue, nausea, alopecia, hand-foot syndrome, and diarrhea, and the most common grade 3 or higher toxic reactions were elevated lipase, hypertension, fatigue, and hypophosphatemia[43]. The incidence of adverse reactions is lower with Ripretinib compared to Sunitinib[44].

Avapritinib was approved in January 2020, becoming the first effective targeted agent for advanced GIST with the PDGFRA D842V mutation and establishing a standard treatment regimen for patients with this molecular subtype[46]. As a potent and highly selective type I kinase inhibitor, Avapritinib binds to the active conformation of KIT/PDGFRA and inhibits all activating loop mutations[47].PDGFRA exon 18 D842V mutations account for 70% of PDGFRA mutations[47]. Patients with these mutations are resistant to anti-GIST drugs such as imatinib, sunitinib and regorafenib[48], and prior to the approval of Avapritinib, these patients had no effective treatment options and a poor prognosis, with median progression-free survival of only 3-5 months and overall survival of approximately 15 months[48,49]. The NAVIGATOR study is an open-label phase I clinical trial that enrolled 231 patients with advanced GIST, 56 of whom harbored the PDGFRA exon 18 D842V mutation. A preliminary report showed that 49 patients (88%) achieved objective remission (ORR), with 5 patients (9%) achieving complete remission (CR) and 44 (79%) achieving partial remission (PR)[50]. Follow-up analysis showed that at a median follow-up of 27.5 months, ORR improved to 91%, median duration of remission (DOR) was 27.6 months, and median progression-free survival (PFS) was 34 months[51], far exceeding previous treatment expectations and significantly improving the long-term prognosis of patients.

3.1.5. Next-generation TKI Inhibitors

THE-630 is a next-generation oral pan-KIT inhibitor with potent inhibitory activity against primary and secondary KIT mutations, capable of inhibiting both ATP-binding pocket and activation loop mutations. In preclinical studies, THE-630 has shown anti-tumor activity over existing therapeutic agents. For example, for ATP-binding pocket mutations (e.g. V654A), THE-630 demonstrated 86% tumor inhibition, which was significantly better than Ripretinib (26%). For activating loop mutations (e.g., N822K and D820A), THE-630 inhibited 88% and 59%, respectively, significantly better than sunitinib (25%) and Ripretinib (1%)[52]. A phase I/II study evaluating the safety, pharmacokinetics and antitumor activity of THE-630 in patients with advanced gastrointestinal mesenchymal stromal tumors (NCT051 60168) is ongoing[53].

NB003 (formerly known as AZD3229) is also a broad-spectrum inhibitor of KIT and PDGFRA-mutant GISTs[54]. Preclinical in vitro studies have shown superior potency against both primary and secondary KIT mutations compared to Imatinib and other approved agents[55]. An open-label, multicenter Phase I clinical trial (NCT04936178) of NB003 is currently underway to evaluate safety, tolerability and pharmacokinetics in patients with advanced malignancies[56].

CGT-9486 (formerly known as PLX-9486) is an oral type I KIT inhibitor with potent in vitro activity against primary KIT exon 9 and 11 mutations and secondary KIT exon 17/18 mutations, including the exon 17 D816V mutation[57]. In a non-randomized phase Ib/IIa clinical trial involving 39 GIST patients, the recommended phase II dose of CGT9486 alone at 1000 mg/day resulted in a single-agent objective response rate (ORR) of 8%, a clinical benefit rate (CBR) of 50% and a median progression-free survival (PFS) of 5.75 months. Further studies showed that CGT-9486 in combination with sunitinib had better efficacy with an ORR of 20%, a CBR of 80% and a PFS of 12.1 months. Their ctDNA analysis showed that CGT-9486 reduced KIT exon 17/18 mutations, while combined treatment with sunitinib further suppressed KIT exon 13/14 mutations[58]. A randomized open-label phase III trial (NCT05208047) is currently underway to compare the efficacy of CGT-9486 in combination with sunitinib versus sunitinib alone in imatinib-resistant or intolerant patients[59].

3.2. Pharmacologic Therapy for Wild-type GIST

3.2.1. Temozolomide in SDH-deficient GIST

Approximately 8% of GISTs exhibit the SDH (succinate dehydrogenase)-deficient phenotype, which is the third largest molecular subtype after KIT- and PDGFRA-mutant GISTs. The treatment of SDH-deficient GISTs has been a challenge. Although the approved indications for KIT/PDGFRA TKIs such as imatinib, sunitinib, regorafenib, and Ripretinib include patients with SDH-deficient GIST, they are of limited utility in these patients[10], and therefore there is an urgent need for the development of new therapeutic approaches for SDH-deficient GIST. Temozolomide (TMZ) is an alkylating agent currently approved by the FDA for the treatment of glioblastoma multiforme and refractory mesenchymal astrocytoma[60]. The use of temozolomide in SDH-deficient GIST is still in the exploratory phase, but preliminary findings suggest its potential efficacy.De Silva et al. reported a case of a patient with SDH-deficient GIST, who was switched to temozolomide for 18 cycles (28 days/cycle) without significant progression after ineffective treatment with imatinib and sunitinib[61]. A phase II clinical trial of temozolomide in patients with advanced SDH-deficient GIST (NCT03556384) is ongoing, and a preliminary report showed that two of the five patients enrolled achieved partial remission (PR), and the disease was controlled in another three patients[62]. Temozolomide has shown potential efficacy in SDH-deficient GIST, providing a new therapeutic idea for patients with this particular molecular subtype. Further large-scale studies will help to validate its efficacy and safety and promote its application in the clinic.

3.2.2. Larotrectinib and Entrectinib in NTRK Fusion GIST

NTRK fusion gene mutations are very rare in gastrointestinal mesenchymal tumors[63,64], and tyrosine kinase inhibitors (TKIs) targeting NTRK fusions have entered clinical research and shown significant efficacy in a few cases. Larotrectinib, a potent and highly selective ATP-competitive inhibitor of the TRKA, B, and C receptor tyrosine kinases, was pooled with data from three phase I/II clinical trials showing that a total of three patients with GIST harboring NTRK fusions were treated with Larotrectinib and all achieved complete remission (CR), demonstrating significant efficacy[65]. Entrectinib is another NTRK-targeted TKI that has received FDA approval for the treatment of NTRK-fusion solid tumors[66]. In a pooled analysis of three phase I/II studies, only one patient with NTRK-fusion GIST was treated with Entrectinib, but efficacy data are unknown[67]. Due to the extreme rarity of NTRK-fusion GIST, the total number of cases in the relevant studies is currently only four. However, the preliminary results of Larotrectinib and Entrectinib provide important therapeutic options for this type of patient.

3.2.3. Dabrafenib and Trametinib in BRAF V600E Mutant GIST

BRAF V600E-mutated GISTs account for approximately 0.8% of all GIST cases, and this subtype is also very rare. Targeted therapies for the BRAF V600E mutation have shown significant efficacy in other solid tumors (e.g. melanoma, non-small cell lung cancer) and have been gradually applied to the treatment of GIST in recent years. A case report showed the success of dabrafenib monotherapy for BRAF V600E-mutant GIST[68], providing a new direction for the treatment of patients with this subtype.2022 In June 2022, the FDA accelerated the approval of the combination of dabrafenib and trametinib for the treatment of BRAF V600E-mutant solid tumors, including GIST, in patients with prior treatment failure who have no satisfactory treatment options[69]. This combination regimen has previously been approved for the treatment of BRAF-mutant melanoma, metastatic non-small cell lung cancer and undifferentiated thyroid cancer[70]. Despite the small number of cases of BRAF V600E-mutant GIST, the approval of the combination of Dabrafenib and Trametinib provides a new therapeutic option for these patients and is expected to improve their clinical prognosis.

3.3. Heat Shock Protein Inhibitor Pimitespib

Pimitespib was approved in June 2022 in Japan for the treatment of refractory GIST patients with disease progression after treatment with imatinib, sunitinib, and Regorafenib. Pimitespib a selective heat shock protein 90 (Hsp90α and Hsp90β) inhibitor. Hsp90 is a class of adenosine triphosphate (ATP)-dependent chaperone proteins involved in the folding and stabilization of KIT and PDGFRA proteins[71]. In a mouse model of multiple GIST families carrying the Asp820Tyr mutation in exon 17 of KIT, Pimitespib was shown to inhibit the phosphorylation of KIT and significantly reduce the volume of cecum GIST[72]. Furthermore, in addition, Pimitespib demonstrated inhibition of proliferation and induction of apoptosis in in vitro assays in imatinib-resistant and imatinib-primed GIST cells; Pimitespib was similarly effective in inhibiting tumor growth in imatinib-resistant GIST in a xenograft mouse model[73].CHAPTER-GIST-301 is a randomized placebo-controlled phase III clinical trial enrolling 86 patients with refractory GIST, which showed that Pimitespib significantly prolonged median progression-free survival (2.8 months vs. 1.4 months) and median overall survival (13.8 months vs. 7.6 months) compared to the placebo group[74]. Pimitespib's phase I trial demonstrated its safety, with significantly lower ocular toxicity compared to previous Hsp90 inhibitors[75,76]. Pimitespib, as a novel Hsp90 inhibitor, provides a new treatment option for patients with multidrug-resistant GIST, and it has shown positive effects in prolonging patient survival and improving prognosis. Follow-up studies will further clarify the value of its clinical application and potential strategies for combination therapy.

3.4. mTOR Inhibitors

mTOR inhibitors (e.g., Everolimus) act on the downstream signaling pathways of KIT and PDGFRA to inhibit the activity of the PI3K/Akt/mTOR pathway, thereby suppressing tumor cell proliferation. In preclinical studies, the combination of mTOR and KIT inhibitors showed significant efficacy in imatinib-resistant GIST[77]. A phase I/II study evaluated the safety and efficacy of Everolimus in combination with imatinib in the treatment of patients with imatinib-resistant GIST. The results of the study showed that the treatment regimen of Everolimus in combination with imatinib had an acceptable safety profile while demonstrating potential clinical efficacy after failure of imatinib and sunitinib[78].

3.5. Immunotherapy

Immunotherapy, which involves the elimination of tumor cells by activating the host immune system, has developed rapidly in recent years and has shown some potential in GIST. Since there is a large infiltration of immune cells in GIST[79,80] and the antitumor effects of imatinib are partially dependent on the immune system[81], immune-related cells and molecules are thought to play an important role in the development and progression of GIST.

3.5.1. Immune Checkpoint Inhibitors (ICI)

Immune checkpoint inhibitors (ICIs), such as anti-PD-1 and PD-L1 antibodies, have achieved significant success in other cancers but have had more limited effects as monotherapy in patients with GIST; however, the combination of ICIs with targeted therapies may improve the prognosis of patients with GIST, as shown in a study in which monotherapy with either anti-PD-1 or anti-PD-L1 antibodies failed to significantly inhibit a mouse GIST model of tumor growth, while the combination of imatinib significantly reduced tumor proliferation[82]. Currently, many studies on the combination of TKIs and immunosuppressants for the treatment of advanced drug-resistant GIST are underway, such as: Spartalizumab (PDR001) in combination with Imatinib[83], avelumab in combination with Axitinib[84], Avelumab and Regorafenib[85].

3.5.2. Antibody-drug Couplings (ADCs)

Antibody-drug conjugates (ADCs) are another direction in which immunotherapy has shown great potential in advanced drug-resistant GIST, and several ADCs, including anti-KIT ADCs (LOP628-DM1 and NN2101-DM1) and an anti-GPR20 ADC (DS-6157a), have been developed and tested in GIST. LOP628-DM1 exhibited potent antiproliferative activity against c-KIT-positive cell lines and showed excellent efficacy in both a mouse GIST xenograft model and an imatinib-resistant GIST model[86]. Similarly, NN2101-DM1 inhibited GIST tumor growth both in vivo and in vitro and showed potent inhibition of imatinib-resistant GIST cells[87]. DS-6157a, an anti-GPR20 (G protein-coupled receptor 20) ADC, demonstrates antitumor activity against KIT-mutant GIST cells in vitro and in patient-derived xenograft models with or without secondary resistance mutations[88]. A Phase I, multi-center, open-label, first-in-human study of DS-6157a for the treatment of patients with advanced gastrointestinal mesenchymal stromal tumors enrolled 34 patients with GIST, of which a total of 18 patients achieved SD and 1 patient with SDH-deficient GIST achieved PR[89].

Although the application of immunotherapy in GIST is still in its early stages, current studies have shown that by combining the strategies of targeted therapy and immune microenvironment modulation, it is expected to overcome the limitations of the existing treatments and provide new directions and potential solutions to improve the prognosis of patients.

4. Summary and Future Prospects

Since the introduction of imatinib in 2001, the treatment of

GIST has changed dramatically. The use of tyrosine kinase inhibitors (TKIs) has gradually expanded from first-line treatment to second-, third- and fourth-line treatment, including sunitinib, regorafenib, repitinib and avastinib. These drugs have significantly improved patient survival and quality of life. In addition, emerging therapies such as heat shock protein inhibitors, mTOR inhibitors and immunotherapy offer new hope for the treatment of drug-resistant GIST. However, current therapies still face a number of challenges, including limited efficacy, significant toxicities and inadequate benefit in certain patient populations. In addition, effective therapeutic options for wild-type GIST are still urgently needed, and limitations in therapeutic options limit the improvement of prognosis in this patient population.

Future research should focus on the following directions: first, to delve deeper into the drug resistance mechanism of GIST through multi-omics analysis (e.g, genomics, proteomics, and metabolomics) to provide the basis for the discovery of new targets; second, to explore the synergistic effect of targeted drugs and immunotherapy to improve the efficacy and overcome the resistance; and finally, to promote the innovation of molecular diagnostic technology to improve the therapeutic effect through personalized therapeutic strategies, especially in the treatment of rare types of GIST.

With the gradual deepening of the understanding of drug resistance mechanisms and the continuous advancement of innovative therapies, the future of GIST treatment is promising. In the future, personalized, combined and precise treatment strategies are expected to further improve the survival and quality of life of GIST patients.

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