The Current State of Target Therapy for Subtypes of Gastrointestinal Stromal Tumors

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumor of the gastrointestinal tract, although with a very low incidence rate. GISTs were classified into mutant and wild-type according to whether the patient has KIT/platelet-derived growth factor (PDGFR) mutations. The radical surgery may be the only opportunity for cure, but the treatments of traditional radiation and chemotherapy are ineffective for advanced GISTs. In recent years, targeted therapy of GISTs has obtained remarkable effect, but the locus mutations/secondary mutations of KIT/PDGFR gene have become a key factor for the prognosis. This review mainly introduced GISTs on gene mutation and tyrosine kinase inhibitor (TKI) therapy. The characteristics, molecular mechanism, and research progress of targeted drugs for different genotypes of mutant GIST were discussed.

Abbreviations: GISTs: Gastrointestinal Stromal Tumors; PDGFRA: Platelet-Derived Growth Factor; TKI: Tyrosine Kinase Inhibitor; ICC: Interstitial Cells of Cajal; SCF: Stem Cell Growth Factor; SDH: Succinate Dehydrogenase; BRAF: Rapidly Accelerated Fubrosarcoma B; NF1: Neurofibromatosistype; IGF-1R: Insulin-Like Growth Factor 1 Receptor; MAPK: Mitogen-Activated Protein Kinase; PI3K: Phosphatidlinositol 3-Kinase; IM: Imatinib

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumor of the gastrointestinal tract, although with low incidence. They are connective tissue tumor arising from the interstitial cells of Cajal (ICC) cells. The most common tumor location is the stomach (50%-70%), followed by the small intestine (25%-35%), rectum (5%-10%), and esophagus (<5%) [1]. The signs and symptoms of GISTs, which grow slowly and generally occur in 50 to 70 years old, are gastrointestinal hemorrhage, trouble in swallowing and metastases [2]. About 30% of GISTs can be defined as evil and led to metastasize occurring drug resistance during the treatment because of gene mutuation [3]. Some study show that the patients of GIST have mutations in PDGFR (PDGFRα or PDGFRA) but not in the wild-type GISTs without c-kit or PDGFRA mutations were accounted for 10-15% of the total number of GISTs (Table 1) [4] According to researchs, wild-type GISTs might lack succinate dehydrogenase (SDH) leading by mutations of SDH.
The occurrence of GISTs are related with KIT/PDGFRA gene mutations, which c-kit mutations were accounted for 80~90% and PDGFRA mutations for 7% [5].

The radical surgery may be the only chance of cure, but the treatments of traditional radiation and chemotherapy are ineffective for advanced GIST (recurrent, inoperable or distant metastasis). In recent years, the targeted therapy of GISTs has obtained significant efficacy with the development of precision medical. Tyrosine kinase inhibitor (TKI) is the first-line treatment drug of GISTs, such as imatinib mesylate (IM). The locus secondary mutations of KIT/PDGFRA genes were key factors for prognosis. At the same time, the application of targeted drugs to achieve the maximum therapeutic effect has become the focus of research. The latest NIH classification system for GISTs declare that Mid- to Late GISTs are applicable for the adjuvant therapy, which preoperative IM is widely available. This article aims to make a summary of different genotype, mutation and molecular mechanism of GISTs, and the progress of targeted drugs.

Table 1: Genetic mutation in GIST.

| Genetic Subtype          | Region                  | Relative Frequency |
|--------------------------|-------------------------|--------------------|
| KIT mutation (75~80%)    | Exon 11                 | Juxtamembrane domain | 70%     |
|                          | Exon 9                  | Extracellular domain | 7-10%   |
|                          | Exon 13                 | ATP-binding         | 1%      |
|                          | Exon 17                 | Activation loop     | 1%      |
| PDGFRA mutation (10~15%) | Exon 18                 | Activation loop     | 5%      |
|                          | Exon 12                 | Juxtamembrane domain | 1%      |
|                          | Exon 14 BRAF            | ATP-binding         | <1%     |
| “Wild-type” GIST(10~15%) | SDH (A, B, C, D other  | V600E              | 7-15%   |
|                          |                         |                    | 2%      |
|                          |                         |                    | rare    |

Genetic Mutation in GISTs

KIT Mutation

C-kit gene is considered at the homologue of HZ4 feline sarcoma Virus KITs oncogene. C-kit proto-oncogene, which consisting of 21 coding exons in III type of protein tyrosine kinase receptor superfamily members, is located in chromosome 4q11-12. It is a kind of Kit protein receptor, which consist of extra-cellular region, trans-membrane region, near-membrane region and 2 tyrosine kinase (TK) region. Its ligand is stem cell growth factor (SCF). The most common mutations are exon11 mutations (70%), exon9 mutations (5%~10%), and exon13 mutations (1%) [6]. Exon14, 17, 18 mutations are relatively rare [7]. The main mutation types are deletion mutation, point mutation, mixed mutation and insert mutation [8].

When c-kit mutated, CD117 protein expresses and forms a dimer autonomously without the participation of the ligand. Therefore, it cannot precisely regulate the differentiation, proliferation, and programmed cell death. Finally, c-kit mutations can cause more cells enter the neoplastic hyperplasia stage from the quiescent stage, which may be one of the key mechanisms causing malignant transformation of GIST. Studies have found that tumors with c-kit exon11 deletion are more likely to appear in the patients who are older than 50 years, with a tumor diameter of 5~10cm and the NIH grade as high risk. Moreover, the secondary and high-risk GISTs are susceptible to secondary mutations that cause recurrence and metastasis because of the deletion of exon 11 of c-kit gene [9], which has potential value for predicting poor prognosis of patients.

PDGFRA Mutation

PDGFRA gene stretches approximately 65 kb on human chromosome 4 (4, q11-13) and consists of 23 exons in III type of protein tyrosine kinase receptor superfamily members, including exon3-10 coding region exocellular five immunoglobulin sample, exon11 coding intracellular membrane area, near exon13-15 and exon17-21 coding intracellular kinase 2 cheese ammonium acid (tyrosine kinase, TK) area. Similar to c-kit, PDGFRA gene mutation is also a function-acquired mutation and most of them occur in CD117 negative GISTs [10]. In the absence of ligand binding, the autonomous dimerization leads to cell division and proliferation by promoting DNA synthesis through downstream signaling pathways, thus the growth, proliferation, attachment, metastasis, differentiation, and apoptosis of cells are regulated. The mutations of PDGFRA essentially clustered in three regions and the most common of these is exon18 that accounting for 82.5%, the most common site is D842V [11-13]. The process of GISTs formation by PDGFRA mutation is similar to c-kit, the tyrosine kinase receptor encoded by PDGFRA located on the cell membrane is abnormally and continuously activated, resulting in the loss of autoinhibition function.
Wild-Type GIST

The morphology of wild type GIST is in line with the GIST, CD117 positive or negative expression, at the same time cannot detect c-kit and PDGFRA gene mutations, but often coupled with abnormalities in the structure or expression of other genes, such as, subunits of succinate dehydrogenase (SDH) complex. Rapidly accelerated fibrosarcoma B (BRAF) gene, neurofibromatosistype1 (NF1) gene mutation, multiple gene fusion and other abnormalities. The most common type in the wild type is the SDH expression deficient or decreased, which can be accompanied by other neoplastic diseases, including paraganglioma, pulmonary chondroma, pheochromocytoma, etc. At first, the disease was recognized as Carney triad and Carney Stratakis syndrome [14]. The high expression of insulin-like growth factor 1 receptor (IGF-1R) receptor RNA or protein in the GISTs due to SDH gene defects is detected. IGF-1R binds to ligand and is activated by autophosphorylation, leading to the activation of mitogen-activated protein kinase (MAPK) and phosphatidilinositol 3-kinase (PI3K) cascades [15].

IGF signaling can inhibit IGF-1R-induced apoptosis in SDH-deficient GIST cells and inhibit the signaling of Akt and MAPK pathways in GIST cells [16]. For BRAF gene mutant GIST, most of the mutation sites are V600E of exon 15, which can affect the function of PI3K [17], BRAF mutations have been found in a small number of patients with imatinib (IM) resistance, suggesting that BRAF mutations may be the cause of secondary resistance [18]. KRAS mutations are also one of the wild-type GIST, some scholars analyzed the gene sequence of 578 cases of GIST and found no KRAS mutation, So KRAS mutations may be extremely rare [19].

Other Biological Markers

Many research experiments show that c-kit mutations represent a poor prognosis in high-risk GISTS, PDGFRA mutations associated with less malignant GIST [20]. However, these alone are not absolute and require more biological indicators related to prognosis and efficacy. In addition, the proliferation index Ki-67 is a very effective marker for predicting the aggressive behavior and malignant potential of GIST and can be employed as an independent predictor of GIST [21]. P16 expression is also related to the malignant of GIST [22]. Moreover, there are evidence from 19 studies showing p53 have the predictive value in the risk of GIST [23].

TKI Therapy in GIST

Complete surgical resection is the only chance for cure for the disease, but there is still a possibility of recurrence and metastasis. For advanced (unresectable or recurrent, metastatic) GISTs, molecular targeted therapy is the preferred treatment [24].

First-Line Imatinib Therapy for Advanced GIST

Imatinib is a derivative of 2-phenylaminopyrimidine, which is a kind of small molecule selectively activated tyrosine enzyme inhibition agent to inhibit the BCR-ABL protein, ABL, KIT and PDGFRAs. Though selective inhibition of tyrosine kinase lives sex, blocking the phosphate group on tyrosine residues. In 2002, the FDA approved STI571 for the treatment of unresected or metastatic GIST. Demir et al conducted a trial, 147 patients with advanced GIST were randomly assigned to receive 400mg and 600mg of imatinib per day. The results showed that imatinib has achieved a good objective response in patients with advanced GIST, and there were no significant differences in the safety of treatment dose [25]. Subsequent phase 2 and phase 3 trials of metastatic GIST also confirmed the efficacy of imatinib in advanced GIST (Table 2). Treatments which provided the sites to inhibit tumor cell proliferation were widely applied advanced and metastatic tumor, and the preoperative and postoperative adjuvant therapy.

However, an effective dose of imatinib cannot inhibit other open sites in the tyrosine kinase pathway except for c-kit or PDGFRAs gene mutations, allowing cell proliferation signals to bypass cell proliferation inhibition caused by imatinib, c-kit exon11 mutant GIST is generally sensitive to imatinib and not sensitive to ex09 and PDGFRAs mutation types [26]. Further research found that the relationship between kinase genotype and treatment outcome, Kit exon11 genotype mutation has better benefit than other genotype mutations [27]. Our previous meta-analysis estimated the imatinib treatment for different genotypes of GIST and found that personalized treatment makes patients with exon 11 mutation more profitable [28]. To optimize the treatment of imatinib, a meta-analysis of 1,640 patients with advanced disease showed that the patient could get a small PFS advantage of 2 times the standard dose (800mg/d) of imatinib, but no significant difference in OS between the dosages, especially in kit exon9 mutation.

Compared with exon11 mutation, exon9 mutation and wild mutation have a worse prognosis [29]. Moreover, Asian Consensus Guidelines agreed that a higher dose may also be beneficial in Asian patients with KIT exon 9 mutation [30]. To assess long-term survival with two doses of imatinib, one long-term result of a randomized trial showed the 800mg/d group had a better 10-year PFS rate and an average OS rate than the 400mg/d group [31]. Whether patients with advanced GIST benefit significantly in terms of long-term survival and will they differ due to the differences of mutations? An analysis of Phase 3 SWOG Intergroup Trial S0033 showed that imatinib as a first-line drug in advanced GIST has resulted in long-term survival of 10 years for a significant number of patients, especially those with KIT exon11 mutations or KIT/ PDGFRAs mutations lacking (mainly succinic dehydrogenase mutant tumors) [32]. Most people can benefit from imatinib, but this result
does not lasting. Many patients will initially be resistant even if they were recommended to extend the duration of medication from one year to three years [20].

GIST resistance of imatinib can be divided into primary and secondary, primary resistance is no response to imatinib treatment, while secondary resistance occurs 6 months after the initial treatment is effective. The secondary gene mutation of KIT/PDGFR is considered closely related to secondary resistance. The secondary mutation of KIT occurred in exons 13, 17, 14 [33] and occurred in exon 18 of PDGFRA [34]. Further research found that heterogeneity of KIT secondary mutations is the principal mechanism of tumour progression to KIT inhibitors in imatinib-resistant GIST patients [35]. The sensitivity of PDGFRA mutant GISTs to targeted drugs is also primary resistance to imatinib, so it is difficult to achieve satisfactory efficacy even if the dose of imatinib is increased [36]. Many resistance mechanisms are still being researched due to the diversity of mutation sites, heterogeneous multitarget inhibitors and precise personal treatment are more worthy of promotion.

**Second-line Sunitinib for Advanced GIST**

Secondary drug resistance occurred in more than 50% of patients after treatment with imatinib, thus the second-line treatment drugs such as sunitinib, an oral multitarget tyrosinase inhibitor, emerged. The growth, proliferation and metastasis of malignant tumors were affected by blocking the signaling pathway by inhibiting tyrosine kinases such as VEGFR, PDGFR, KIT, and RET. Sunitinib is considered as a second line TKI because of its considerable benefit in patients with advanced imatinib resistance and intolerance. A randomized, blank-control phase 2 clinical trial of random taking sunitinib 50mg / d and placebo in the blank control group. The results of this experiment showed that progression-free survivals were 27.3 weeks and 6.4 weeks, respectively. Overall survival was 24.1 weeks and 6 weeks, respectively (Table 2) [37]. However, Lile Wu et al. conducted a meta-analysis clinical efficacy of second-generation TKI in imatinib-resisitant GISTS showed that sunitinib are effective for improving PFS but not OS in patients with imatinib-resistant GIST [38].

| Trial     | Phase | Patients                                      | Treatment Dose/Duration                          | Results                                      |
|-----------|-------|-----------------------------------------------|------------------------------------------------|---------------------------------------------|
| B2222[25] | 2     | 147 patients with metastatic or unresectable GIST | Imatinib 400mg qd (N=73) vs 600mg qd(N=74)       | PR:49.3% vs 58.1%(either dose PR is 53.7%)  |
|           |       |                                               | Imatinib 400mg daily(N=473) vs 800mg daily (N=473) | TTP:20 months vs 26 months                  |
| EORTC 62005[43] | 3     | 946 patients with advanced GIST               |                                                | PD:56% vs 50%                               |
|           |       |                                               |                                                | 1-year-OR:85% vs 86%                        |
|           |       |                                               |                                                | CR:5%                                       |
|           |       |                                               |                                                | PR:47%                                      |
|           |       |                                               |                                                | SD:32%                                      |
| S0033[45] | 3     | 694 Patients with KIT-positive GIST           | Imatinib 400mg daily (N=345) vs 800mg daily (N=349) | PFS:18 months vs 20 months                  |
|           |       |                                               |                                                | OS:5.5 months vs 51 months                  |
| NCT00075218[35] | 2     | 312 patients with resistant or tolerant to imatinib | Sunitinib 50mg daily vs placebo                | PFS: 27.3 weeks vs 6.4 weeks                |
|           |       |                                               |                                                | OS: 24.1 weeks vs 6.0 weeks                 |
| ENESTg1[40] | 3     | 647 patients with unresectable / metastatic GIST | Imatinib 400mg daily vs Nilotinib 800mg daily  | PFS: 59.2% vs 51.6%                         |
| GRID[41]  | 3     | 199 Patients with failure of at least previous imatinib and sunitinib | Regorafenib 160 mg daily vs placebo            | PFS:4.8 months vs 0.9 months                |
| NCT02606097[45] | 2     | 18 patients with metastatic/ unresectable GIST, harboring secondary mutation of exon 17 | Regorafenib 160mg/day on days 1-21 of a 28-day cycle | 16-weeks CBR:93.3%                         |
|           |       |                                               |                                                | PFS:22.1 months                            |
| NCT00117299[51] | 2     | 25 patients with advanced GIST (who failed to respond to both imatinib and sunitinib) | Regorafenib 100 mg p.o. daily was administered continuously | DCR-12-weeks:64%                          |
|           |       |                                               |                                                | PFS:7.3 months                             |
|           |       |                                               |                                                | 1-year survival rates:64.5%                 |
One of our previous pooled analysis showed that sunitinib treatment after imatinib resistance varied according to the genetic subtypes of GIST. Compared with PDGFRA, the mutation of KIT gene showed better clinical rate of cure, especially the mutation of KIT exon 9, 11. Furthermore, the mutation cure rate of KIT exon 9 was better than that of exon 11 [39]. Other second-line TKI drugs such as nilotinib, a tyrosine kinase activity of ABL/BCR, and KIT, PDGFRs, significantly improve PFS [40]. In a phase III study of nilotinib versus imatinib as first-line therapy for unresectable or metastatic GIST, Blay JY et al. divided 324 advanced patients on nilotinib 400 mg twice daily and 320 advanced patients on imatinib 400 mg daily. The results showed that the 2-year progression-free survival rate was better in the imatinib group (59.2%) than in the nilotinib group (51.6%). There was no difference between the two groups for progression-free survival of KIT exon 11 mutation, but imatinib group was better than nilotinib of the exon 9 mutation. Therefore, in the future, first-line drugs need to be determined based on subtype analysis [41].

Third Line Regorafeniband Ripretinib for Advanced GIST

Regorafenib, a multikinase inhibitor was candidate as a third-line treatment option for patients with advanced GIST, which is recommended after failure of both high-dose imatinib and sunitinib. In a randomized phaseIII trial of regorafenib GRID, the results showed that median progression-free survival was 4.8 months for regorafenib and 0.9 months for placebo, with no significant difference in overall survival [42]. Another study of regorafenib showed the efficacy and safety of manageable profile in Japanese were consistent with the overall GRID study population of patients with advanced GIST. As a third line TKI, the effectiveness of regorafenib has been proven in GRID, however, frequent dose reductions were required of the administration plan. In a study involving 25 patients who failed treatment with imatinib and sunitinib, low-dose continuous treatment with regorafenib showed that the disease control rate for at least 3 months in 64% of patients and had a median progression-free survival of 7.3 months. Maybe this method of administration has become a better choice [43,44].

In addition, regorafenib prolonged progression-free survival of patients with advanced mutations in exon17 [45-48]. Another threeline targeted therapy, ripretinib is a II type switchpocket inhibitor that binds to the switchpocket and acts as a structural substitute for an inhibitory switch, preventing the activation loop from entering the switchpocket, thus locking the kinase in an inactive state and inhibiting downstream signaling. Ripretinib has strong inhibitory effects on different secondary drug resistance mutations because it is acting on the final link of the kinase pathway [49-50]. However, clinical data on ripretinib therapy and genotyping have not been reported yet, so there may be differences in the efficacy of ripretinib in GIST with different genetic mutation types.

Other TKIs

Other TKIs identified in clinical trials, such as sorafenib, as a third line / four-line TKI. A Korean clinical trial used two or more TKIs to treat unresectable or distant metastatic, 36% of patients had more than six months of disease control after using sorafenib [51]. Moreover, including vatalanib (PTK789), masatinib (AB1010), pazopanib (PAZOGIST), dasatinib (NCT0056875) (Table 2) [52-54].
Conclusion

Despite the many benefits of targeted drugs for advanced GIST, drug resistance presents a new challenge. Through the understanding of the mutation sites of GIST and the collection of information about current treatment regimens, we can see that the efficacy of targeted drugs in different genotypes still needs a large number of standardized clinical open trials. Similarly, to leverage the strength of targeted drugs to make up for the shortcomings, personalized treatment and evaluation are essential. New therapeutic ideas should be applied to more actions, such as the combination of targeted and chemotherapy drugs, new targets to be discovered, updated TKIs and combined immunotherapy. Further studies on drug resistance mechanisms and new molecular markers are the breakthrough points for the treatment of advanced GIST to optimize the treatment of advanced GIST.

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Ethics Approval and Consent to Participate

Not applicable.

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Competing Interests

The Author(s) declare(s) that there is no conflict of interest.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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