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Correlation of Imatinib Resistance with the Mutational Status of *KIT* and *PDGFRA* Genes in Gastrointestinal Stromal Tumors: a Meta-analysis

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ABSTRACT

Background & Aims: Imatinib resistance is the most important clinical issue in patients with gastrointestinal stromal tumor (GIST). However, the association of imatinib resistance with the genetic characteristics of GIST has not been clearly defined. Our meta-analysis aimed to investigate the association between imatinib resistance and *KIT* and *PDGFRA* mutations in GIST.

Methods. We identified all relevant studies in PubMed and Embase. The effect sizes were calculated as prevalence or odds ratio (OR) with a random–effects model.

Results. We identified 10 eligible studies that included 1083 GIST cases. Total imatinib resistance was found in 35.5 % of *PDGFRA*-mutant tumors (OR = 2.9, P = 0.038), 33.7% of wild-type tumors (*KIT* and *PDGFRA* non-mutant tumors; OR = 2.8, P = 0.002), and 27.4% of *KIT*-mutant tumors (OR = 0.3, P = 0.001). Primary imatinib resistance was found in 50.0% of *PDGFRA*-mutant tumors (OR = 10.9, P = 0.031), 33.4% of wild-type tumors (OR = 5.9, P = 0.060), and 8.9% of *KIT*-mutant tumors (OR = 0.2, P = 0.025). *KIT* exon 9-mutant tumors showed primary resistance more frequently than exon 11-mutant and other tumors (OR = 7.6, P < 0.001). Regarding secondary resistance associated with *KIT* second-site mutations, the exon 17 mutation (54.5%) was most frequent, followed by exon 13 (38.3%) and 14 (13.4%) mutations.

Conclusion. Our meta-analysis indicates that imatinib resistance is closely associated with *KIT* and *PDGFRA* genotypes in GIST. Thus, the mutational status of *KIT* and *PDGFRA* might predict response to imatinib in GIST patients.

Key words: gastrointestinal stromal tumor – imatinib – resistance.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal gastrointestinal tumors, and most express the KIT (CD117) protein [1]. GISTs present with highly variable clinicopathologic features including the occurrence site, patient age, a morphologic spectrum ranging from benign nodules to malignant sarcomas, and prognosis [1]. Despite its clinicopathologic heterogeneity, most GISTs share similar oncogenic mutations that involve the *KIT* gene or the platelet–derived growth factor receptor alpha (*PDGFRA*) gene. *KIT* and *PDGFRA* mutations are mutually exclusive in GISTs [1-3].

Imatinib mesylate is a competitive inhibitor of ATP binding that blocks the kinase activities of BCR–ABL, KIT, and PDGFRA and thus has dramatically improved the treatment of GIST [4,5]. Currently, imatinib is the first-line agent for surgically unresectable or metastatic GISTs, in which it acts to delay the disease progression and prolong patient survival [6]. However, the long-term use of imatinib induces drug resistance [7-16].

Imatinib resistance is classified into primary resistance or early progression and secondary resistance or late progression [12-17]. When GIST patients continue to progress within 3–6 months of initiating imatinib therapy, the patients are classified as having primary imatinib resistance. In contrast, some GIST patients initially respond to imatinib treatment and develop imatinib resistance within 12–36 months. These patients are classified as having secondary resistance [17].

Although imatinib resistance is very important in the treatment of advanced GIST patients, the association of imatinib resistance with the genetic characteristics of GISTs has not been clearly defined. To elucidate the association between the mutational status of *KIT* and *PDGFRA* and imatinib resistance, we conducted a meta-analysis of the published studies that evaluated imatinib resistance in GIST patients.

METHODS

Data collection and selection criteria for meta-analysis

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (http://www.embase.com) using the keywords "GIST," "imatinib," "resistance," and "mutation." Next, we manually searched the reference lists of the identified articles. Duplicate data and overlapping articles were excluded by examining the authors' names and affiliations. The following types of articles were included in the analysis: original articles that reported imatinib resistance according to different *KIT* and *PDGFRA* mutations in GIST patients (articles dealing with animal tissues or cell lines were excluded); articles that were published in English before March 2013; the most recent or informative single article among multiple articles using the same materials published by the same authors or institutions. Articles that lacked data for meta-analysis, review articles without original data, conference abstracts, and case reports were excluded. The study quality was independently scored by two reviewers according to the Newcastle-Ottawa Scale [18]. The Newcastle-Ottawa Scale is frequently used for case-control studies. The maximum case-control score is 9. The selection process for this meta-analysis is shown in Fig. 1.

Data pooling and statistics

The meta-analysis was performed as previously described [19, 20]. Briefly, effect sizes for each study were calculated as the prevalence or odds ratio (OR) and the corresponding 95% confidence interval (CI) using the Mantel–Haenszel method. The prevalence or ORs were combined according to a random-effects model (DerSimonian-Laird method). Statistical heterogeneity among the studies was evaluated with the Cochrane Q test and I^2 statistics. The I^2 statistic describes the percentage of variation across studies that results from heterogeneity rather than chance and does not inherently depend upon the number of studies considered (I^2=100% × (Q–df)/Q). Sensitivity analyses were performed to examine the influence of each study on the pooled OR by serially omitting an individual study and pooling the remaining studies. Publication bias was examined by funnel plots and Egger's tests for the degree of asymmetry. $P < 0.05$ was considered statistically significant. The pooled analysis was performed with the Comprehensive Meta-analysis Software version 2.0 (Biostat, Englewood, NJ, USA).

RESULTS

A total of 10 articles satisfied the eligibility criteria. The characteristics of the selected studies are summarized in Table I. Of the 10 papers, 5 studies described imatinib resistance according to *KIT* and *PDGFRA* mutations in GIST patients. In these studies, imatinib resistance was not classified as primary or secondary resistance [7-11]. To evaluate imatinib resistance, we regarded progressive disease as resistant according to the Response Evaluation Criteria in Solid Tumor (RECIST) criteria [21]. The other 5 studies presented primary and/or secondary imatinib resistance data [12-16].

Total imatinib resistance according to the different genotypes

We regarded 10 studies as reports of total imatinib resistance in GIST patients according to the *KIT* and *PDGFRA*

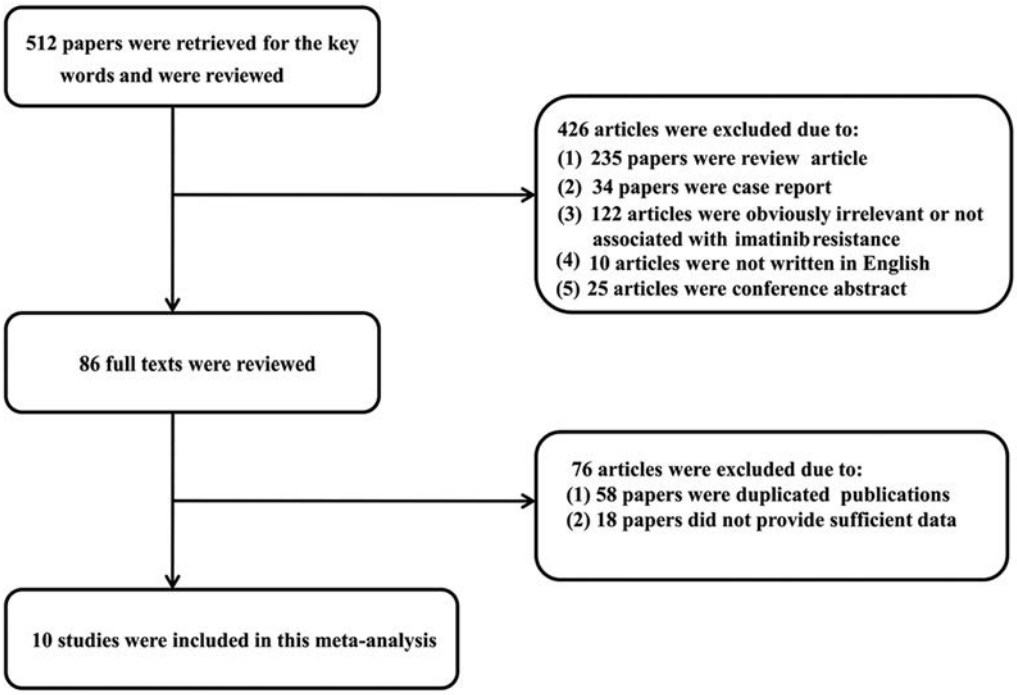

Fig. 1. Flow diagram of article selection for the meta-analysis.

Table I. Characteristics of individual studies included in the meta-analysis.

Study	Patient's country	Study design	Response estimation	Genotyping method	Imatinib dosage (mg/day)	Score
Debiec–Rychter M [7]	Europe–Australia	Case control	RECIST	DHPLC, Seq	400 or 800	6
Rutkowski P [8]	Poland	Case control	RECIST	DHPLC, Seq	400 or 800	6
Heinrich MC [9]	USA, Canada	Case control	RECIST	DHPLC, Seq	400 or 800	6
Sym SJ [10]	Korea	Case control	RECIST	Seq	400 to 800	6
Li J [11]	China	Case control	RECIST	PCR	400 to 800	5
Antonescu CR [12]	USA	Case control	NA	Seq	400 to 600	5
Wardelmann E [13]	Germany	Case control	RECIST	Seq	NA	5
Wang CM [14]	China	Case control	RECIST	Seq	NA	6
Yeh CN [15]	Taiwan	Case control	RECIST	DHPLC, Seq	400	6
Armbrust T [16]	Germany	Case control	NA	NA	400 to 800	6

RECIST, response evaluation criteria in solid tumor; NA, not available; DHPLC, denaturing high–pressure liquid chromatography; Seq, sequencing; PCR, polymerase chain reaction; Score, Newcastle-Ottawa score

mutations [7-16]. The overall total patient number was 1083 and the individual studies ranged from 13 to 363. The prevalence of total imatinib resistance was 31.7% (95% CI: 0.178–0.498) of the GIST patients. Total imatinib resistance was found in 35.5% (95% CI: 0.181–0.578) of *PDGFRA*-mutant tumors, 33.7% (95% CI: 0.220–0.478) of wild-type tumors (*KIT* and *PDGFRA* non-mutant tumors), and 27.4% (95% CI: 0.133–0.483) of *KIT*-mutant tumors.

PDGFRA-mutant GISTs were more resistant to imatinib than wild-type and *KIT*-mutant GISTs combined (OR = 2.890, 95% CI: 1.061-7.877, P = 0.038, Q = 4.278, df = 4, I^2=6.501) (Fig. 2). Wild-type GISTs showed more imatinib resistance than *PDGFRA*-mutant and *KIT*-mutant GISTs combined (OR = 2.829, 95% CI: 1.467–5.458, P = 0.002, Q = 14.017, df = 9, I^2 = 35.792) (Fig. 3). The pooled OR for imatinib resistance in *KIT*-mutant GISTs was 0.349 (95% CI: 0.183–0.665, P = 0.001, Q = 14.880, df = 9, I^2 = 39.517) (Fig. 4) (Table II).

With respect to the different *KIT* exon mutations, imatinib resistance was found in 94 (12.7%) of 740 *KIT* exon 11-mutant GISTs and in 36 (25.9%) of 139 *KIT* exon 9-mutant tumors. The pooled ORs for imatinib resistance in the tumors with *KIT* exon 11 and exon 9 mutations were 0.577 (95% CI: 0.234–1.421, P = 0.232, Q = 22.245, df = 9, I^2 = 59.541) and 2.006 (95% CI: 0.791–5.089, P = 0.143, Q = 20.856, df = 9, I^2= 56.846), respectively.

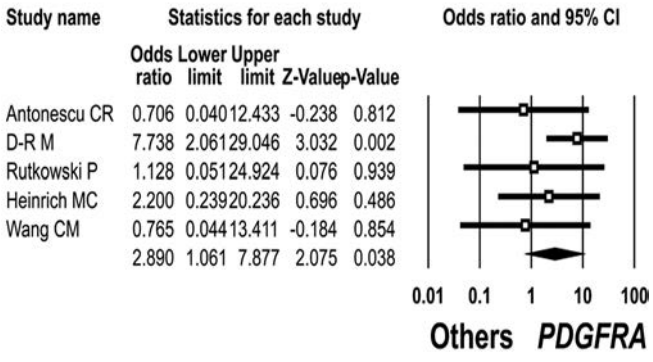

Fig. 2. Odds ratios with corresponding 95% confidence intervals (CIs) for the individual studies and pooled data for the association between total imatinib resistance and *PDGFRA*- mutant tumors. Forest plot demonstrates the effect sizes and 95% CIs for each study and overall.

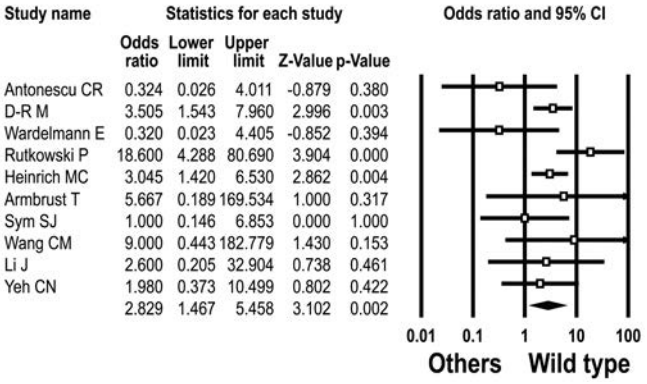

Fig. 3. Pooled estimates of the relationship between total imatinib resistance and wild- type GISTs.

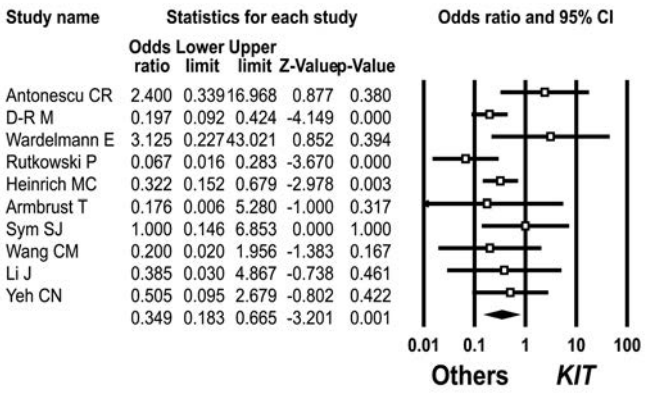

Fig. 4. Pooled estimates of the association between total imatinib resistance and *KIT*-mutant tumors.

However, the association between *KIT* exon mutations and imatinib resistance was not statistically significant.

Primary imatinib resistance

Four studies included 215 GIST patients who presented with primary imatinib resistance according to the *KIT* and *PDGFRA* mutations. The prevalence of primary imatinib resistance was 11.9% (95% CI: 0.082–0.171) [12-15]. Primary imatinib resistance was found in 50.0% (95% CI: 0.123–0.877)

of *PDGFRA*-mutant tumors, 33.4% (95% CI: 0.133–0.622) of wild-type tumors (*KIT* and *PDGFRA* non-mutant tumors), and 8.9% (95% CI: 0.045–0.166) of *KIT*-mutant tumors.

The pooled ORs for primary imatinib resistance in *KIT*-mutant and *PDGFRA*-mutant GISTs were 0.152 (95% CI: 0.029–0.791, P = 0.025, Q = 5.016, df = 3, I^2 = 40.194) and 10.947 (95% CI: 1.250–95.846, P = 0.031, Q = 0.034, df = 1, I^2 = 0), respectively. The pooled OR for primary imatinib resistance in wild-type GISTs was 5.866 (95% CI: 0.930–37.005, P = 0.060, Q = 5.784, df = 3, I^2 = 48.132), which was not statistically significant. The pooled ORs for primary imatinib resistance were 7.645 (95% CI: 2.652–22.038, P < 0.001, Q = 0.464, df = 2, I^2 = 0) in *KIT* exon 9-mutant GISTs and 0.135 (95% CI: 0.047–0.388, P < 0.001, Q = 0.665, df = 2, I^2 = 0) in *KIT* exon 11-mutant GISTs (Table II).

Table II. Pooled odds ratios of imatinib resistance in gastrointestinal stromal tumors.

	GIST genotype					
	KIT exon 9-mutant	P	*PDGFRA*-mutant	P	Wild-type	P
Total resistance	2.0	0.143	2.9	0.04	2.8	0.002
Primary resistance	7.6	< 0.001	10.9	0.03	5.9	0.06

GIST, gastrointestinal stromal tumor

Secondary imatinib resistance due to second-site *KIT* or *PDGFRA* mutations

Seven studies presented 156 cases of GIST with second-site *KIT* or *PDGFRA* mutations [12-14,22-25]. The prevalence of second-site *KIT* or *PDGFRA* mutations was 61.3% (96/156) (95% CI: 0.500–0.715). Among these, the second-site *KIT* mutation occurred in 92 cases and the *PDGFRA* mutation in 4 cases. The second-site mutations after initial imatinib therapy developed in 70.7% (95% CI: 0.608–0.789) of *KIT* exon 11-mutant tumors and 39.2% (95% CI: 0.213–0.606) of *KIT* exon 9-mutant tumors [12, 13, 22-25]. Of the second-site *KIT* mutations, the prevalence of exon 17 mutation (54.5%, 95% CI: 0.409–0.675) was the most frequent, followed by exon 13 (38.3%, 95% CI:0.281–0.496) and exon 14 (13.4%, 95% CI:0.054–0.295) mutations [12, 13, 22-25].

Sensitivity analysis and publication bias

The sensitivity analysis revealed that none of the studies on total imatinib resistance according to *KIT* mutation affected the ORs (Fig. 5). Three studies affected the total imatinib resistance result in *PDGFRA*-mutant GISTs [7-9]. Three studies influenced the result of primary resistance in *KIT*-mutant tumors [12-14]. Yeh et al [15] influenced the primary imatinib resistance result according to *KIT* exon mutations. In funnel plots with Egger's regression tests, no study except those regarding the total imatinib resistance according to *PDGFRA* mutation status showed evidence of publication bias (Fig. 6).

DISCUSSION

This meta-analysis revealed that imatinib resistance in GIST is highly associated with types of *KIT* and *PDGFRA* mutations.

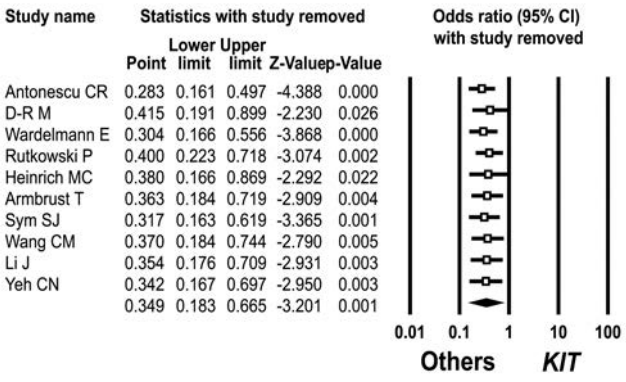

Fig. 5. Sensitivity analysis of the association between total imatinib resistance and *KIT* mutation (*KIT*). The pooled ORs remained the same when each study was sequentially removed and the meta-analysis was repeated with the remaining studies.

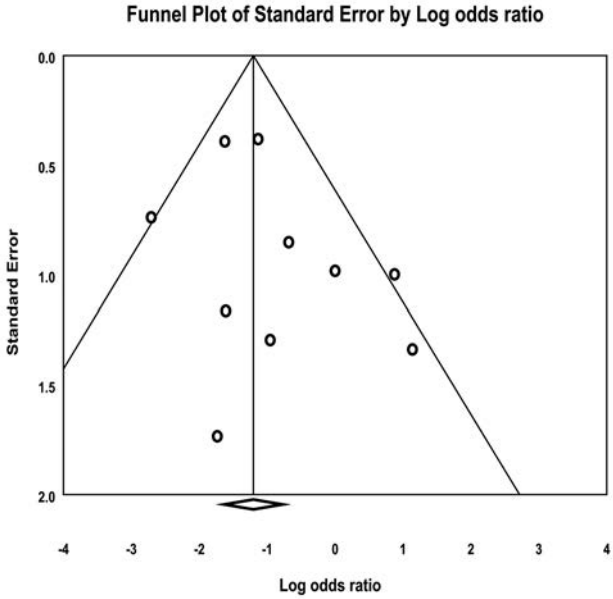

Fig. 6. Funnel plot of publication bias for total imatinib resistance in *KIT*-mutant tumors. Individual studies are represented by small circles.

Total imatinib resistance occurred most frequently in GIST patients with *PDGFRA* mutated and wild-type GISTs. Primary imatinib resistance was significantly increased in *PDGFRA*-mutant and *KIT* exon 9-mutant tumors. Secondary imatinib resistance developed because of second-site *KIT* mutations. Of the second-site *KIT* mutations, exon 17 mutations occurred most frequently, followed by exon 13 and exon 14 mutations.

Our meta-analysis indicates that total imatinib resistance is more frequent in *PDGFRA*-mutant and wild-type tumors than in *KIT*-mutant tumors. A brief meta-analysis reported that imatinib efficacy differed according to *KIT* genotypes in GISTs [26], which is in agreement with our results. Approximately 5%-7% of GISTs harbor oncogenic mutations in 3 different *PDGFRA* regions: exon 18 (activation loop domain), exon 12 (juxtamembrane domain), and exon 14 (kinase I domain) [27, 28]. Neither *KIT* nor *PDGFRA* mutations are found in 10%–15% of GISTs, which are referred to as wild-type GISTs [27]. Previous studies reported that *KIT* exon mutations as well

as the mutational status of *KIT* and *PDGFRA* are significantly associated with imatinib resistance in GISTs [7-9], whereas others did not suggest any significant relationships between imatinib resistance and *KIT* and *PDGFRA* mutations [10-14]. However, our meta-analysis found that total imatinib resistance was significantly associated with *KIT* and *PDGFRA* mutations, but not with specific *KIT* exon mutations.

The effects of imatinib therapy in GIST patients are limited by primary or secondary imatinib resistances. This meta-analysis confirmed that *PDGFRA* mutations, particularly the point mutation D842V in its exon 18, the most frequent *PDGFRA* mutation, lead to primary imatinib resistance [12,14]. Moreover, *KIT* exon 9-associated primary imatinib resistance occurred 8 times more frequently than resistance caused by other *KIT* mutations. Oncogenic *KIT* mutations that constitutively induce kinase activation are discovered in 80%–85% of GISTs [1, 27]. Four *KIT* mutation hotspots are exon 11 (intracellular juxtamembrane domain, 70% of GIST), exon 9 (extracellular domain, 10%–15%), exon 13 (kinase I domain, 1%), and exon 17 (activation loop, 1%) [27]. Primary imatinib resistance seemed to occur 6 times more frequently in wild-type GISTs than in the other groups, but this difference was not statistically significant. Previous studies described newly developed second-site mutations in *KIT* or *PDGFRA* [12-14, 22, 23]. The second-site *KIT* mutations involve either the ATP binding pocket in the kinase I domain (exons 13 and 14) or the kinase activation loop (exon 17). The second-site mutations lead to a shift from the inactive state to the active conformation of KIT or to inhibition of imatinib–KIT binding.

Imatinib mesylate only binds to the inactive conformation of KIT and inhibits its kinase activity by blocking ATP binding. Tyrosyl-phosphorylation or mutations of *KIT* induces the active conformation of the KIT kinase domain, to which imatinib cannot bind [27]. Imatinib sensitivity differs according to the location of the mutation within the *KIT* gene. *KIT* exon 11 mutant-tumors displayed a > 10-fold increase in imatinib sensitivity than GISTs with other exon mutations. Drug responses to imatinib in *KIT* exon 9-mutant tumors can be improved by increasing the imatinib dose to 800 mg/day [29]. The therapeutic effects of imatinib depend on the conformational status of KIT and the ability of imatinib to bind to KIT.

Second-site *KIT* mutations lead to secondary imatinib resistance. This meta-analysis found that second-site mutations occur most frequently in *KIT* exon 17, followed by exons 13 and 14. To overcome imatinib resistance, new drugs are currently being developed. Sunitinib maleate, an inhibitor of KIT, PDGFRs, vascular endothelial growth factor receptors-1, 2, and 3, FLT3, and RET, has been approved as a second-line therapy for imatinib-resistant GIST patients [27, 30, 31]. Like imatinib, sunitinib can only block the inactive conformation of KIT. However, sunitinib has strong potency against imatinib-resistant ATP binding pocket mutations (exons 13 and 14) but a lower potency against activation loop mutations (exons 17 and 18) [27]. Thus, the exact pharmacologic mechanisms of sunitinib need to be elucidated for effective targeted therapy.

There are several limitations in our meta-analysis. Although we pooled prior results according to a statistically weighted method, the previous studies presented heterogeneous parameters that included different imatinib resistance criteria, numbers of studied *KIT* exons or genes, imatinib dosages and duration, and patient ethnicities.

CONCLUSION

Our meta-analysis indicates that total imatinib resistance occurs most frequently in *PDGFRA*-mutant and wild-type tumors. Primary imatinib resistance is significantly increased in *PDGFRA*-mutant and *KIT* exon 9-mutant tumors. Second-site *KIT* mutations that lead to secondary imatinib resistance occur most frequently in exon 17, followed by exons 13 and 14. Therefore, *KIT* and *PDGFRA* genotyping might predict therapeutic responses to imatinib and help to choose second-line agents for GIST patients.

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Conflicts of interest. The authors declare no conflicts of interest.

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