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Efficacy evaluation of nilotinib treatment in different genomic subtypes of gastrointestinal stromal tumors: A meta-analysis and systematic review

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ABSTRACT

Nilotinib has been used as a third-line drug for gastrointestinal stromal tumors (GISTs) after a failure of sunitinib. In this study, we aimed to evaluate the efficacy of nilotinib in different genomic subtypes of GISTs. We searched the English articles through EMBASE, Cochrane Library and PubMed Database regarding to the use of nilotinib on GISTs, which published up to February 15, 2019. Inclusion criteria were: GISTs patients received nilotinib in a clinical trial and had detailed genetic subtype records (such as KIT exon 9, KIT exon 11, or PDGFRA mutations, or wild-type). The clinical benefit rate was used to assess the efficacy of nilotinib. A total of 3 studies involving 218 GISTs were included in this meta-analysis. The overall OR

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(KIT group vs WT group) was 3.26 (95% CI: 1.14-9.28; $P = 0.027$, $P_{heterogeneity} = 0.613$). The overall OR in KIT exon 11 group vs WT group was 5.30 (95% CI: 1.79-15.68; $P = 0.003$, $P_{heterogeneity} = 0.409$). The overall OR in KIT exon 9 group vs WT group was 0.13 (95% CI: 0.02-0.86; $P = 0.035$, $P_{heterogeneity} = 0.229$). The overall OR in KIT exon 11 group vs exon 9 group was 9.96 (95% CI: 0.39-254.66; $P < 0.0001$, $P_{heterogeneity} = 0.024$). Different genotypes of GISTs showed different responses to nilotinib, and KIT exon 11-mutant GISTs mostly benefited from nilotinib, followed by KIT exon 9-mutant or WT one.

ARTICLE INFO

Keywords: GISTs; Genotypes; Nilotinib; Meta-analysis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract and are considered as malignant tumors, especially for high-risk GISTs [1]. Approximately 85%-90% of GISTs express KIT and PDGFRA mutation [2]. KIT mutation most occur in exon 11, followed by exon 9, less frequently in the exon 13 and exon 17 [3]. In the PDGFRA mutations, D842V site mutation is the most frequent, followed by the exon 12, exon 18, and very rarely in exon 14 [4]. Wild-type (WT) is the remaining 10%-15% of GISTs without mutations of KIT and PDGFRA kinase domains, includes the succinate dehydrogenase defects (succinate dehydrogenase mutation (A/B/C/D)) and NF1, BRAF, HRAS, NRAS, etc. [5,6].

At present, surgical resection is still the first choice for localized GISTs according to the clinical guideline [7], but the 5-year survival rate is only around 50% after complete resection. Liver or abdominal metastasis can be present at time of diagnosis, and approximately 50% surgery patients will recurrence after curative surgery, especial primary high-risk GISTs patients [8]. Imatinib has been widely used as a first-line therapy for advanced or unresectable GISTs. The clinical benefit rate achieved around 85% under a standard dosage of 400 mg once a day. Further, sunitinib has been used as a second-line therapy after a failure of imatinib therapy. In a large phase III trial, approximately 70% of imatinib resistant patients achieved complete or partial response or disease stabilization [9,10]. The treatment of sunitinib had significant clinical benefit in disease control and superior survival for patients with advanced GIST after a failure of imatinib [9]. Based on Kim Westerdijk's results, the tolerant dose of sunitinib in GIST patients is 37.5-60 ng/mL for continuous dosing and 50-80 ng/mL for intermittent dosing, respectively [11]. Further, Maddalena Centanni et al demonstrate that dose increases of sunitinib based on the pharmacodynamic biomarkers neutrophil count and sVEGFR-3 can be recommended because of prolonged OS [12].

Still, some GISTs can develop resistance to imatinib and sunitinib. Therefore, Third-line therapy is urgently needed for these patients. Ripretinib (DCC-2618) is a novel, type II tyrosine switch control inhibitor designed to broadly inhibit activating and drug-resistant mutations in KIT and PDGFRA. Regorafenib is type II kinase inhibitor and bind to the inactive conformations of KIT and PDGFRA, which Nilotinib is a new Tyrosine Kinase Inhibitor (TKI), which can inhibit the receptor kinases for stem cell factor (KIT), platelet-derived growth factor receptor alpha (PDGFR-a) and platelet-derived growth factor receptor beta (PDGFR-ß). Nilotinib has showed clinical benefit in GISTs patients resistant to imatinib and sunitinib [13]. In our previous studies, we showed that imatinib and sunitinib have different efficacy depending on different genomic subtypes. Imatinib showed a higher clinical benefit rate in KIT exon 11-mutant GISTs patients, while sunitinib is more effective for GISTs patients with KIT exon 9 mutation [14,15]. Therefore, we suppose that genomic subtypes of GISTs could be used to stratify patients' response to nilotinib. In this study, we aim to clarify which genomic subtype of GISTs would benefit most from nilotinib treatment.

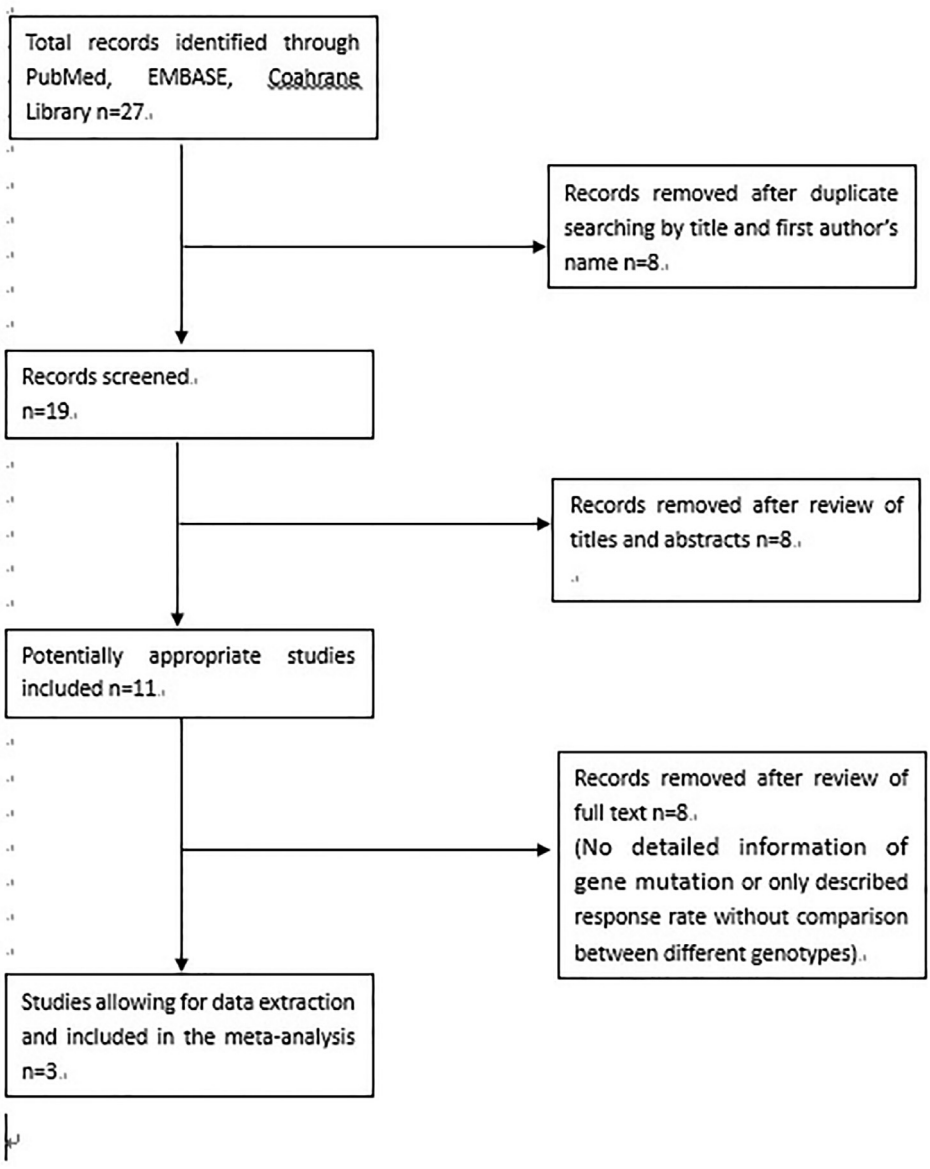

Fig. 1. Flow diagram of included and excluded studies.

Methods

Search strategy

We searched the English articles through EMBASE, Cochrane Library, and PubMed Database regarding to the use of nilotinib on GISTs, which published up to February 15, 2019. A searching strategy was made using the key words: "gastrointestinal stromal tumor" and "nilotinib." When several studies contain the identical patient populations, we only choose the most recent or complete study. A searching process was shown in the flow chart (Fig 1).

Table 1
Genomic subtypes of GIST patients included in the meta-analysis.

Author's name	Publication year	Therapeutic regimen	Exon 9	Exon 11	Exon 13	Exon 17	PDGFRα	WT	Other	Unknown	CBR (%)
Sawaki et al. [17]	2011	400 mg bid	1/5	6/17	NA	NA	0/1	1/4	NA	2/8	29
Cauchi et al. [18]	2011	400 mg bid	0/1	2/7	0	0	0	0/2	NA	2/2	33
Blay et al. [19]	2015	400 mg bid	0/24	100/125	NA/2	0	NA/11	4/13	5/9	NA	64

Bid, twice a day; CBR, clinical benefit rate=n/N; WT, wild-type; Unknown: the number of GIST patients who did not genetic test in each original article; NA: Not available; n=number of patients with complete response (CR) + partial response (PR) + stable disease (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST); N = total number of patients with genotype.

Inclusion criteria

(a) a phase II/III clinical trial; (b) detailed genomic subtype records (such as KIT exon 9, KIT exon 11, or PDGFRA mutations, or WT); (c) clear clinical benefit rate (CBR) among different genomic subtypes; (d) sufficient data to assess odds ratio (OR) and 95% Confidence interval (CI).

Data extraction

Two investigators (Zong L and Xu Y) independently reviewed and screened the articles, and extracted the data. First, we reviewed the titles and abstracts, and then obtained the full text of any potentially relevant articles. According to Response Evaluation Criteria in Solid Tumors (RECIST), CBR is defined as the proportion of patients with a best overall response to complete response, partial response, or stable disease. Finally, the author's name, publication year of article, treatment regimen of nilotinib, number of various genomic subtype of GISTs, and the CBR in different genomic subtypes were collected (Table 1).

Statistical analysis

Odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated as efficacy endpoint to assess the efficacy of nilotinib by using the Mantel-Haenszel method. P value and $P_{\text{heterogeneity}}$ were calculated as previous studies [16]. The Z test was used to determine the combined OR or HR, and statistically significant was defined as $P \leq 0.05$. The funnel plot assesses potential publication bias: we suggest that there is a publication bias when the funnel plot is asymmetrical. In this case, we use trimming and fill analysis to adjust the asymmetry. All analyses were performed using STATA software (STATA 14.0, Stata Corporation, College Station, TX, USA).

Results

Study selection

In Fig. 1, many studies were excluded due to no detailed information of gene mutation. The studies by Reichard et al [17] and Demetri et al [18] were excluded because they only described CBR in all patients without reporting CBR among different GISTs genomic subtypes. Finally, a total of three studies involving 218 GISTs were included in this meta-analysis [19-21] (Table 2).

Table 2
Baseline Characteristics of GIST patients included in the meta-analysis.

Author's name	Publication year	Gender		Age (year)		ECOG[1]/WHO[2] PS			Primary location					Site of metastasis			
		Male	Female	Median	Range	0	1	2	Stomach	Small bowel	Large bowel	Other	Unknown	Liver	Lung	Abdomen	Other
Sawaki et al. [17]	2011	22	13	57	26-76	38[2]	24[2]	6[2]	11	21	1	1	1	23	0	0	12
Cauchi et al. [18]	2011	9	4	63	54-78	4[1]	9[1]	0[1]	6	5	2	0	0	11	2	7	7
Blay et al. [19]	2015	89	82	59	18-84	121[2]	46[2]	4[2]	51	71	10	35	4	100	17	56	41

[1] ECOG PS(Eastern Cooperative Oncology Group Performance Status)
[2] WHO PS(World Health Organization Performance Status)

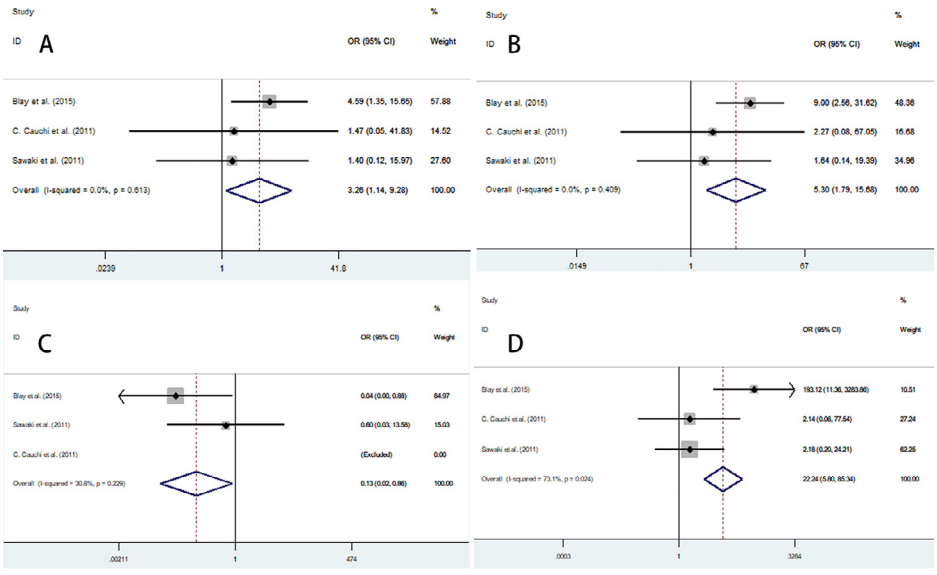

Fig. 2. Forest plots comparing clinical benefit rates in GISTs with different genotypes: (A: KIT vs WT; B: KIT exon 11 vs WT; C: KIT exon 9 vs WT; D: KIT exon 11 vs KIT exon 9).

Comparison of CBR among different GISTs genomic subtypes

The overall OR (KIT group vs WT group) was 3.26 (95% CI: 1.14-9.28; $P = 0.027$, $P_{\text{heterogeneity}} = 0.613$), suggesting that patients with KIT mutation will benefit more than that with WT (Fig 2A). Further, the overall OR in KIT exon 11 group vs WT group was 5.30 (95% CI: 1.79-15.68; $P = 0.003$, $P_{\text{heterogeneity}} = 0.409$), confirming that patients with KIT exon 11 mutation will benefit more than that with WT (Fig 2B). In addition, the overall OR in KIT exon 9 group vs WT group was 0.13 (95% CI: 0.02-0.86; $P = 0.035$, $P_{\text{heterogeneity}} = 0.229$), confirming that patients with KIT exon 9 mutation will benefit more than that with WT (Fig 2C). Finally, the overall OR in KIT exon 11 group vs exon 9 group was 9.96 (95% CI: 0.39-254.66; $P < 0.0001$, $P_{\text{heterogeneity}} = 0.024$; Fig 2D), suggesting that patients with KIT exon 11 mutation will benefit more than that with KIT exon 9 mutation.

Publication bias

We used a funnel plot to evaluate the publication bias for each study after using the trimming and filling analysis to adjust the asymmetry. However, the shape of the funnel plot does not show a significant publication bias (Fig 3).

Discussion

Nilotinib is used as third-line therapy for GISTs [22]. In this study, we evaluated the efficacy of nilotinib in different genomic subtypes of GISTs. We only made an analyses among KIT exon 9 mutation, KIT exon 11 mutation, and WT due to lacking data for PDGFRA genotypes. Our study showed that GISTs patients with KIT exon 11 mutation mostly benefit from nilotinib, followed by KIT exon 9 mutation, and WT.

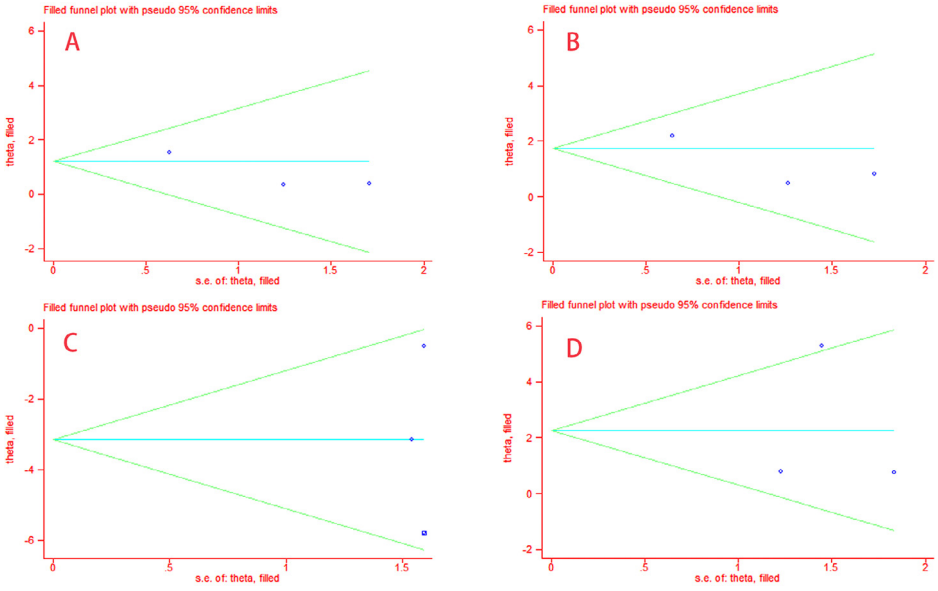

Fig. 3. Funnel plots after trim and fill analysis. (A: KIT vs WT; B: KIT exon 11 vs WT; C: KIT exon 9 vs WT; D: KIT exon 11 vs KIT exon 9).

In previous studies, we found that the prognosis of patients with GISTs is related to the primary location of the tumor, the size of the tumor, and the type of gene mutation [23]. Genetic mutations are widely presented in GISTs, the KIT mutations are the most common and described in exon 11 (66%-71%), exon 9 (10%-13%), exon 13, 14, 17 (3%). And exon 18 accounted for (5%-6%), exon 12 (1%), and exon 14 (1%) among the detected PDGFRA mutations, the remaining of GISTs called WT. The development of primary and secondary mutations during treatment is a fundamental step in disease progression [24]. Our previous studies has demonstrated that the response of GISTs patients to sunitinib and imatinib is strongly associated with the type of gene mutations [14,15].

GISTs patients are most likely to develop clinical resistance to these kinase inhibitors (such as imatinib and sunitinib) because of secondary mutations in the KIT and/or PDGFRA kinase domains, so it is other chemotherapy drugs that are needed instead of these kinase inhibitors for treatment, such as ripretinib (DCC-2618) and regorafenib. Some studies have been shown that (Table 3): JAE-JOON KIM et al demonstrated that regorafenib proved effective for GIST patients at the standard intermittent dosing schedule [25]; Chun-Nan Yeh and George D Demetri et al suggested that regorafenib prolonged progression free survival in advanced GIST patients [26,27]. And other studies indicated that the ripretinib improved median progression free survival and had an acceptable safety profile in advanced GIST patients who were resistant to approved treatments [28,29]. Moreover, KIT and PDGFRA resistance mutations are heterogeneous in any given patient [30]. Among the three studies we included, only Cauchi et al's research referred to gene secondary mutation. Among 10 patients with genetic mutations, 2 samples showed 2 mutations: a primary KIT exon 11 mutation with a KIT secondary exon 17 mutation, which clinical outcomes showing prolonged stable disease [20].

In three researches we included, the patients in two studies had been previously treated with at least imatinib and sunitinib. Only in Baly et al's research, these patients had not undergone any medication [21], the clinical benefit rate of Baly et al's study was significantly higher than the other 2 studies. We considered previous drug treatments caused these patients to develop resistance to these TKIs, given that the most common mechanism of TKIs' resistance is acquisition of secondary mutations in either KIT or PDGFRA in GISTs patients [31]. Therefore, we rec-

Table 3
Some important trials about Regorafenib and ripretinib.

Trial	Phase	Patients	Treatment Dose/Duration	Results
NCT01271712	3	199 Patients with failure of at least previous imatinib and sunitinib	Regorafenib 160 mg daily (n133)vs placebo(n66)	PFS:4.8months vs 0.9months
NCT02606097	2	18patients with metastatic/unresectable GIST,harboring secondary mutation of exon17	Regorafenib 160mg/day on days 1-21 of a 28-day cycle	weeks CBR:93.3% PFS:22.1months
NCT02889328	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:7.3months 1-year survival rates:64.5%
NCT03353753	3	129 Patients with advanced GIST who received prior treatment with at leastmatinib, sunitinib, and regorafenib	Ripretinib 150 mg daily (N85) vs placebo(N44)	PFS : 6.3months v 1 months HR=0.15
NCT03673501	3	358Patients progressed on or have documented intolerance to imatinib	Ripretinib 150 mg daily (N179) vs sunitinib50 mg daily(N179)	completion date is March 2022.

ommend that the treatment of patients with GISTs should be standardized as much as possible, because once the patient is resistant or intolerant, the effect of subsequent treatment will be greatly reduced.

A significant weakness of our study is limit size of included studies, so a large sample study is still necessary for validation in future. In addition, there are still many confounding factors that may prevent us from reaching more accurate conclusions. For example, different drug doses, different treatment options, patient source, age, gender, tumor size, tumor sites, combined with other tumors, and publication bias.

Conclusion

Our meta-analysis suggests that GISTs patients harboring KIT exon 11 mutations may have the best benefit from nilotinib treatment among all known genotypes. However, further study of large sample data is needed to include larger GISTs patient samples in each genotype, longer follow-up, presence of secondary gene mutations, secondary mutation genotypes, and different pre-treatments in different GIST genotypes. These studies will enable us to obtain the best guidance for the treatment of nilotinib in GISTs patients. Based on our meta-analysis, KIT exon 11-mutant GISTs benefit the most from the treatment of nilotinib when. In addition, we recommend that all patients with prior treatment of other TKIs test the mutant genotype again, therefore, GISTs patients can get better individualized treatment.

Authors' contributions

Zhao Z, Zhang J, Zhang W and Zong L performed the majority of study, and Guo S drafted the manuscript; Tan S and Wei H collected and processed the clinical data; You J, Xu Y and Wang J literature reviewed; Chen P data analyzed. All authors read and approved the final manuscript. Zhao Z, Zhang J, and Zhang W revised the manuscript.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in our study.

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Conflict of interest

The authors have declared that no competing interests exist.

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None.

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