Systematic Review and Meta-Analysis

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Relationship between efficacy of sunitinib and KIT mutation of patients with advanced gastrointestinal stromal tumors after failure of imatinib

A systematic review

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Abstract

Background: A large number of studies have shown that KIT mutations are closely related to the prognosis of gastrointestinal stromal tumors (GISTs). At the same time, sunitinib (SU) has become the second-line recommended drug for GISTs because of its efficacy. We initiated a systematic review to compare the efficacy of SU after failure of Imatinib (IM) in different KIT mutations.

Methods: We searched for SU-treated patients with advanced GISTs after failed IM treatment by using databases such as PubMed, EMBASE, and the Cochrane Library, up to March 2018. We conducted statistical analyses to calculate the odds ratio (OR), hazard ratio (HR), and 95% confidence interval (CI) using fixed-effects and random-effects models by Review Manager 5.3 software.

Results: We included a total of 474 patients from 3 retrospective studies and 2 cohort studies. Patients with exon 9 mutations had higher clinical benefit (OR = 2.61, 95% CIs = 1.32–5.18, $P = .006$) rates and longer progression-free survival (progressive disease, HR = 0.51, 95% CIs = 0.36–0.72, $P = .0001$) compared with exon 11, but there was no statistically significant difference in overall survival (OS, HR = 0.93, 95% CIs = 0.34–2.55, $P = .89$) and there was greater heterogeneity ($Tau^2 = 0.72$, $Chi^2 = 21.45$, df = 3, $P < .001$, $I^2 = 86\%$). Subgroup analysis suggests that race may be one of the sources of heterogeneity.

Conclusion: The results show that efficacy of SU is closely associated with KIT genotypes in GISTs. Moreover, racial factor also directly affects the prognosis of different KIT mutational status, so GISTs patients of different genotypes might also consider the use of targeted drugs in consideration of ethnic differences.

Abbreviations: CB = clinical benefit, CI(s) = confidence interval(s), CR = complete response, GISTs = gastrointestinal stromal tumors, HR = hazard ratio, IM = imatinib, M/F = male/female, N/A = not available, OS = overall survival, PD = progressive disease, PDGFRA = platelet-derived growth factor receptor alpha, PFS = progression-free survival, PR = partial response, SD = stable disease, SU = sunitinib.

Keywords: gastrointestinal stromal tumors, imatinib, KIT mutation, sunitinib, systematic review

1. Introduction

Gastrointestinal stromal tumors (GISTs) are a common primary sarcoma in the gastrointestinal tract, accounting for nearly 2% of all gastrointestinal tumors.[1] The biological behavior of GISTs varies, which is related to the tumor size and mitotic rate. The majority of GISTs contain an activating mutation in gene encoding KIT or platelet-derived growth factor receptor alpha (PDGFRA) receptor tyrosine kinase.[2,3] Roughly speaking, 95% of the GISTs would express cell-surface transmembrane receptor KIT with tyrosine kinase activity.[4] The resulting abnormal receptor tyrosine kinases are superior targets for treatment with tyrosine kinase inhibitors. A large amount of researches have shown that tumor survival, angiogenesis, and resistance to anticancer treatment are derived from mutations of KIT.[5,6]

Currently, advanced or metastatic GISTs remain a huge challenge which resists general chemotherapy. Imatinib (IM) which is a selective inhibitor of KIT and PDGFRA and it is also the first tyrosine kinase inhibitor (TKI) approved for the therapy of advanced GISTs.[7] IM is considered a standard first-line therapy for its beneficial effects to advanced GISTs. However, the

Editor: Xiao-Dong Chen.

No funding or financial support was received for this study.

The authors have no conflict of interest to disclose.

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Medicine (2019) 98:19(e15478)

Received: 12 November 2018 / Received in final form: 3 April 2019 / Accepted: 8 April 2019

http://dx.doi.org/10.1097/MD.0000000000015478

clinical benefits observed in GISTs patients with IM vary according to KIT and PDGFRA genotype.[8–10] A number of multicenter trials have compared the prognosis of IM treatment with different advanced GISTs genotypes, and Demetri's study reported that mutations of the KIT gene in GISTs occur most frequently in KIT exon 11, followed by those in KIT exon 9, and tumors containing deletions in the KIT exon 11 are clinically more aggressive than tumors with other types of mutations.[11,12]

Resistance and intolerance to IM is one of serious problems in practical use.[13] About 5% to 14% of GISTs patients show evidence of primary resistance to IM.[14] Even high doses of IM frequently do not significantly improve the prognosis.[15] Sunitinib (SU) is another small-molecule TKI that selectively targets KIT and PDGFRs, all 3 isoforms of vascular endothelial growth factor receptor, FMS-like tyrosine kinase 3, colony-stimulating factor 1 receptor, and glial cell line-derived neurotrophic factor receptor (rearranged during transfection).[16] International, randomized, double-blind Phase III clinical trials have demonstrated the clinical benefit of SU in patients with IM resistance or intolerance to failure in advanced GISTs, which led to the approval of SU as a second-line therapy for GISTs in many countries.[17] Similarly, clinical benefit has a relationship with SU-treated patients with GISTs is thought to be influenced by mutational status. Like the other inhibitors of tyrosine kinase, SU works by means of targeting certain constitutive activated sites of tyrosine kinase caused by gain-of-function mutations.[18,19] Considering of the lack of large-sample, multi-center clinical RCTs, the potential predictive value of KIT mutation on the efficacy of SU against GISTs after failure of IM therapy remains obscure. Although, it is essential to predict the mutation's response to prognosis after treatment of SU.

In the present study, we performed a systematic review on patients treated with SU after failed IM treatment to analyze and summarize the clinical effect and prognostic value of genotypes of KIT exon 9 and exon 11 mutational status in GISTs.

2. Materials and methods

Ethical approval or patient consent was not required due to the present study is a review of previously published literatures.

2.1. Searching strategy

Our present study was shown related results in adherence to the PRISMA statement.[20] This study was used medical subject headings and keywords to search comprehensively in databases such as PubMed, EMBASE, and Cochrane library was conducted up to March 2018. We used the following keywords

"Gastrointestinal Stromal Tumors," "Imatinib Mesylate," "Sunitinib." The searching fields for these terms are set to: title/abstract. These terms were contacted by "AND" or "OR." Only published studies of English full-text articles on human subjects could be included. Other than this, we also searched for the reference of included articles and relevant reviews manually. We contacted a part of authors to acquire complete raw data information if necessary.

2.2. Inclusion and exclusion criteria

Our inclusion criteria were as follows:

(1) subjects were patients diagnosed with advanced GISTs, without other malignant tumors;
(2) SU was used as a treatment after failure with IM treatment;
(3) without chemotherapy, or have ended chemotherapy for more than 4 weeks;
(4) the pathological data was complete, and primary tumor tissues were obtained for c-KIT mutations;
(5) clinical outcomes included the following outcomes: complete response (CR), partial response (PR), stable disease (SD), or clinical benefit (CB: defined as the percentage of patients who experienced a CR, PR, or SD lasting at least 24 weeks as per RECIST);
(6) included at least: progression-free survival (PFS) or overall survival (OS), with 95% confidence interval (CI).

The exclusion criteria were:

(1) duplicated publications;
(2) reviews, letters, case report, or comments.
(3) Subjects taking other drugs that may affect outcomes (eg, immunosuppressive agents, etc);
(4) patients concurrently used other treatments during the experiment (eg, surgery, radiofrequency ablation, etc);
(5) incomplete or useless data.

2.3. Data extraction

One investigator performed data extraction while another one checked independently for accuracy. This study extracted following information: author, publication year, study location, study design, sample size, patient age, gender ratio, mutational status, and outcomes (included: PFS, OS, CR, PR, SD, PD, CB). In the survival analysis, some included studies have not published hazard ratio (HR) and 95% CI. Studies must show the definitive number of patients with KIT exon 9 and exon 11 mutation, along with the number of observed GISTs progression or death, so that we are able to achieve mathematical HR approximation by established methods.[21] When the vital data has not been published entirely, but a Kaplan–Meier curve was provided, data can extract from the curve by Engauge Digitizer version 10.4.[22]

2.4. Quality assessment

Two independent investigators performed quality assessment of each included studies. The included cohort and retrospective studies were on the basis of the Newcastle–Ottawa scale. We graded quality in 3 fields which include the selection of research group, group's comparability, and outcomes or exposure. A score of study at least 5 is considered to be of high quality. Different authors discussed to resolve the discrepancies of quality assessment in the results respectively.

2.5. Statistical analysis

All analysis was performed by Review Manager 5.3 provided by Cochrane Collaboration. Heterogeneity between studies was checked by chi-square test and I^2. Odds ratio (OR) and HRs with 95% CIs were calculated by fixed or random effect model depending on heterogeneity (a fixed effect model for I^2 not more than 50% while a random effect model for I^2 more than 50%). A systematic review compared the OR of CB and the HR of PFS and OS in c-KIT exon 9 and exon 11 in patients with advanced GISTs using SU after the failure of IM therapy.[23] Publication bias was detected by using Funnel plot. One study was removed at a time to assess the resulting stability as a sensitivity analysis. For all analysis, P values less than .05 indicated statistical significance.

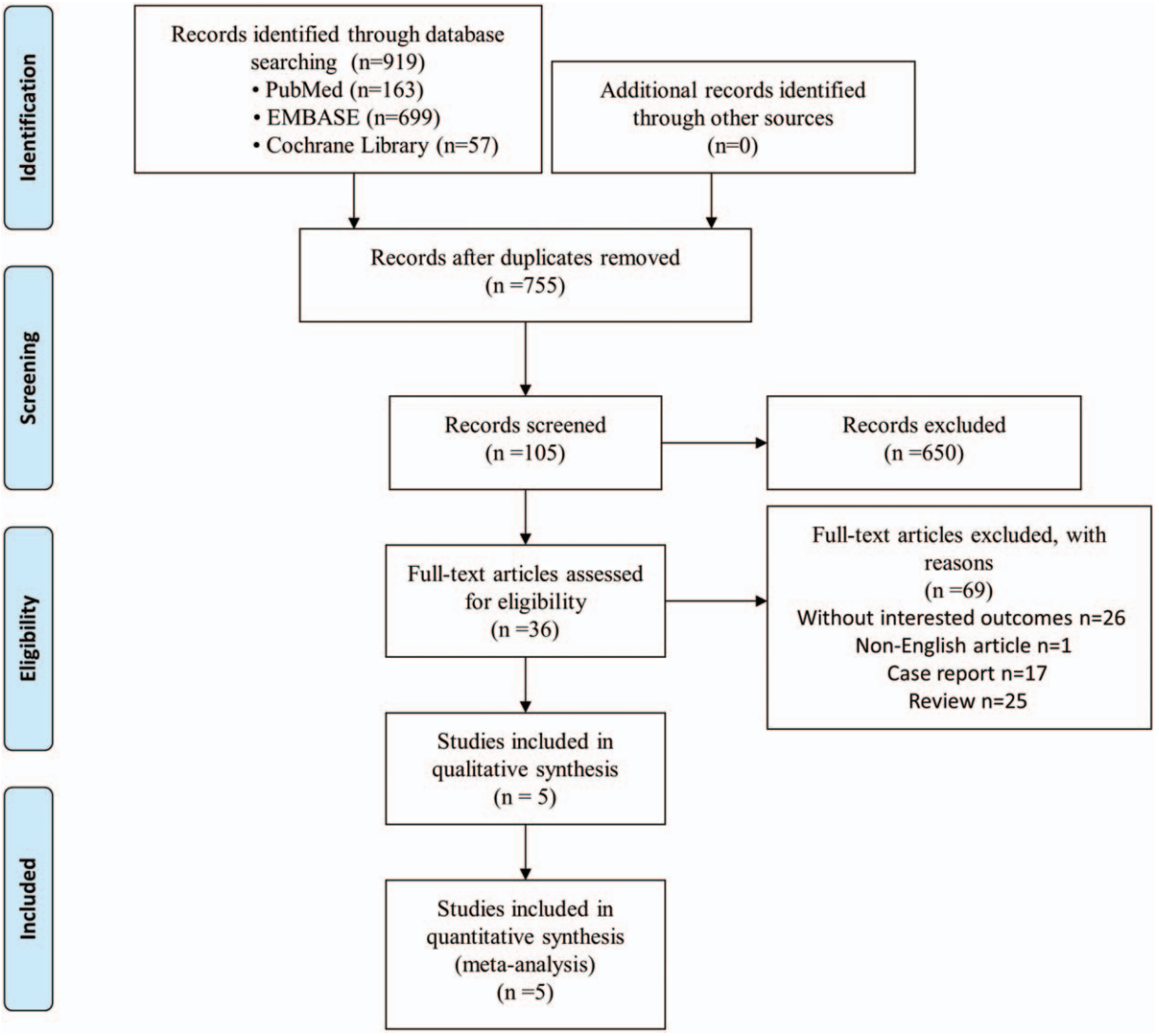

Figure 1. Flow diagram of identifying relevant studies.

3. Results

3.1. Characteristics of the included studies

There were identified 163 articles, 699 articles, and 57 articles, respectively searched from PubMed, EMBASE, and Cochrane Library. A total of 36 citations were thought to be potentially relevant after reviewing titles and abstracts. A total of 10 articles satisfied the eligibility criteria after reading the full text carefully. Finally, 5 studies were included in our systematic review.[24–28] Literatures screening flow was shown in Figure 1.

The 5 studies involving 474 patients satisfied the eligibility criteria were reanalyzed in this systematic review. The publication year ranged from 2011 to 2016. The follow-up durations varied among these studies (from 10 to 100 months). The items above are all collected. Their basic characteristics are reported in Table 1.

Table 1

Characteristics of individual studies included in the meta-analysis.

Author	Publication yr	Study location	Study design	Sample size (M/F)	Age, y median (range)	Mutational status	Follow-up, mo	Outcomes
Reichardt et al[20]	2016	Germany	Retrospective	230 (139/91)	60 (11–83)	Exon 9, 11	58–100	PFS, OS, CR, PR, SD, PD
Yoon et al[21]	2012	Korea	Cohort	88 (55/33)	59 (25–76)	Exon 9, 11	19–48	OS, CB
Li et al[22]	2012	China	Retrospective	55 (40/15)	N/A	Exon 9, 11	12–15	PFS, CR, PR, SD, PD
Chen et al[23]	2011	Taiwan	Retrospective	23 (7/16)	59 (24–83)	Exon 9, 11	10–30	PFS, OS, CR, PR, SD, PD
Heinrich et al[24]	2008	USA	Cohort	78 (53/25)	55(26–76)	Exon 9, 11	30-54	PFS, OS

CB = clinical benefit, CR = complete response, M/F = male/female, N/A = not available, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, SD = stable disease.

Table 2

Assessable quality of including studies.

	Selection					Exposure			
Case control studies	Adequate definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Total score
Reichardt et al[20]	–	*	–	*	*	*	*	–	5
Li et al[22]	–	*	–	*	*	*	*	–	5
Chen et al[23]	–	*	–	*	*	*	*	–	5
Cohort studies	Selection	Comparability	Outcome	Total score					
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	outcome of interest was not present at start of study		Ascertainment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Yoon et al[21]	*	–	*	*	*	*	–	*	6
Heinrich et al[24]	*	–	*	*	*	*	–	*	6

* =1, – =0.

As for quality assessment, the quality of included 5 studies was generally high; specific data are shown in Table 2.

3.2. Systematic review regarding the efficacy of SU

3.2.1. Clinical benefit. Four studies reported the data of clinical benefit.[24–27] The combined results showed that There was no heterogeneity among 4 studies ($Chi^2 = 5.14$, df = 3, $P = .16$, $I^2 = 42\%$), so the fixed effects model did. The difference was statistically significant between KIT exon 9 and exon 11 mutations group (OR = 2.61, 95% CIs = 1.32–5.18, $P = .006$), suggesting that group of exon 9 mutations was able to improve the clinical benefit rate, compared with exon 11 mutations group for advanced GISTs patients after failure of IM therapy (Fig. 2).

3.2.2. Progression-free survival. Four studies reported PFS data included 2 genotypes of KIT exon 9 and exon 11 mutations, involving 73 and 221 cases, respectively.[24,26–28] The minor heterogeneity was observed among 4 studies ($Chi^2 = 3.94$, df = 3, $P = .27$, $I^2 = 24\%$), so the fixed effects model was used. The results show that the difference was obvious statistically significant (HR = 0.51, 95% CIs = 0.36–0.72, $P = .0001$). It showed that the efficacy of SU in the treatment of KIT exon 9 mutations compared with exon 11-induced GISTs was superior in the PFS rate (Fig. 3A).

3.2.3. Overall survival. Four studies reported OS data included 2 genotypes of KIT exon 9 and exon 11 mutations, involving 78 and 246 cases, respectively.[24,25,27,28] Because of significant heterogeneity observed among 4 studies ($Tau^2 = 0.72$, $Chi^2 = 21.45$, df = 3, $P < .001$, $I^2 = 86\%$), a random effects model was used. The results showed no statistically significant difference (HR = 0.93, 95% CIs = 0.34–2.55, $P = .89$), suggesting that no mutations of either exon 9 or exon 11, there was no apparent longer OS (Fig. 3B).

3.2.4. Subgroup analysis. Due to the significant heterogeneity of OS in this study, the subgroup analysis was used to explore the source of heterogeneity. The specific results are shown in Figure 4. The subgroup data of OS of Asian and other countries are statistically different respectively. And each subgroup of the heterogeneity is significantly lower ($I^2 = 0$). The ethnic differences may be one of the sources of heterogeneity for this research. There was no statistically significant difference in analysis methods, year of publication, the initial dose of IM, or SU dose.

3.2.5. Sensitivity analysis. A sensitivity analysis was performed to explore potential sources of heterogeneity. The pooled ORs of CB for patients with advanced GISTs after the failure of IM therapy in exon 9 and exon 11 were not significantly changed, while the pooled HRs of PFS for patients in KIT exon 9 and exon 11 mutations were not significantly changed, which confirmed the stability of these 2 analyses. One study affected the OS result for patients with advanced GISTs after the failure of IM therapy in exon 9 and exon 11.[25] Consistent with the conclusion that the aforementioned, race may be one of the sources of heterogeneity.

3.2.6. Publication bias. Due to the small number of included studies (n = 5), the funnel bias was not used for publication bias analysis.

4. Discussion

According to the latest NCCN Clinical Practice Guidelines in Oncology of the GIST, regardless of the limitations or widespread of GISTs for first-line treatment (IM 400 mg/d) after the failure, the program to SU treatment has been changed by 2A

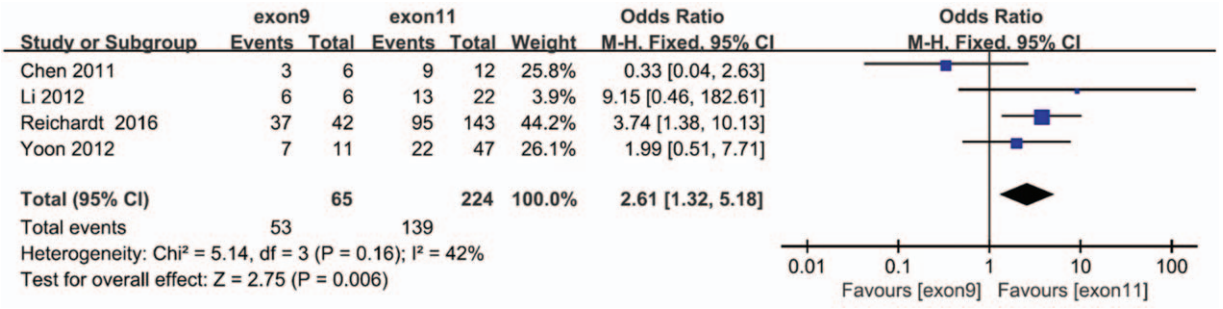

Figure 2. Forest plot diagrams of CB for patients with advanced GISTs after the failure of IM therapy in exon 9 and exon 11. CB = clinical benefit, GISTs = gastrointestinal stromal tumors, IM = imatinib.

Recommended for category 1.[29,30] Mutation testing for patients with advanced GISTs has been recommended by NCCN before taking TKIs to predict drug response. Related studies have demonstrated the efficacy of different genotypes of GIST treated with IM. There is a 2.29-fold improvement in cumulative response of KIT exon 11-mutant group compared with exon 9-mutant group. GISTs patients with KIT exon 9 mutations have higher risk of progression than those with exon 11 mutations, and 5-year RFS rate was significantly higher in patients with KIT exon 11 deletion than in those with other types of KIT exon 11 mutations. But there is not consistent suggest for SU in the current studies.[31–34] Therefore, to further evaluate the efficacy of SU treatment on different genotypes of advanced GISTs after failure of IM therapy, we did this systematic review to identify the better reference for the treatment of GISTs patients.

To the best of our knowledge, this is the first systematic review to illustrate a significant benefit from SU therapy for advanced GISTs after failure of IM therapy who harbor a KIT mutation in PFS and OS. More importantly, the present systematic review revealed that clinical benefits of patients with advanced GISTs after failure of IM therapy is associated with types of KIT mutations. Regardless of ethnicity, the overall incidence of clinical benefit and PFS was higher in patients with exon 9 mutations compared to KIT exon 11. We also did a subgroup analysis to demonstrate the possible benefits from SU treatment for advanced GISTs who harbor a KIT mutation in OS in Asian and other people respectively. In Asian group, we found that the OS of GISTs patients with KIT exon 9 mutations was significantly higher than that of patients with KIT exon 11 mutations, and other groups excluding Asians showed the opposite result. It might be that the SU sensitivity of different types of KIT mutations in different populations is different, with the fact that vast majority used standard doses (37.5 mg/d).

It was reported that different mutational subtypes of KIT exon 9 and 11 may have a differential impact on treatment outcome (eg, GISTs with exon 11 deletions are more aggressive than those

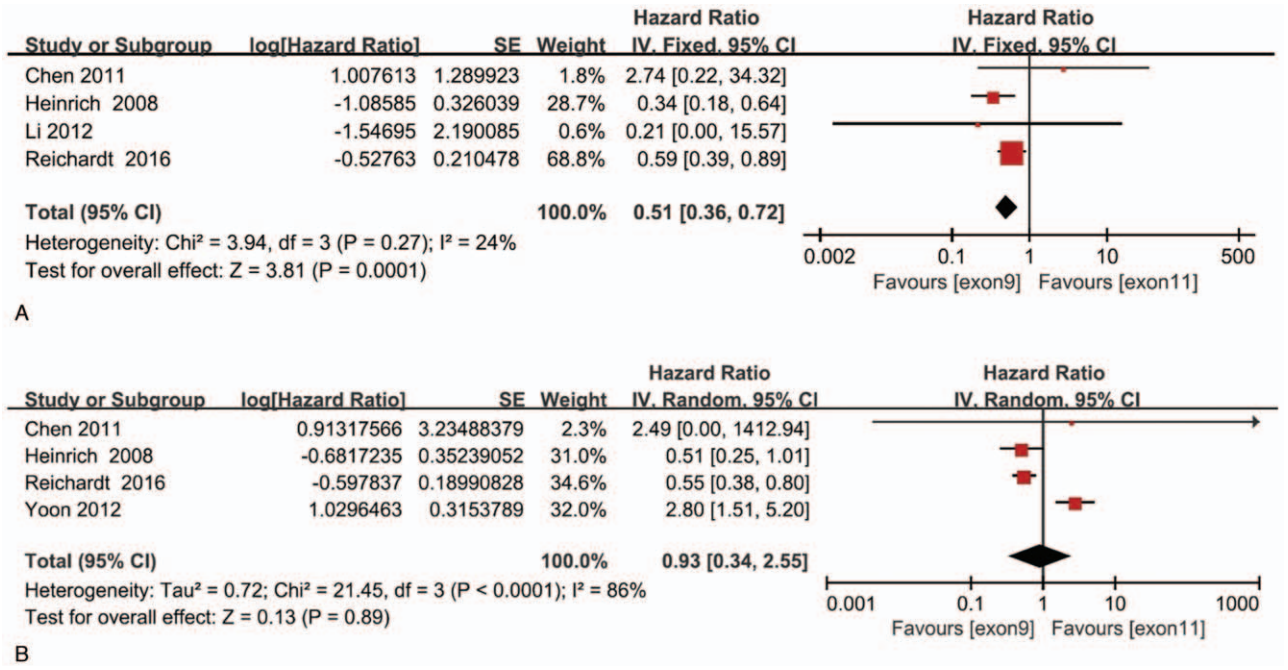

Figure 3. Forest plot diagrams of hazard ratios for patients with advanced GISTs after failure of first-line therapy in exon 9 and exon 11. (A) Progression-free survival. (B) Overall survival. GISTs = gastrointestinal stromal tumors.

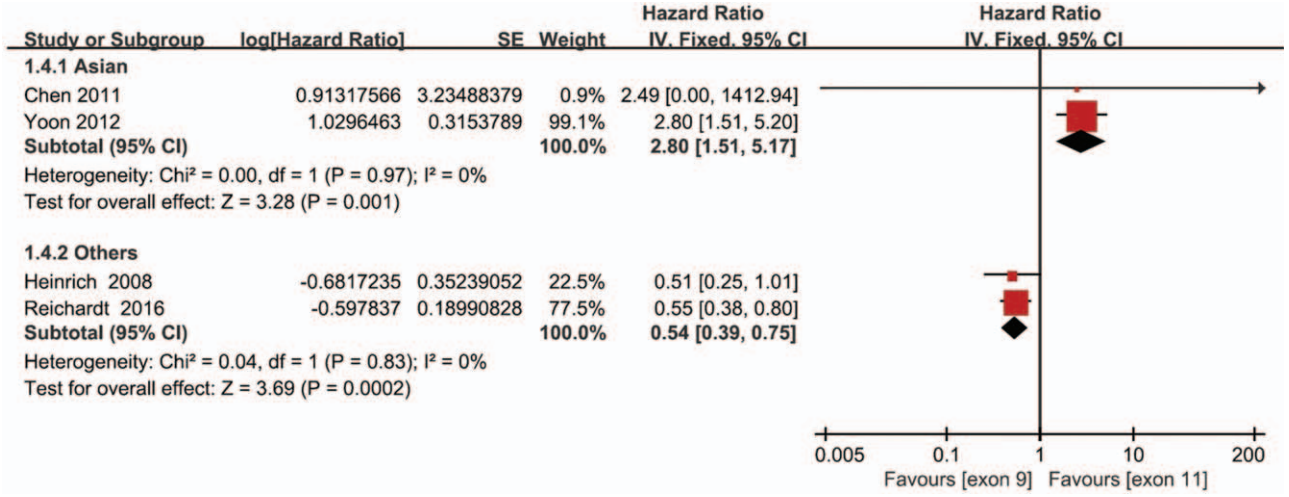

Figure 4. Subgroup of forest plot diagrams of hazard ratios of overall survival for patients with advanced GISTs after failure of first-line therapy in exon 9 and exon 11. GISTs = gastrointestinal stromal tumors.

with substitutions).[35] The following mutation types have been identified in KIT: deletions (del), deletion-insertion (delins), point mutations (pm), duplications (dup), insertions (ins), and inversion (inv).[36] Due to the lack of specific individual information, the actual mutation subtypes included in the study cannot be statistically classified. Although our analysis had limited ability to assess very rare mutational subtypes or impact of various mutations in PDGFRA,[24] we still need to have complete mutation data from included studies to reduce the heterogeneity brought about by different subtypes.

An acquired resistance during IM based treatment has been reported and is linked to secondary KIT or PDGFRA mutations.[31–33,37] Secondary mutations may also influence response to SU.[38–40] Secondary point mutations associated with IM resistance are usually located in the drug/adenosine triphosphate binding pocket of the receptor (encoded by exons 13 and 14) or in the activation loop (encoded by exon 17).[41–44] Unfortunately, information on secondary mutation status of the patients in this study was not analyzable with the limited availability of data (only 1 study provided data about primary and secondary mutations).[28] Given the retrospective nature of some included studies, in some cases, only 1 biopsy was taken for each patient. As a result of this limitation and the fact that biopsy collection timings varied between patients inflated heterogeneity can be concluded from the data.

In addition to above factors, there are still many possible variables which would affect the efficacy of SU in advanced GISTs, including the kinase mutational status pre- and post-treatment, initial SU dose, pharmacokinetics, pharmacodynamics, adherence to therapy, site of the primary tumor, and metastatic site.[45,46] At the same time, due to lack of data and other reasons, we have not conducted statistical analysis of adverse events after SU treatment. This result may also have an impact on the final treatment decisions. The incidence rate of different gene mutations is different between the exon 9 and exon 11 group, and the baseline may be inconsistent, which may affect the accuracy of the results of this systematic review. Therefore, additional research in the future, especially larger, prospective, randomized controlled studies, are needed to evaluate the correlation between mutation status of KIT and/or other genes and their clinicopathological significance in SU-induced GISTs patients after first-line treatment failure. Another limitation of our study is that all survival analysis data, especially HR and CI, were extracted from included studies' results by software, and therefore, individual patient information was lost, and there may be errors with the original information.

SU is currently approved only as second-line therapy for GIST, but studies are being planned to evaluate its efficacy and safety as first-line treatment. And the results of genotyping have become an essential baseline work-up in patients with GIST to predict treatment outcomes and possibly to individualize TKI therapy as a means to maximize clinical efficacy in patients with GIST.[47] The present study may advance understanding of the mechanisms of resistance and may facilitate the development of strategies or therapy to circumvent it.

In conclusion, this systematic review confirms advantages of clinical benefits and PFS of KIT exon 9 mutation group, but as for OS, it could reflect different efficacy through subgroup analysis. In the present study, we first proposed that patients with advanced GISTs after failure of IM in exon 9 mutation had better efficacy with SU than patients with exon 11 mutation in the Asian population. Therefore, determination of differential KIT mutation status is still a potential prognostic marker for GIST patients after failure of IM. For that GISTs is a disease originating from genotype mutations, the biological role and clinical significance of most of the mutation, in GIST pathogenesis and development remain undefined, more high-quality research is required to define better the individualize precision therapy and SU treatment based on tumor genotype characteristics.

Author contributions

F.-M.X. and W.-D.X. contributed equally to this study. F.-M.X. and Y.-X.W. conceived the study idea. X.X. and Y.-H.J. performed literature search, study selection, and data extraction. F.-M.X. performed statistical analyses and interpretation of corresponding results. F.-M.X. drafted the initial manuscript. W.-D.X. proposed valuable suggestions for revising the manuscript and carefully edited the entire manuscript. Y.-X.W. had primarily responsibility for the final content.

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