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Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumor after failure with imatinib and sunitinib treatment

A meta-analysis

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Abstract

Aims: This meta-analysis aimed to evaluate the safety and efficacy of regorafenib as a treatment for patients with advanced (metastatic and/or unresectable) gastrointestinal stromal tumor (AGIST) after developing resistance to imatinib and sunitinib.

Methods: A literature search of databases such as PubMed, Embase, and Cochrane library was conducted up to February 2017. The pooled percentages and the corresponding 95% confidence intervals (CIs) were calculated using the Stata 11.0 software.

Results: Four studies involving 243 patients with AGIST were included. Results revealed that approximately 49% (95% CI 30–67), 14% (95% CI 5–23), and 41% (95% CI 21–61) of patients with AGIST showed clinical benefit (including complete response), partial response, and stable disease, respectively, after regorafenib treatment, which was given after failure with imatinib and sunitinib treatments. No complete response was found in the included studies. Pooled progression-free survival was 6.58 months (95% CI 4.62–8.54). Hypertension (20%; 95% CI 7–33), hand–foot skin reaction (22%; 95% CI 17–27), and hypophosphatemia (18%; 95% CI 5–41) were common grade ≥3 regorafenib-related adverse events in patients treated with regorafenib after failure with imatinib and sunitinib treatments.

Conclusions: Forty-nine per cent of patients with AGIST benefited after regorafenib treatment after the development of resistance to imatinib and sunitinib. More studies should be performed to improve the clinical survival of patients with AGIST. Close monitoring and appropriate management of grade ≥3 regorafenib-related adverse events should be considered during treatment.

Abbreviations: AGIST = advanced (metastatic and/or unresectable) gastrointestinal stromal tumor, CB = clinical benefit, CBR = clinical benefit rate, CIs = confidence intervals, CR = complete response, GIST = gastrointestinal stromal tumor, PFS = progression-free survival, PR = partial response, PRR = partial response rate, SD = stable disease, SDR = stable disease rate, VEGF = vascular endothelial growth factor.

Keywords: gastrointestinal stromal tumor, meta-analysis, regorafenib, tyrosine kinase inhibitor

1. Introduction

In the digestive tract, the most common mesenchymal tumor is the gastrointestinal stromal tumor (GIST), which most commonly arises in a gastric location (40%–60%) as a primary disease, with the 2 next most common sites being the small intestine and colon.[1,2] Previous studies found that approximately 80% to 85% of GIST cases have mutations in the oncogene receptor tyrosine kinase (KIT) or Platelet-derived growth factor alpha receptor (PDGFRA).[3,4]

The small molecule imatinib, a tyrosine kinase inhibitor against PDGFRA and KIT, has been approved for treating metastatic or unresectable GIST yearly.[3,5,6] However, delayed resistance to imatinib ultimately develops in the majority of patients with advanced GIST (AGIST), which is mostly caused by secondary mutations in the PDGFRA or KIT gene.[7,8] Then, sunitinib, another inhibitor of PDGFRA and KIT, is used as a second-line therapy after developing resistance to imatinib and has shown clinically meaningful efficacy in phase I to III trials.[9,10] However, drug resistance to sunitinib can also subsequently develop, generally within 1 year of treatment, but there is no proven efficient therapy after failure with imatinib and sunitinib treatment.[11,12]

Many studies have been currently performed to identify effective drugs for treating GISTs after failure with imatinib and sunitinib treatment.[13–15] Among these drugs, regorafenib is an oral multikinase inhibitor, which can block the activity of multiple protein kinases (including KIT, PDGFRA, and other related proteins).[16] Many studies have proved that regorafenib is effective for treating AGISTs after failure with imatinib and sunitinib treatment.[17–21] However, because of the limited sample size in individual studies and the controversial results, no definite

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conclusion has been made regarding its effectiveness. Thus, we performed this meta-analysis to evaluate the safety and efficacy of regorafenib for treating patients with (metastatic/unresectable) AGIST who were resistant to imatinib and sunitinib.

2. Materials and methods

The methods used for this meta-analysis and generation of inclusion criteria were based on preferred reporting items for systematic review and meta-analysis recommendations. A statement of patient consent or the approval of ethics committee is not provided in our manuscript, as it is not relevant for a meta-analysis.

2.1. Literature search strategy

Databases such as PubMed, Embase, and Cochrane library were used for the literature search up to February 2017, using the following keywords: ("gastrointestinal stromal tumor" OR "GIST") AND ("stivarga" OR "regorafenib" OR "second-generation tyrosine kinase inhibitor"). In addition, the references of relevant reviews were searched for additional studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) subjects were patients with metastatic/unresectable GISTs and were aged >18 years; (2) regorafenib was used as a treatment after failure with imatinib and sunitinib treatment; and (3) clinical outcomes included at least 1 of the following outcomes: complete response (CR), partial response (PR), stable disease (SD), progression-free survival (PFS), grade ≥3 treatment-related toxicity, and clinical benefit (CB; defined as the proportion of patients with a clinical outcome of CR, PR, or SD).

The exclusion criteria were: (1) duplicated publications; or (2) reviews, letters, or comments. Only articles with full-text access were included.

2.3. Data extraction

The following data were recorded in a predesigned form: first author name, country, publication year, recruitment time, follow-up duration, sample size, age, sex, treatment, and outcome. Data extraction was independently performed by 2 investigators. Differences were resolved by discussion to ensure consistent evaluation.

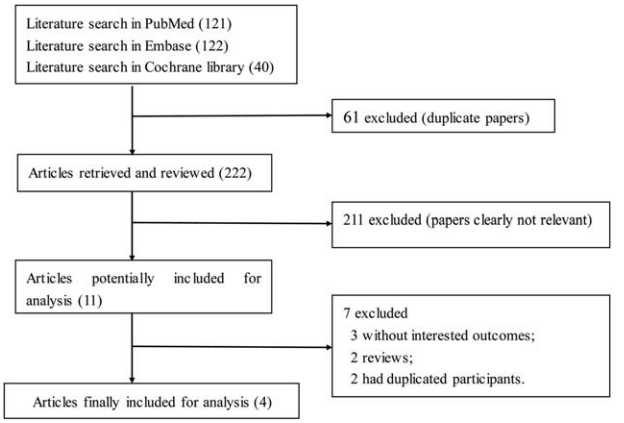

Figure 1. Flow diagram of the study selection process.

2.4. Statistical analysis

The Stata 11.0 software was used for this meta-analysis. The I^2 and Cochran Q tests were used to assess heterogeneity among the included studies, with P values of <.1 or I^2 values of >50% being considered to be significant. An appropriate statistical model (fixed or random-effects model) was used to pool the percentages and corresponding 95% confidence intervals (CIs) based on the results of the heterogeneity test. For all of these analyses, P values <.05 indicated statistical significance.

3. Results

3.1. Characteristics of the included studies

After an initial literature search, 283 articles (PubMed, n=121; Embase, n=122; Cochrane library, n=40) were identified. After excluding duplicates, 222 potentially relevant articles remained. Of these, 211 articles irrelevant studies were excluded by scanning the titles or abstracts, whereas 7 articles were excluded after reading the complete text. Finally, 4 studies[17,19–21] were included in this meta-analysis (Fig. 1).

The 4 studies involving 243 patients with GISTs were reanalyzed in this meta-analysis. The publication year ranged from 2013 to 2016. The recruitment time was between 2010 and 2014. The follow-up durations varied among these studies (from 12 to 44.9 months; Table 1).

Table 1

Characteristics of the included studies.

Study	Year	Country	Recruitment time	Design	Follow up time, mos	Sample size	M/F	Age, y	Outcomes
Ben-Ami et al[21]	2016	USA	February 2010 to January 2014	Cohort	41 (3.2–44.9)	33	19/14	56 (25–76)	CB, PR, SD, PFS, grade ≥3 treatment-related toxicity
Son et al[19]	2016	Korea	December 2012 to December 2013	Cohort	12.7 (0.2–27.6)	57	34/23	56 (50–62)	CB, SD, PFS, grade ≥3 treatment-related toxicity
Kollàr et al[17]	2014	UK	March 2013 to September 2013	Cohort	12.6	20	13/7	68 (45–87)	CB, PR, SD, PFS, grade ≥3 treatment-related toxicity
Demetri et al[20]	2013	Multicenter	January 2011 to August 2011	RCT	12	133	85/48	60 (18–82)	CB, SD, PFS, grade ≥3 treatment-related toxicity

CB=clinical benefit, F=female, M=male, NA=not available, PFS=progression-free survival, PR=partial response, RCT=randomized controlled trial, SD=stable disease.

3.2. Meta-analysis regarding the efficacy of regorafenib

In the 4 included studies, no patients attained CR after regorafenib treatment. However, the rates of PR, SD, and CB were reported and reanalyzed in this meta-analysis.

Among the studies, significant heterogeneity ($I^2 > 50\%$; $P < .001$) was observed for the CB rate (CBR) and SD rate (SDR) (Fig. 2); thus, the random-effects model was used for pooling data. Furthermore, among the studies, no significant heterogeneity ($I^2 = 0\%$; $P = .389$) was observed for the PR rate (PRR); hence, the fixed-effects model was used. The pooled estimate indicated that approximately 49% (95% CI 30–67; Fig. 2A), 14% (95% CI 5–23; Fig. 2B), and 41% (95% CI 21–61; Fig. 2C) of patients with AGISTs attained CB, PR, and SD, respectively, after regorafenib treatment, which was given after failure with imatinib and sunitinib treatments.

Progression-free survival was determined for all 5 studies, and significant heterogeneity ($I^2 = 86.1\%$; $P < .001$) was observed among the studies. This meta-analysis revealed that the pooled PFS was 6.58 months (95% CI 4.62–8.54; Fig. 2D) in patients after regorafenib treatment, which was given after failure with imatinib and sunitinib treatments.

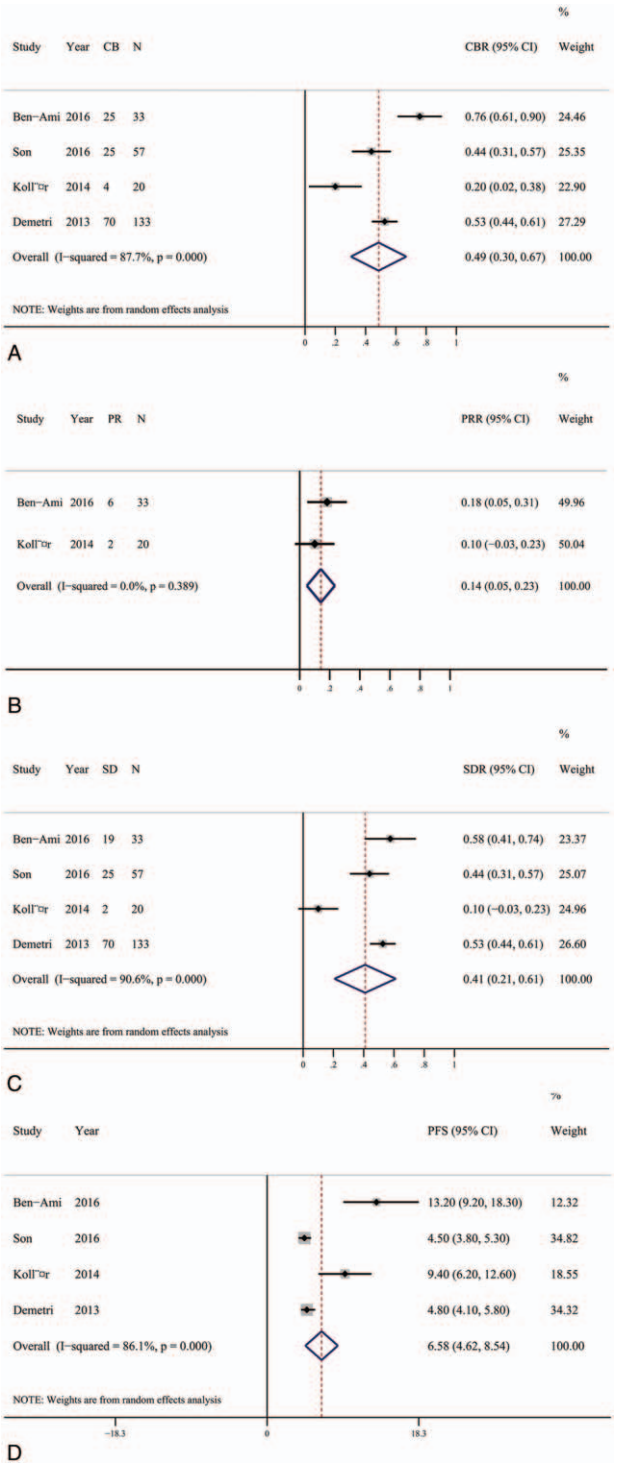

Figure 2. Forest plots for the pooled estimate of the clinical benefit rate (CBR), partial response rate (PRR), stable disease rate (SDR), and progression-free survival (PFS) after failure with imatinib and sunitinib treatment in patients with advanced gastrointestinal stromal tumor. A, CBR; B, PRR; C, SDR; D, PFS.

Table 2

Outcomes of subgroup analyses.

Grade ≥3 treatment-related toxicity	Number of study	Percentage (95% CI)	*P*	I^2 (%)
Hypertension	4	0.20 (0.07, 0.33)	<.001	83.9
Hand–foot skin reaction	4	0.22 (0.17, 0.27)	.129	47.0
Hypophosphatemia	1	0.18 (0.05, 0.31)	—	—
Diarrhea	2	0.06 (0.02, 0.09)	.476	0.0
Fatigue	4	0.03 (0.01, 0.05)	.783	0.0
Vomiting	3	0.01 (0.00, 0.02)	.684	0.0

CI = confidence interval.

3.3. Meta-analysis regarding the safety of regorafenib

Table 2 shows the results for grade ≥3 regorafenib-related adverse events. Among the studies, significant heterogeneity ($I^2 = 83.9\%$; $P < .001$) was observed only in the analysis of hypertension; thus, the random-effects model should be used. Nevertheless, the fixed-effects model should be used for pooling other adverse events owing to the lack of significant heterogeneity ($I^2 < 50\%$; $P > .1$). Pooled data showed that the incidences of hypertension, hand–foot skin reaction, and hypophosphatemia were 20% (95% CI 7–33), 22% (95% CI 17–27), and 18% (95% CI 5–31), respectively, indicating that they were common adverse events. In addition, approximately 6%, 3%, and 1% of patients had diarrhea, fatigue, and vomiting, respectively, among patients with AGIST after regorafenib treatment, which was given after failure with imatinib and sunitinib treatment.

4. Discussion

This study indicates that although no patients showed CR to regorafenib and had limited PFS (6.58 months), approximately 49% of patients with AGIST obtained CB (PR and SD) after regorafenib treatment, after the development of resistance to imatinib and sunitinib. Moreover, grade ≥3 regorafenib-related adverse events, particularly hypertension, hand–foot skin reaction, and hypophosphatemia, should be noted in clinical practice.

Secondary mutations in PDGFRA and KIT genes are the main mechanisms of resistance to imatinib and sunitinib.[12,16,22,23] The effect of regorafenib on AGISTs may occur through other signaling pathways in patients with resistance to imatinib and sunitinib. Apart from inhibiting KIT and PDGFRA, regorafenib is an inhibitor of vascular endothelial growth factor (VEGF) receptors, tyrosine kinase with immunoglobulin and EGF

homology domain 2, and fibroblast growth factor receptors,[16] which are related to the angiogenic pathways.[24–26] Angiogenic markers such as VEGF have some prognostic value in patients with GIST.[27] Moreover, the VEGF pathway may play an important role in the differentiation of GISTs.[28] Thus, we speculated that regorafenib acts via the angiogenic pathways to prevent AGISTs. However, only approximately half of the patients obtained CB, and PFS was only half a year. Therefore, more studies should be performed to explore approaches for improving the effectiveness of regorafenib and the survival of patients with AGISTs after failure with imatinib and sunitinib treatment. Some factors such as age, sex, and follow-up may influence the effectiveness of regorafenib and the survival of patients, which should be investigated in further studies.

In this study, the results showed that hypertension, hand–foot skin reaction, and hypophosphatemia were adverse events with a high incidence in patients treated with regorafenib after failure with imatinib and sunitinib treatment. For patients with cancer undergoing regorafenib treatment, hypertension is a high-risk adverse reaction,[29] which may be associated with the VEGF pathways.[30] Thus, close monitoring for hypertension should be performed, and this condition should be appropriately prevented during regorafenib treatment in patients with GISTs. In addition, monitoring for hypophosphatemia and hand–foot skin reaction, which were the other 2 common adverse events, should be performed for patients treated with regorafenib after failure with imatinib and sunitinib treatments; the mechanisms should be explored in further studies.

As the first meta-analysis to evaluate regorafenib as a treatment in patients with AGIST, some limitations of this study should be noted. First, the number of included studies and the sample size were small. Second, no comparison between regorafenib and a placebo was performed because of a lack of sufficient clinical control studies. Third, significant heterogeneity was observed among the studies. Confounding factors such as ethnicity, study design, follow-up duration, and age may be sources of heterogeneity. However, no subgroup analyses based on these confounding factors were performed because of a lack of sufficient data. In addition, Son et al[19] and Kollàr et al[17] did not report any mature data. Further clinical control studies should be performed with a large sample size to verify the benefit of regorafenib as a treatment after the development of resistance to imatinib and sunitinib in patients with AGISTs.

5. Conclusions

In conclusion, our results indicate that the effectiveness of regorafenib and patient survival need to be improved after failure with imatinib and sunitinib treatment in patients with AGIST. Moreover, close monitoring of potential grade ≥3 regorafenib-related adverse events, particularly hypertension, hand–foot skin reaction, and hypophosphatemia, should be performed during treatment.

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