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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A comparison of regorafenib and fruquintinib for metastatic colorectal cancer: a systematic review and network meta-analysis

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Abstract

Background The optimal treatment in the third-line and later-line setting for metastatic colorectal cancer (mCRC) has not been established. As reported, regorafenib and fruquintinib have shown to be superior to placebo in mCRC. However, no direct clinical comparison of regorafenib and fruquintinib has been conducted; we performed a systematic review and network meta-analysis to compare the efficacy and safety of regorafenib and fruquintinib.

Methods PubMed, Embase, and the Cochrane Library were systematically searched and randomized-controlled trials (RCTs) assessing the effect and safety of regorafenib or fruquintinib versus placebo for patients with mCRC were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. After that, we performed pairwise direct meta-analyses (regorafenib vs. placebo and fruquintinib vs. placebo) and indirect comparison (regorafenib vs. fruquintinib) using network meta-analyses methods.

Results Three RCTs involving 1380 patients were included in the meta-analysis. In the direct meta-analysis, regorafenib and fruquintinib both showed survival benefits when compared with placebo. For the indirect comparison, fruquintinib shows no significant difference in OS compared to regorafenib (HR 0.97; 95% CI 0.64–1.46). Regarding PFS, there was a tendency that fruquintinib was superior to regorafenib (HR 0.65; 95% CI 0.39–1.08); however, there was no statistic difference. For the safety analysis, in indirect comparison, fruquintinib showed significant difference in all-grade toxicity compared to regorafenib (OR 0.73; 95% CI 0.65–0.82), especially in subgroup of proteinuria (OR 0.31; 95% CI 0.11–0.86). For the grade 3–5 toxicity, fruquintinib showed no significant difference when compared with regorafenib (OR 0.92; 95% CI 0.64–1.32).

Conclusion Based on efficacy and safety, there was a tendency that fruquintinib was superior to regorafenib, as a whole, regorafenib and fruquintinib demonstrated similar clinical benefit for patients with refractory mCRC. It seems that fruquintinib has less toxic in all-grade toxicity when compared with regorafenib.

Keywords Comparative effectiveness · Network meta-analysis · Metastatic colorectal cancer · Regorafenib · Fruquintinib

Introduction

Colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality in global, accounting for an estimated 1.8 million new colorectal cancer cases and 881,000 deaths in 2018 (Bray et al. 2018; Ferlay et al. 2019). At the time of diagnosis, only 20% of patients have metastatic disease; however, some patients will develop disease progression in the course of the disease. First-line and second-line treatment options for patients with metastatic colorectal cancer (mCRC) include doublet or triplet chemotherapy plus a targeted biologic, such as epidermal growth factor receptor (EGFR) inhibitor for RAS wild-type (WT) disease. For patients with mCRC who are refractory to these therapies or for whom standard therapies, regorafenib and trifluridine/tipiracil (TAS-102) are available in the third-line and later-line setting. Regorafenib is an oral multi-kinase inhibitor which inhibit angiogenic kinases (VEGFR1/3, PDGFR, and FGFR) and mutant oncogenic kinases (KIT, RET, and B-RAF), it was approved in 2012 (US Food and Drug Administration 2012).

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The pharmacological properties, efficacy, and tolerability of regorafenib have been reviewed previously by many clinical trials (Bozzarelli et al. 2016; Hofheinz et al. 2016; Jprn 2013; Ciardiello et al. 2015; Kopeckova et al. 2017). Meantime, TAS-102 is an orally administered drug, which is a fixed combination (1:0.5) of trifluridine and tipiracil hydrochloride. It mainly inhibits thymidine phosphorylase to inhibit tumor growth and was approved in 2015 (Lenz et al. 2015; Marcus et al. 2017). A few clinical trials also showed that TAS-102 improved the overall survival (OS) and progression-free survival (PFS) moderately (Mayer et al. 2015; Yoshino et al. 2012). However, regorafenib and TAS-102 were associated with only modest improvement in OS and PFS in patients with mCRC who have progressed after the standard therapy, some patients even have obvious toxicity in clinical practice. Thus, the optimal treatment in the third-line and later-line setting has not been established. Recently, fruquintinib, an oral multi-kinase inhibitor which potently and highly inhibits angiogenic kinases (VEGFR1/2/3), showed strong anti-tumor activity in various preclinical models (Sun et al. 2014; Gu et al. 2014). In a phase Ib study with 42 participants, fruquintinib showed promising anti-tumor activity and tolerable toxicities (Cao et al. 2016). In another phase II study, 71 patients were randomly allocated to fruquintinib and placebo, and PFS was significantly improved with fruquintinib versus placebo (4.73 vs. 0.99 months, HR 0.30; 95% CI 0.15–0.59). However, the median OS showed no significant difference between fruquintinib and placebo (7.72 vs. 5.52 months, HR 0.71; 95% CI 0.38–1.34) (Xu et al. 2017). In the phase III study, of the 416 randomized patients, oral fruquintinib resulted in a statistically significant increase in PFS and OS compared to placebo (PFS: 3.7 vs. 1.8 months, HR 0.26; 95% CI 0.21–0.34; OS: 9.3 vs. 6.6 months, HR 0.65; 95% CI 0.51–0.83). Based on the present trials, fruquintinib showed good performance in safety and efficacy and might be a suitable treatment for mCRC resistant to standard treatment.

A comparison of regorafenib and TAS-102 for mCRC demonstrated that regorafenib and TAS-102 have similar efficacy, but regorafenib was associated with more toxicity compared with TAS-102 using network meta-analysis (Abrahao et al. 2018). However, to date, no clinical comparison of regorafenib and fruquintinib has been reported, we performed a systematic review and network meta-analysis to assess the efficacy and safety of regorafenib versus fruquintinib (Fig. 1).

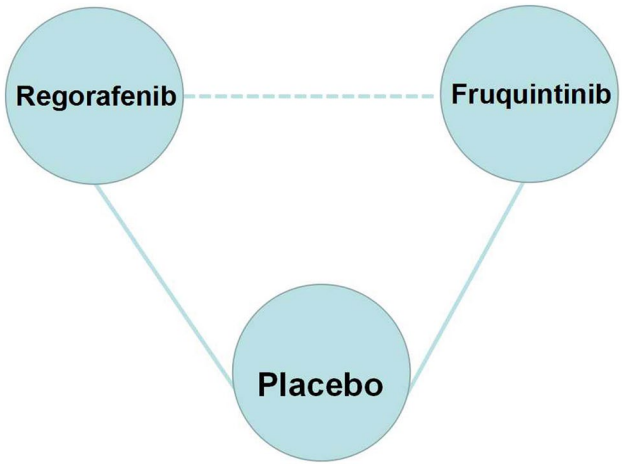

Fig. 1 Network of treatment comparison

Materials and methods

Search strategy

These systematic reviews and meta-analysis were conducted according to PRISMA guidelines (Knobloch et al. 2011).

We searched PubMed, Embase, and the Cochrane Library from inception until 15 April 2019 for relevant articles. The search strings were based on MeSH terms, including: "Colorectal cancer", "Regorafenib", and "Fruquintinib". These terms were used in different combinations and no limitation was placed on publication status or language. The reference lists of retrieved studies and relevant reviews were also searched to identify additional eligible studies missed by the search strategies, the process was performed repeatedly until no further article was found. Two investigators independently performed the reference search; when disagreement appeared, a third investigator was consulted.

Inclusion and exclusion criteria

The inclusion criteria were determined on the basis of "PICOS" principle: P, population: adult patients with mCRC; I, intervention: Fruquintinib or Regorafenib; C, comparison: Placebo; O, outcomes: effect and safety; S, study: randomized, controlled phase III trial. The outcomes should include overall survival (OS, time from randomisation to death from any cause), progression-free survival (PFS, time from randomisation to first radiological or clinical finding of disease progression or death from any cause), all-grade toxicity, and at least or over than grade 3 toxicity (toxicity G3–5).

The exclusion criteria were: (1) studies lacking data integrity; (2) duplicate studies, systematic reviews, case–control studies, or nonhuman studies.

Data extraction

Two investigators independently extracted data from the included articles, including publication time, country, characteristics of enrolled patients, sample size, the regimens of

therapy, study design, the primary end point, the secondary endpoints, and outcomes of the various subgroups.

The primary end point outcomes were OS, and the secondary endpoints included PFS, all-grade toxicity, and grade 3 or higher toxicity.

Statistical analysis

The meta-analysis was conducted using RevMan software version 5.3 (Cochrane Collaboration, Oxford, UK). The 95% confidence interval (CI) and hazard ratio (HR) of all results were extracted directly from the trial results, and the relevant variance estimates were calculated from the CIs. The odds ratio (ORs) with 95% CIs for dichotomous outcomes (all-grade toxicity and grade 3–5 toxicity) were also calculated and used to estimate the pooled effects. First, we performed a traditional pairwise meta-analysis of studies that directly compared different treatment modalities (regorafenib vs. placebo and fruquintinib vs. placebo), for the endpoints of OS and PFS, all meta-analyses were performed using random-effects models by HRs with 95% CIs. Second, we performed network meta-analysis indirectly compared regorafenib with fruquintinib through R package "netmeta" (Rucker and Schwarzer 2016; Salanti et al. 2008; Neupane et al. 2014; Caldwell et al. 2005). We did not examine publication bias because of the small number of included trials (< 10).

Assessment for risk of bias

The bias risk assessment was conducted according to the Cochrane's hand book for systematic reviews of interventions (Higgins et al. 2011), which consists of the following five domains: random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting. Two reviewers independently evaluated the methodological quality; a third investigator was consulted when disagreement arose. Each study was evaluated and rated three categories of biases: low risk of bias (when the risk of bias was low in all key domains); unclear risk of bias (when the risk of bias was low or unclear in all key domains); and high risk of bias (when the risk of bias was high in one or more key domains).

Results

Literature search and study characteristics

The flowchart of the selection process and detailed identification are presented in Fig. 2. The initial search through PubMed, Embase, and the Cochrane Library yielded 883 studies; moreover, four studies come from other sources such as reading review. After the duplicate removal, 562 articles were submitted to the first step of the screening. After more detailed evaluation, 50 articles were submitted; of all the remaining reports, 47 were excluded: 3 studies cannot extract the data, 7 studies were phase I/II trials, 2 studies were duplicates, 36 studies were other types of articles such as abstract, review, and case reports. Ultimately, three RCTs were included in the meta-analysis (Li et al. 2015, 2018; Grothey et al. 2013). Figure 2 shows the flowchart of the selection process and detailed identification.

The identified trials are shown in Table 1. These three studies were published between 2013 and 2018, and the accrual periods of these studies were inconsistent, ranging from April 30, 2010 to May 2016. All the three trials were phase III randomized-controlled trials that evaluated the therapeutic efficacy and toxicities of regorafenib or fruquintinib for refractory mCRC who had failed standard chemotherapies (fluoropyrimidines, oxaliplatin, and irinotecan). Biologic therapies vascular endothelial growth factor (VEGF)-targeting drugs (bevacizumab) and epidermal growth factor receptor (EGFR)-targeting drugs (cetuximab and panitumumab) agents in patients with RAS wild-type tumors were allowed but not mandatory. In the CONCUR and CORRECT trial, patients received best supportive care plus oral regorafenib 160 mg once daily or placebo for the first 3 week of each 4 week cycle. The patients were allowed to modified predefined drug dose to manage clinically significant toxic effects. In FRESCO trial, the patients received best supportive care plus oral fruquintinib 5 mg once daily or placebo for the first 3 weeks of each 4 week cycle. Protocol-predefined dose reduction was also permitted to manage significant treatment-related toxic effects.

The characteristics and baseline of the included studies are summarized in Table 2. Among the 3 trials, there were 1380 patients, 641 patients received regorafenib, 278 patients received fruquintinib, and 461 patients received placebo. The CONCUR and FRESCO trials solely involved Asian patients, whereas the CORRECT trial involved White, Asian, and Black patients. In general, the baseline data of CONCUR and CORRECT trials are more detailed. It seems that the ECOG PS and average age of patients in the CORRECT trial were better and older than patients in CONCUR and FRESCO trials, respectively.

Assessment of risk of bias

The risk of bias in included RCTs is summarized in Fig. 3, and the three trials were rated with low risk of bias. No trial was judged to be high risk of bias or unclear risk of bias. Funnel plot analysis for publication bias was not carried out because of the small size.

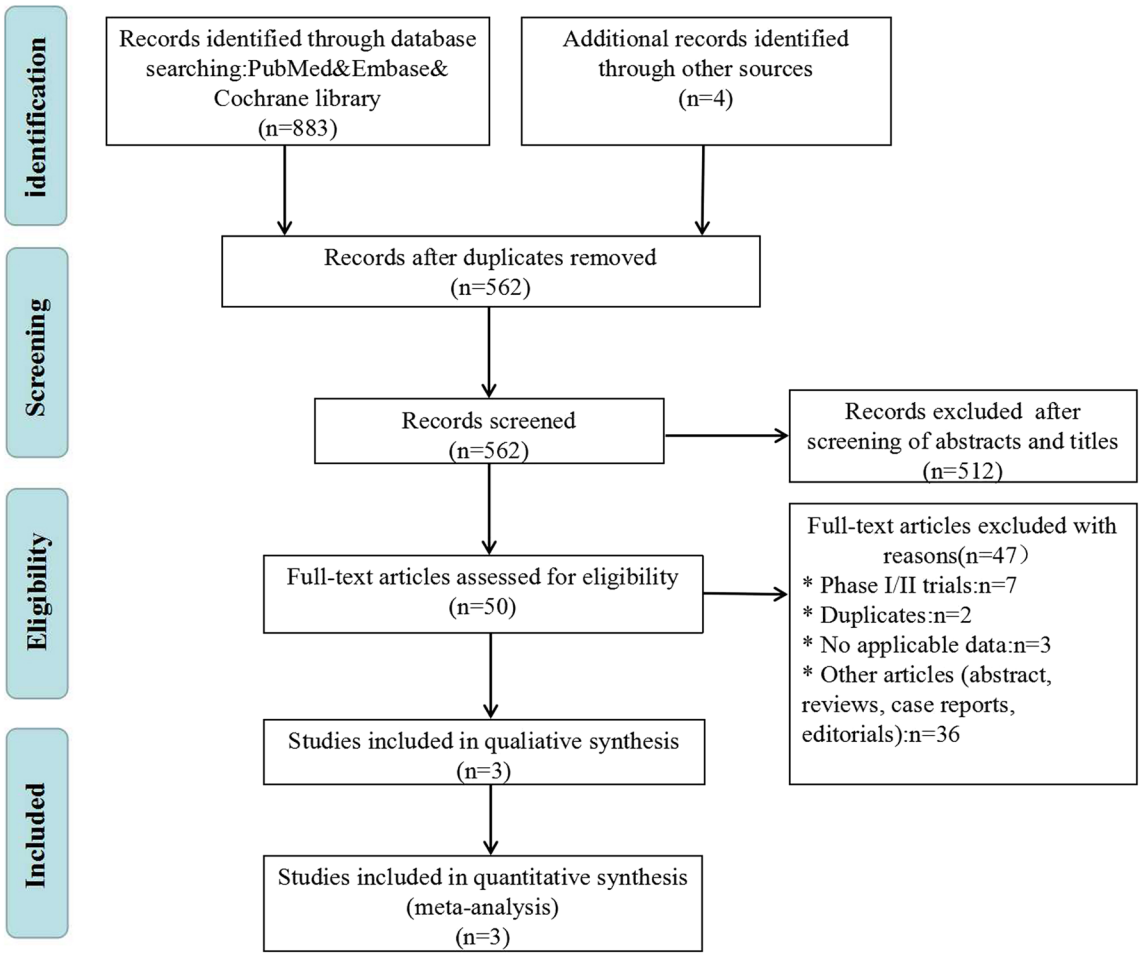

Fig. 2 The flowchart for the selection process and detailed identification

Table 1 Main characteristics of the three RCTs included in the meta-analysis

	CORRECT	CONCUR	FRESCO
Year of publication	2013	2015	2018
Type of study	Prospective phase III randomized trial	Prospective phase III randomized trial	Prospective phase III randomized trial
Primary endpoint	Overall survival	Overall survival	Overall survival
Patients enrolled	mCRC who had progression during or within 3 months after the last standard therapy	mCRC who had received at least two previous treatment lines or were unable to tolerate standard treatments.	mCRC who had progression after at least two previous treatment
Number of patients	760	243	416
Treatment arm	Regorafenib 160 mg once daily on days 1–21 of each 28 day cycle	Regorafenib 160 mg once daily on days 1–21 of each 28 day cycle	Fruquintinib 5 mg once daily on days 1–21 of each 28 day cycle
Control arm	Placebo on days 1–21 of each 28 day cycle	Placebo on days 1–21 of each 28 day cycle	Placebo on days 1–21 of each 28 day cycle

Efficacy

No patients in the three trials had a complete response. First, we performed a traditional pairwise meta-analysis of studies that directly compared different treatment modalities. In an analysis of OS in the direct meta-analysis, regorafenib and fruquintinib both showed survival benefits compared to placebo (regorafenib: HR 0.67; 95% CI 0.48–0.93; fruquintinib HR 0.65; 95% CI 0.51–0.83) (Fig. 4). In the direct pairwise meta-analysis for PFS, regorafenib showed benefit

Table 2 Baseline characteristics of the studies

	CORRECT		CONCUR		FRESCO	
	Regorafenib $N=505$ (%)	Placebo $N=255$ (%)	Regorafenib $N=136$ (%)	Placebo $N=68$ (%)	Fruquintinib $N=278$ (%)	Placebo $N=138$ (%)
Average age (year)	61	61	57.5	55.5	55.0	57.0
Sex						
Man	311 (62)	153 (60)	85 (63)	33 (49)	158 (56.8)	97 (70.3)
Woman	194 (38)	102 (40)	51 (38)	35 (51)	120 (43.2)	41 (29.7)
ECOG PS						
0	265 (52)	146 (57)	35 (26)	15 (22)	77 (27.7)	37 (26.8)
1	240 (48)	109 (43)	101 (74)	53 (78)	201 (72.3)	101 (73.2)
Race						
White	392 (78)	201 (79)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	76 (15)	35 (14)	136 (100)	68 (100)	278 (100)	138 (100)
Black	6 (1)	8 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Nonspecified	31 (6)	11 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Time from diagnosis of metastases						
Median (months)	31.0	29.9	20.3	19.9	NA	NA
<18 months	91 (18)	49 (19)	53 (39)	32 (47)	163 (59)	75 (54)
≥ 18 months	414 (82)	206 (81)	83 (61)	36 (53)	115 (41)	63 (46)
Primary site of disease						
Colon	323 (64)	172 (68)	79 (58)	48 (71)	147 (53)	70 (51)
Rectum	151 (30)	69 (27)	53 (39)	19 (28)	125 (45)	60 (44)
Colon and rectum	30 (6)	14 (5)	4 (3)	1 (1)	6 (2.2)	7 (5.1)
KRAS mutation						
No	205 (41)	94 (37)	50 (37)	29 (43)	157 (56.5)	74 (53.6)
Yes	273 (54)	157 (62)	46 (34)	18 (26)	121 (43.5)	64 (46.4)
Unkown	27 (5)	4 (2)	40 (29)	21 (31)	NA	NA
Prior systemic chemotherapy (second-line or third-line)						
1–2	135 (27)	63 (25)	48 (35)	24 (35)	NA	NA
3	125 (25)	72 (28)	32 (24)	17 (25)	NA	NA
≥ 4	245 (49)	120 (47)	73 (54)	27 (40)	NA	NA
Previous anti-VEGF treatment						
Bevacizumab	505 (100)	255 (100)	56 (41)	25 (38)	84 (30.2)	41 (29.7)
Prior use of EGFR inhibitors	219 (43)	107 (42)	48 (35)	69 (32)	40 (14.4)	19 (13.8)

when compared with placebo (HR 0.40; 95% CI 0.26–0.63). Fruquintinib also showed benefit when compared with placebo (HR 0.26; 95% CI 0.20–0.33) (Fig. 5).

For the indirect comparison, fruquintinib showed no significant difference in OS when compared with regorafenib (HR 0.97; 95% CI 0.64–1.46). There was a tendency that fruquintinib was superior to regorafenib in PFS (HR 0.65; 95% CI 0.39–1.08); however, there was no statistic difference (Fig. 6).

Safety

For the safety analysis, 1372 patients were included. In the CORRECT trial, the toxicity profile of five patients in experimental group was missing, the toxicity profile of one patient in control group was missing in the FRESCO trial, and no patient in each arm was missing toxicity data in the CONCUR trial.

The most common all-grade toxicity and grade 3–5 toxicity of regorafenib in CORRECT, CONCUR trials, and fruquintinib FRESCO trial are shown in Table 3. In indirect comparison, fruquintinib showed significant difference in all-grade toxicity when compared with regorafenib (OR 0.73; 95% CI 0.65–0.82), especially in subgroup of proteinuria (OR 0.31; 95% CI 0.11–0.86) (Fig. 7). For the grade 3–5 toxicity, fruquintinib showed no significant difference when compared with regorafenib (OR 0.92; 95% CI 0.64–1.32). In general, it seems that fruquintinib is safer than regorafenib (Fig. 8).

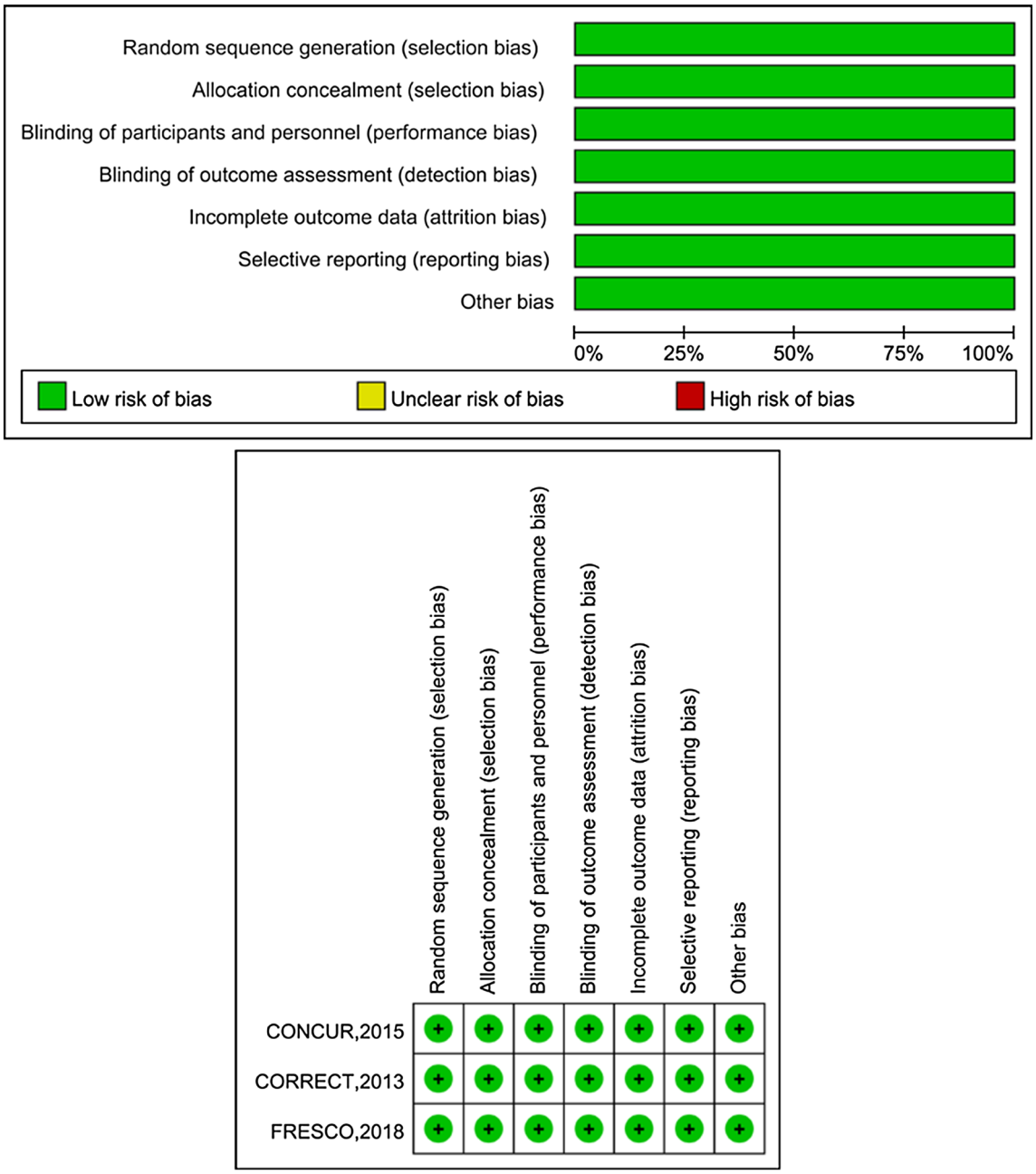

Fig. 3 Risk of bias (upper: risk of bias graph; low: risk of bias summary)

Discussion

The Overall Survival (OS) of patients with metastatic colorectal cancer (mCRC) has been improved much in the last 20 years, and the median OS have reached more than 30 months. This improvement has been driven by several factors, except the improvements of first-line and second-line treatments options [doublet or triplet chemotherapy plus a targeted biologic, such as anti-angiogenic drug or epidermal growth factor receptor (EGFR) inhibitor for patients with RAS wild type], and more available options of third-line and later-line is also an important factor (Benson et al. 2015, 2017; Van Cutsem et al. 2016; Yoshino et al. 2018; Bekaii-Saab et al. 2019; Vogel et al. 2017; Tampellini et al. 2017). Regorafenib and TAS-102 have been approved as salvage treatment drugs for patients with mCRC that progressed after the first-line and second-line chemotherapies. A Comparison of Regorafenib and TAS-102 for mCRC with Network Meta-analysis has shown that regorafenib and TAS-102 demonstrated similar efficacy of these agents, but higher

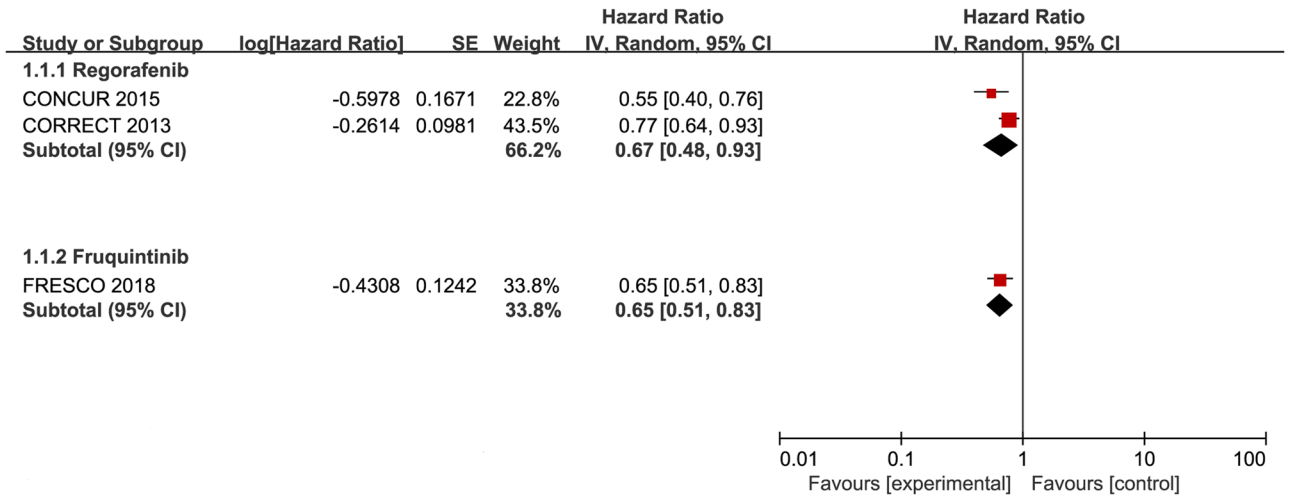

Fig. 4 Direct analysis between regorafenib versus placebo and fruquintinib versus placebo for overall survival

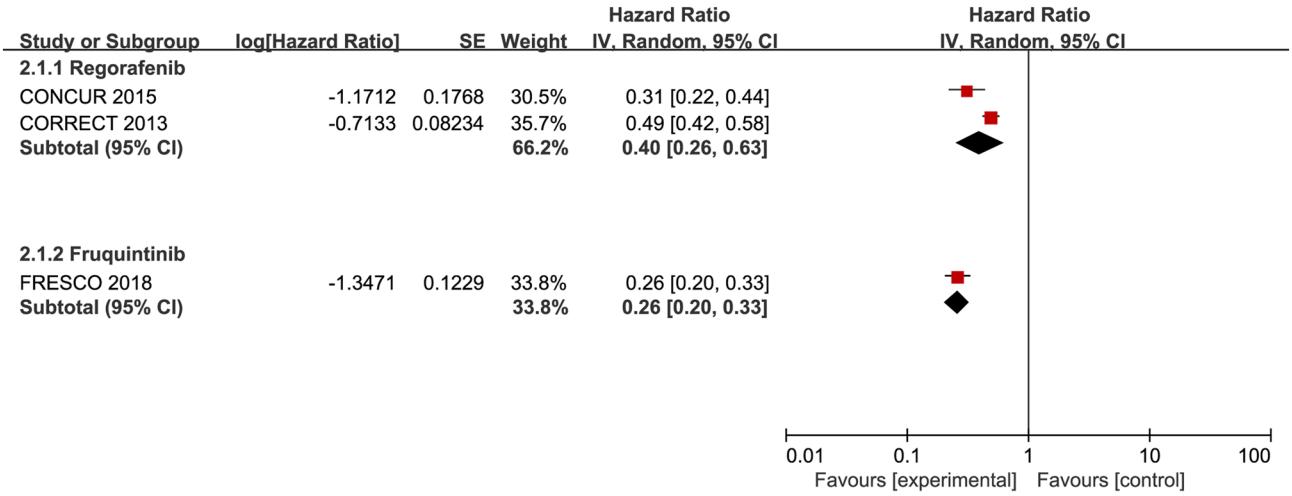

Fig. 5 Direct analysis between regorafenib versus placebo and fruquintinib versus placebo for progression-free survival

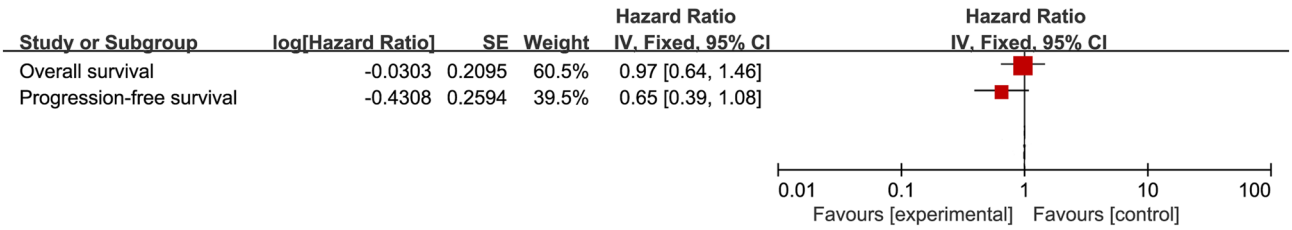

Fig. 6 Indirect analysis of regorafenib and fruquintinib for overall survival and progression-free survival

toxicity with regorafenib in patients with refractory mCRC (Abrahao et al. 2018). After that, a recent research showed that fruquintinib also improved OS and PFS in patients with advanced colorectal cancer who previously treated, compared with placebo. Fruquintinib is a potent and highly selective small molecule inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 tyrosine; it blocks new blood vessel growth associated with tumor proliferation. However, to date, no

Table 3 The most toxicity outcomes

CORRECT: regorafenib					
Any grade	Fatigue (285/500, 57%)	Hand–foot skin reaction (316/500, 64%)	Diarrhea (205/500, 42%)	Anorexia (168/500, 33%)	Hypertension (175/500, 35%)
Grade 3–5 toxicities	Hand–foot skin reaction (83/500, 17%)	Fatigue (51/500, 10%)	Diarrhea (36/500, 7%)	Hypertension (36/500, 7%)	Rash or desquamation (29/500, 6%)
CONCUR: regorafenib					
Any grade	Hand–foot skin reaction (100/136, 73%)	Hyperbilirubinaemia (50/136, 36%)	Alanine aminotransferase concentration increased (32/136, 23%)	Aspartate aminotransferase concentration increased (32/136, 23%)	Hypertension (31/136, 22.8%)
Grade 3–5 toxicities	Hand–foot skin reaction (100/136, 73%)	Hypertension (15/136, 11%)	Alanine aminotransferase concentration increased (9/136, 7%)	Hypophosphataemia (9/136, 7%)	Hyperbilirubinaemia (9/136, 6%)
FRESCO: fruquintinib					
Any grade	Hypertension (154/278, 55%)	Hand–foot skin reaction (137/278, 49%)	Proteinuria (117/278, 42%)	Dysphonia (100/278, 36%)	TSH level elevated (69/278, 25%)
Grade 3–5 toxicities	Hypertension (59/278, 21%)	Hand–foot skin reaction (30/278, 11%)	Proteinuria (9/278, 3%)	Diarrhea (8/278, 3%)	Platelet count decreased (7/278, 3%)

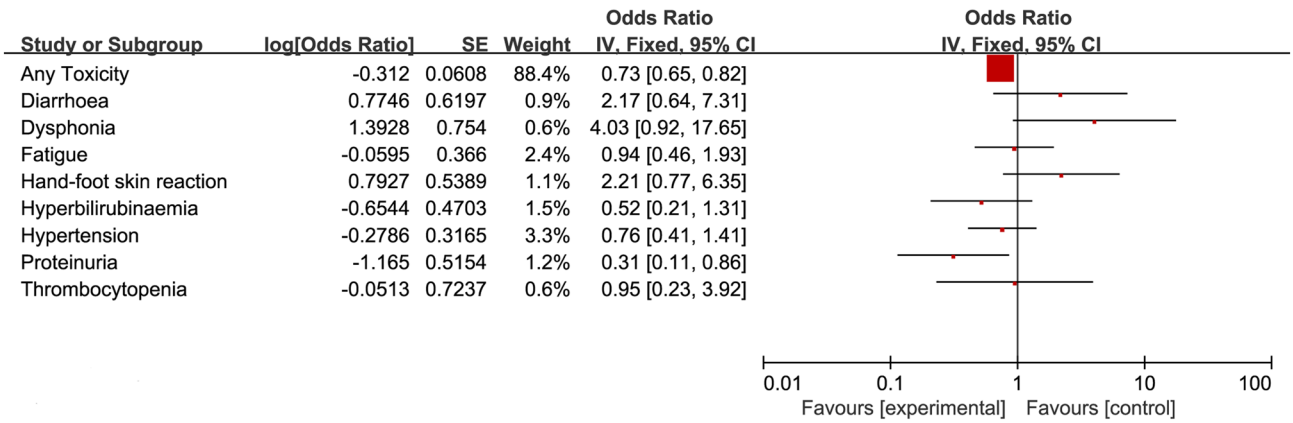

Fig. 7 Indirect analysis of all-grade toxicities between regorafenib and fruquintinib

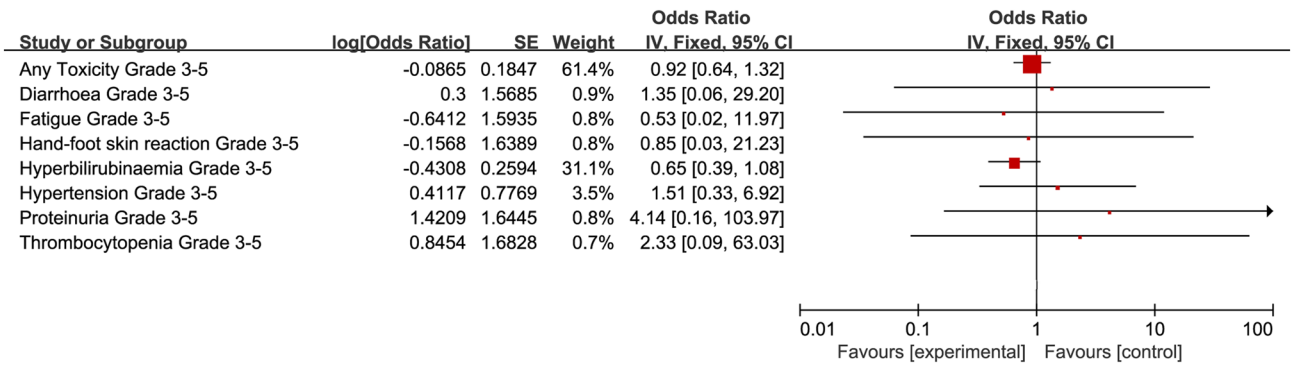

Fig. 8 Indirect analysis of grade 3–5 toxicities between regorafenib and fruquintinib

clinical comparison of regorafenib and fruquintinib has been reported. The aim of this study was to compare the efficacy and safety of regorafenib and fruquintinib in patients with mCRC refractory to standard chemotherapy.

This meta-analysis showed that the baseline characteristics of the three trials were almost similar, but still had some differences. The proportion of patients with ECOG PS 1 in the CONCUR and FRESCO trials was much higher in the CORRECT trial; the scale of race and population in the CORRECT trial was larger than the other two trials. Moreover, in the CORRECT trial, all patients had received previous anti-VEGF treatment, and more patients had prior use of EGFR inhibitors. It is noteworthy that, in the CORRECT trial, regorafenib had a greater effect on OS in the patients with colon cancer than in those with rectal cancer when compared with placebo, the effect of PFS in the patients with colon cancer and rectal cancer was similar. In the CONCUR trial, regorafenib had a greater effect on OS and PFS in the patients who had not previously received targeted treatment than in those had received at least one targeted biological drug. In the FRESCO trial, there were no significant difference on OS between fruquintinib and placebo among women, patients aged ≥ 65 years and patients with right-sided primary tumors; however, fruquintinib had a greater benefit on PFS in the these patients. The small patient numbers in each subgroup and imbalance in the proportion of patients may confounded these results. These results need to be verified in the future work.

Regorafenib and fruquintinib have not been compared in a head-to-head study; our data showed that regorafenib and fruquintinib both showed OS and PFS benefit when compared with placebo. In the indirect comparison, fruquintinib showed no significant difference in OS when compared with regorafenib; however, there was a tendency that fruquintinib was superior to regorafenib in PFS. As a whole, our data concluded that regorafenib and fruquintinib in patients with refractory mCRC both demonstrated similar tumor control (OS and PFS).

Quality of life is crucial to patients with mCRC in the third-line and later-line treatments; therefore, the prevention and management of Adverse Events (AEs) are crucial to best practice for management of this patient population (Byrne and Saif 2019). Unfortunately, regorafenib and fruquintinib both led to adverse events in the majority of patients in the three trials. The most common regorafenib-related AEs observed in the CORRECT and CONCUR trial were hand–foot skin reaction, fatigue, hyperbilirubinemia, and hypertension. The most common fruquintinib-related AEs observed in the FRESCO trial were hypertension, hand–foot skin reaction, proteinuria, and dysphonia. Our data showed that fruquintinib has much less toxic in all-grade toxicity when compared with regorafenib, especially in the subgroup of proteinuria. The grade ≥ 3 toxicity among the three trials were also different, the most frequent regorafenib-related adverse events of grade ≥ 3 were hand–foot skin reaction (83/500, 17%), fatigue (51/500, 10%), diarrhea (36/500, 7%), hypertension (36/500, 7%), and rash or desquamation (29/500, 6%) in the CORRECT trial, and hand–foot skin reaction (100/136, 73%), hypertension (15/136, 11%), alanine aminotransferase concentration increased (9/136, 7%), hypophosphataemia (9/136,7%), and hyperbilirubinemia (9/136, 6%) in the CONCUR trial. The most frequent fruquintinib-related adverse events of grade ≥ 3 were hypertension (59/278, 21%), hand–foot skin reaction (30/278, 11%), proteinuria (9/278, 3%), diarrhea (8/278, 3%), and platelet count decreased (7/278, 3%) in the FRESCO trial. For the grade 3–5 toxicity, fruquintinib showed no significant difference when compared with regorafenib. As a whole, it seems that regorafenib may be more difficult to tolerate; on the basis of it, the ReDOS study (a phase II dose-escalation study) showed that the dosing of regorafenib to be optimized for individual patients was allowed (Bekaii-Saab et al. 2016); however, the dose of regorafenib still needs further research. In general, fruquintinib has much less toxic in all-grade toxicity when compared with regorafenib, especially for proteinuria. Just with this in mind, we can guide the appropriate therapies for mCRC patients using the adverse event profile; for example, regorafenib is a reasonable option for patients with hypertension and good performance status; meantime, fruquintinib is a reasonable option for patients with proteinuria.

Limitation of this meta-analysis should be taken into account. First, the small sample size; only three RCTs were included because of the strict design and it was insufficient to do sensitivity analysis and Begg tests. Some unpublished and missing data might lead bias to the pooled effect. Finally, we were unable to compare the cost-effectiveness of both drugs because of lack of information.

Conclusions

Based on efficacy and safety, our meta-analysis suggests that there was a tendency that fruquintinib was superior to regorafenib in PFS; as a whole, regorafenib and fruquintinib demonstrated similar clinical benefits for patients with refractory mCRC. It seems that fruquintinib has less toxic in all-grade toxicity when compared with regorafenib. Moreover, regorafenib and fruquintinib have different incidence of AEs, and we can guide the appropriate therapies for mCRC patients using the adverse event profile. Further direct well-designed, head-to-head, prospective studies are needed to confirm these findings.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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

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