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ORIGINAL ARTICLE

Safety and efficacy of EFGR and VEGF signaling pathway inhibition therapy in patients with colorectal cancer: a meta-analysis*

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Abstract

Objective Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) inhibitors are two targeted therapies for metastatic colorectal cancer (mCRC). However, few studies have focused on the safety and efficacy of combined targeted therapy against those of a single inhibition therapy of EFGR or VEGF. This meta-analysis aimed to compare the anti-tumor activity of the combined inhibition therapy and single inhibition therapy in patients with mCRC.

Methods We searched PubMed, Medline, the Cochrane library, Embase, and annual meeting proceedings for relevant clinical trials. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events were extracted and calculated.

Results Nine trials comprising 3977 patients were selected for the analysis. The combined inhibition therapy showed a 3.7% improvement in ORR compared with single inhibition, and this difference was statistically significant [hazard ratio (HR) = 1.33; 95% confidence interval (CI), 1.01–1.74; P = 0.04]. Subgroup analysis showed that the combined EGFR and VEGF inhibitor therapy had an 11.65% improvement in ORR compared with VEGF inhibitor therapy (OR = 2.14; 95% CI, 1.34–3.40; P = 0.001). EGFR and VEGF inhibitor therapy and chemotherapy had an 18.08% improvement in ORR compared with chemotherapy (OR = 2.21; 95% CI, 1.05–4.64; P = 0.04). Moreover, EGFR and VEGF inhibitor therapy significantly improved PFS compared with VEGF inhibitor therapy (OR = 0.82; 95% CI, 0.69–0.97; P = 0.02). VEGF inhibitor therapy and chemotherapy significantly improved PFS compared with EGFR and VEGF inhibitor therapy and chemotherapy (OR = 1.20; 95% CI, 1.11–1.30; P = 0.00). In addition, EGFR and VEGF inhibitor therapy showed improved OS compared with VEGF inhibitor therapy (HR = 0.78, 95% CI: 0.65–0.94; P = 0.008). Finally, the combined inhibition therapy showed an obviously increased risk of cutaneous and mucosal effects (RR = 6.45; 95% CI: 2.71–15.36; P < 0.01), diarrhea/abdominal pain (RR = 1.97; 95% CI: 1.45–2.68; P < 0.01), fatigue/asthenia (RR = 1.60; 95% CI: 1.10–2.32; P = 0.01), dehydration or electrolyte disturbance (RR = 2.78; 95% CI: 1.48–5.21; P < 0.01), nail disorder (RR = 8.23; 95% CI: 1.52–44.57; P = 0.01), and dizziness/headache (RR = 3.43; 95% CI: 1.89–6.23; P < 0.01) compared with single inhibition therapy.

Conclusion Compared with single inhibition therapy, the combined inhibition therapy significantly improved ORR, PFS, and OS in the treatment of mCRC patients. Compared with a single-targeted agent, the combined therapy of anti-EGFR and anti-VEGF drug provided an efficacy advantage, although it led to greater toxicity.

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Colorectal cancer (CRC) was a common leading cause of cancer deaths worldwide [1]. Though the treatment with surgery was the same as the initial treatment for CRC, the prognosis was poor for patients with the presence of micrometastases at the time of surgery [2]. Cytotoxic drugs, the standard first-line treatment for metastatic colorectal cancer (mCRC), including capecitabine, oxaliplatin, 5-fluorouracil (5-FU), and irinotecan were used to improve the survival of patients with mCRC [3–5]. However, the toxicity of chemotherapy was unsatisfactory; reducing the side-effects of the therapy was needed [6]. With the introduction of the anti-vascular endothelial growth factor (VEGF) antibodies, such as bevacizumab, axitinib, cediranib, and sorafenib, and the antibodies against epidermal growth factor receptor (EGFR), such as cetuximab, geftinib, and panitumumab, treatment of mCRC has improved, and the survival of patients has improved greatly [7–8].

Tumor cells could promote VEGF production, which might induce the expression of downstream genes and stimulate the signaling pathways [9]. VEGF could promote the production of new vasculature by stimulating the endothelial cells [10]. The expression of EGFR on the surface of many epithelial tumors was high; this is activated by various ligand-transforming epidermal growth factor and transforming growth factor-α [11]. The proliferation, differentiation, and survival of cancer cells could be regulated by key downstream pathways, which are signaled by the receptor activation [12]. Compared with chemotherapy alone or chemotherapy plus placebo, the addition of anti-VEGF or/and anti-EGFR antibodies to chemotherapy could prolong the overall survival (OS) of patients with mCRC, especially those with KRAS and NRAS wild-type mCRC [13]. Although, improvement in outcomes was achieved by blocking the EGFR and VEGF expression, combining the anti-EGFR and anti-VEGF drugs with chemotherapy resulted in high response rate (RR) [14].

Some trials had evaluated the safety and efficacy of the combination of anti-VEGF or/and anti-EGFR antibodies with or without chemotherapy for mCRC [15–17]. In the double blind trial, bevacizumab and panitumumab (40.1%) improved the RR of patients with mCRC compared with folinic acid, 5-FU, and irinotecan (FOLFIRI) (30.1%) when added to FOLFIRI; a series of antibody therapy-associated adverse events (AEs) were observed in the FOLFIRI + bevacizumab and panitumumab group (80.0%) compared with FOLFIRI alone (52.6%) [18]. Moreover, the addition of bevacizumab to FU, irinotecan, and leucovorin (IFL) significantly improved OS (20.3 months), progression-free survival (PFS) (10.6 months), and RR (44.8%) in patients with mCRC compared with IFL alone (15.6 months, 6.2 months, 34.8%) [19]. Even for patients with mCRC that progresses after all approved standard therapies, regorafenib offered a potential new line of therapy for late-stage mCRC patients with longer OS (6.4 months) compared with the placebo group (5.0 months) [20].

In recent years, the safety and efficacy of anti-EGFR and anti-VEGF drugs had been studied in patients with mCRC [15]. For mCRC, the inhibition of both VEGF receptor (VEGFR) and EGFR signaling pathways showed greater anti-tumor efficacy than chemotherapy or inhibition of either pathways alone [16]. However, with regards to the inhibition of both VEGFR and EGFR signaling pathways, the combined therapy might also lead to increased AEs [16]. Despite that some previous researches had explored the therapies that inhibit both VEGFR and EGFR as against single EGFR signaling pathways, no systematic review regarding the optimal strategy on combined targeted drugs in patients with mCRC was available. Hence, a meta-analysis of randomized controlled trials (RCTs) was performed to evaluate the safety and efficacy of EFGR and VEGF signaling pathways inhibition therapy in patients with mCRC.

Materials and methods

Search strategy and selection criteria

RCTs for comparing EFGR and VEGF signaling pathways inhibition therapy in the treatment of patients with colorectal cancer were selected through a standard search in the PubMed, Medline, the Cochrane library and Embase databases. In addition, reference lists of the selected articles were examined. We performed the search by using the following keywords or expressions: "colorectal cancer (i.e., 'colorectal', 'colon*', 'rectal', 'rectum'; 'cancer', 'tumor', 'neoplasms', 'neoplas*', 'carcinom*', 'malignan*')", "EGFR", "VEGFR", "clinical trial", and "randomized trial". All possible combinations of keywords were used as search terms to identify all possible candidates. The final search strategies were as follows: (1) (((colon*) AND (neoplas* OR carcinom* OR malignan*)) OR (colorectal cancer [MeSH])) AND (EGFR [MeSH] OR VEGFR [MeSH]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]); (2) (((rectal OR rectum) AND (tumor OR neoplasms)) OR (colorectal cancer [MeSH]))) AND (EGFR [MeSH] OR VEGFR [MeSH]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]). Article types were restricted to Clinical Trial and RCT.

In addition, the annual meeting proceedings of the

American Society of Clinical Oncology and European Society of Medical Oncology were reviewed. The relevant reviews regarding the role of a therapy that inhibited EGFR and VEGFR signaling pathways for colorectal cancer patients were identified. Moreover, in order not to miss the information of prospective and ongoing trials, we also searched the websites of http://www.ClinicalTrials.gov and http://www.who.int/triasearch.

Inclusion criteria

Articles meeting all the following criteria were eligible for inclusion in the review: (1) English language published articles; (2) those exploring clinical outcomes of colorectal cancer patients treated with either anti-EGFR or anti-VEGFR therapy; (3) those reporting one or more of the following indicators to assess the tumor response and prognosis of patients, including objective RR (ORR), PFS, and OS; (4) RCTs in human, or retrospective trials and prospective trials; and (5) those providing sufficient data to calculate the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs).

Exclusion criteria

Articles meeting all the following exclusion criteria were excluded: (1) case or reviews or meta-analyses or duplicate reports; (2) trials without complete data or full-text online articles or ongoing trials; (3) articles which lacked control groups; and (4) those which lacked critical information.

Data extraction and quality assessment

The data extraction and quality assessment were conducted independently by two investigators (Siwen Liu and Dan Chen) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance. Disagreements were resolved by discussions between the two or by a third reviewer after referring to the original articles (Shaorong Yu). The quantitativeness of articles were assessed using the quantitative 5-point Jadad scale [21].

Using a standardized data recording form, we extracted the following critical information: (1) publication details, including first author's surname, publication year; (2) methodological components; and (3) patient and trial characteristics, such as median age, sex, World Health Organization (WHO) performance status, and number of subjects; and trial phase, treatment protocols, and outcome measures. End points of interest included ORR, PFS, OS, and AEs.

Statistical analysis

All included articles were separated into two groups (combined and single inhibition therapy groups) in order to analyze their efficacy and safety; all the summary effect estimates were conducted with Review Manager 5.3 analysis software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

For time-to-event data, the impact of combined and single inhibition therapy on OS and PFS was measured in terms of the hazard ratios (HRs) [22]. The log HRs and their variances were used directly if provided by the article. If not appropriate for direct analysis, they were computed according to the previous reported method from CIs of the HRs extracted from each trial before data pooling. In addition, the summary HRs and their 95% CIs were estimated in accordance with a general variance-based method. For ORR (including complete response and partial response), the pooled OR of ORR was calculated using the methods reported by Mantel and Haenszel [23]. Moreover, subgroup analyses were performed among the group with (1) chemotherapy; (2) VEGF inhibitor therapy; (3) EGFR and VEGF inhibitor therapy; and (4) EGFR and VEGF inhibitor therapy and chemotherapy. In addition, the AEs of therapy were analyzed as drug-related WHO grade 3 or greater toxicity.

For more reliability, between-trial heterogeneity was assessed by the χ^2 test and I^2 statistic [24]. For the I^2 statistic, an I^2 value above 50% was interpreted as large heterogeneity; between 25% and 50% meant modest heterogeneity; and below 25% suggested low heterogeneity. For χ^2 statistic, significant heterogeneity existed when P value was > 0.10. A fixed-effect model was used to calculate the pooled effect if no statistically significant heterogeneity was detected; otherwise, a random-effect model was conducted.

Additionally, Egger's [25] and Begg-Mazumdar [26] tests were employed to assess the probability of publication bias. The results were regarded as statistically significant when a two-tailed P value < 0.05 was observed.

Results

Literature search results

Based on the above searching strategies, our search identified a total of 26 potentially relevant articles, which were assessed for full-text review, from which 17 were excluded: 12 for not assessing the combined inhibition therapy, four trials for not providing sufficient data on HRs and estimation intervals for PFS, and 1 for not providing the appropriate control arm. Finally, based on the inclusion criteria, 9 potentially eligible trials, which explored the therapy that inhibited EFGR and VEGF signaling pathways, were included in this meta-analysis (Fig. 1).

Characteristics of included trials

The nine eligible trials of the meta-analysis were included. All trials included patients with stage IV mCRC

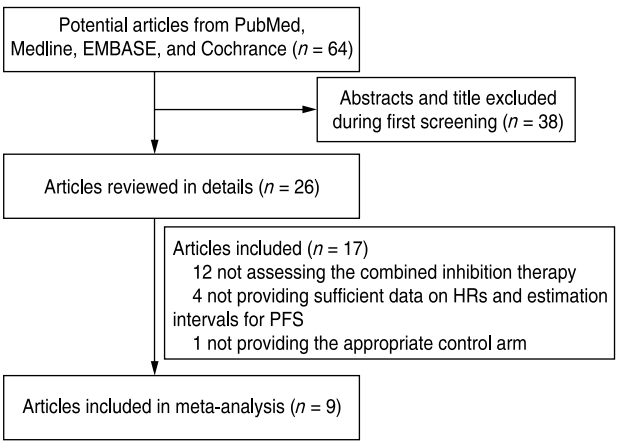

Fig. 1 Identification process for eligible studies

and were published in full articles. All of the patients had a good performance status with the ECOG or WHO score of 0. Five of the included trials were randomized phase II trials and the rest were randomized phase III trials. One trial assessed the multi-targeted agent vandetanib (the inhibition of both VEGFR and EGFR signaling pathways) plus chemotherapy against chemotherapy plus placebo, whereas the rest of the trials compared the combined inhibition therapy (the combination of anti-VEGF and anti-EGFR antibodies or plus chemotherapy or placebo) with a single inhibition therapy (the anti-VEGF antibody or anti-EGFR antibody) or plus chemotherapy or placebo. The detailed characteristics of the included nine trials are summarized in Table 1.

Meta-analysis

Among these trials, patients of four trials were treated with the single inhibition therapy and chemotherapy [27–30], patients of three trials were treated with the single inhibition therapy [31–33], patients of one trial were treated with chemotherapy and placebo [34], and patients of one trial were treated with chemotherapy [35].

ORR

Data for ORR were available from seven trials. Compared with single inhibition (the single inhibition therapy or/and chemotherapy or/and placebo) therapy, combined inhibition therapy yielded a 3.7% improvement in ORR, and this difference was statistically significant (Random-effects model, OR = 1.33; 95% CI, 1.01–1.74; $P = 0.04$; Fig. 2). There was significant heterogeneity for ORR among the individual trials ($I^2 = 51\%$, $P = 0.04$; Fig. 2), and no evidence of significant publication bias was detected (Egger test, $t = 2.22$, $P = 0.06$; Begg test, Z = 1.15, $P = 0.25$).

The results of subgroup analysis showed that the group with EGFR and VEGF inhibitor therapy had an 11.65% improvement in ORR compared with VEGF inhibitor therapy (Random-effects model, OR = 2.14; 95% CI, 1.34–3.40; $P = 0.001$; Fig. 3) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.75$; Fig. 3).

Moreover, the group with EGFR and VEGF inhibitor therapy and chemotherapy had an 18.08% improvement in ORR compared with the group with chemotherapy (Random-effects model, OR = 2.21; 95% CI, 1.05–4.64; $P = 0.04$; Fig. 3) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.72$; Fig. 3).

However, the group with EGFR and VEGF inhibitor therapy and chemotherapy had no improvement in ORR compared with the group with VEGF inhibitor therapy and chemotherapy (Random-effects model, OR = 1.05; 95% CI, 0.84–1.32; $P = 0.65$; Fig. 3) with no significant heterogeneity ($I^2 = 24\%$, $P = 0.26$; Fig. 3).

PFS

All trials provided PFS results. The meta-analysis using a random-effects model revealed that the combined inhibition therapy did not significantly improve PFS compared with the single inhibition therapy (HR = 0.99, 95% CI: 0.86–1.15; $P = 0.94$), with significant

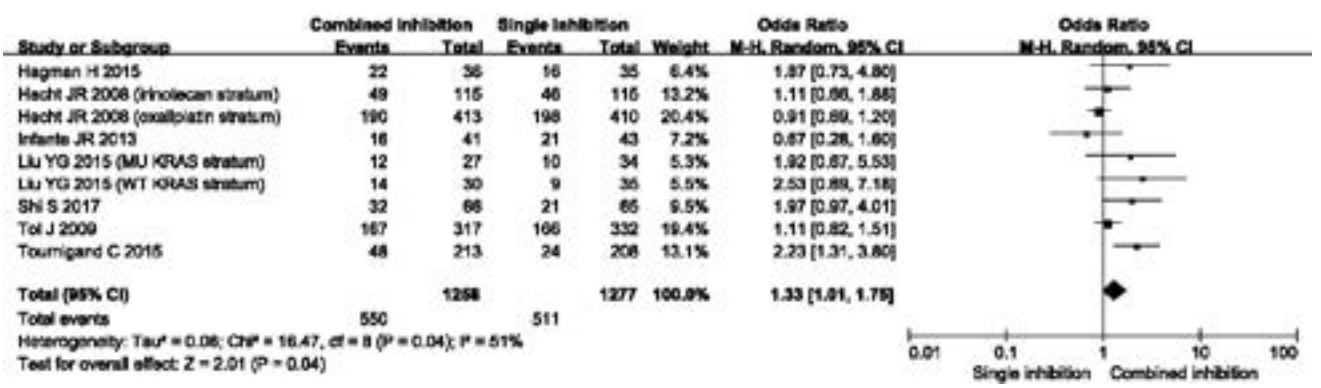

Fig. 2 Comparison of objective response rate between combined inhibition therapy and single inhibition therapy

Table 1 Characteristics of included trials

Authors (year)	Randomized clinical trial	Number of patients	Male (%)	Median age (years)	Stage IV (%)	PS > 2 (%)
Tol J *et al*. (2009) [27]	Phase 3	368/368	205 (55.7%)/ 233 (63.3%)	62/62	368 (100%)/ 368 (100%)	0 (WHO)
Hecht JR *et al*. (2008) (oxaliplatin stratum) [28]	Phase 3	413/410	233 (56%)/ 238 (58%)	61/62	412 (99.76%)/ 410 (100%)	0 (ECOG)
Hecht JR *et al*. (2008) (irinotecan stratum) [28]	Phase 3	115/115	56 (49%)/ 71 (62%)	60/59	115 (100%)/ 115 (100%)	0 (ECOG)
Shi S *et al*. (2017) [29]	Phase 2	65/66	42 (64.6%)/ 47 (71.2%)	61.8/62.5	65 (100%)/ 66 (100%)	0 (ECOG)
Infante JR *et al*. (2013) [30]	Phase 2	43/41	28 (65.1%)/ 26 (63.4%)	64/59	43 (100%)/ 41 (100%)	0 (ECOG)
Johnsson A *et al*. (2013) [31]	Phase 3	79/80	54 (46%)/ 66 (34%)	65/64	79 (100%)/ 80 (100%)	0 (ECOG)
Hagman H *et al*. (2015) [32]	Phase 2	35/36	66 (34%)/ 64 (36%)	61/65	35 (100%)/ 36 (100%)	0 (ECOG)
Tournigand C *et al*. (2015) [33]	Phase 3	228/224	129 (57%)/ 147 (66%)	63/63	228 (100%)/ 224 (100%)	0 (WHO)
Hecht JR *et al*. (2011) [34]	Phase 3	583/585	352 (60.4%)/ 368 (62.9%)	59.6/59.1	583 (100%)/ 585 (100%)	0 (WHO)
Liu YG *et al*. (2015) (WT KRAS stratum) [35]	Phase 2	35/30	22 (63%)/ 18 (60%)	62/59	35 (100%)/ 30 (100%)	0 (ECOG)
Liu YG *et al*. (2015) (MU KRAS stratum) [35]	Phase 2	34/27	20 (59%)/ 17 (63%)	60/61	34 (100%)/ 27 (100%)	0 (ECOG)

(to be continued)

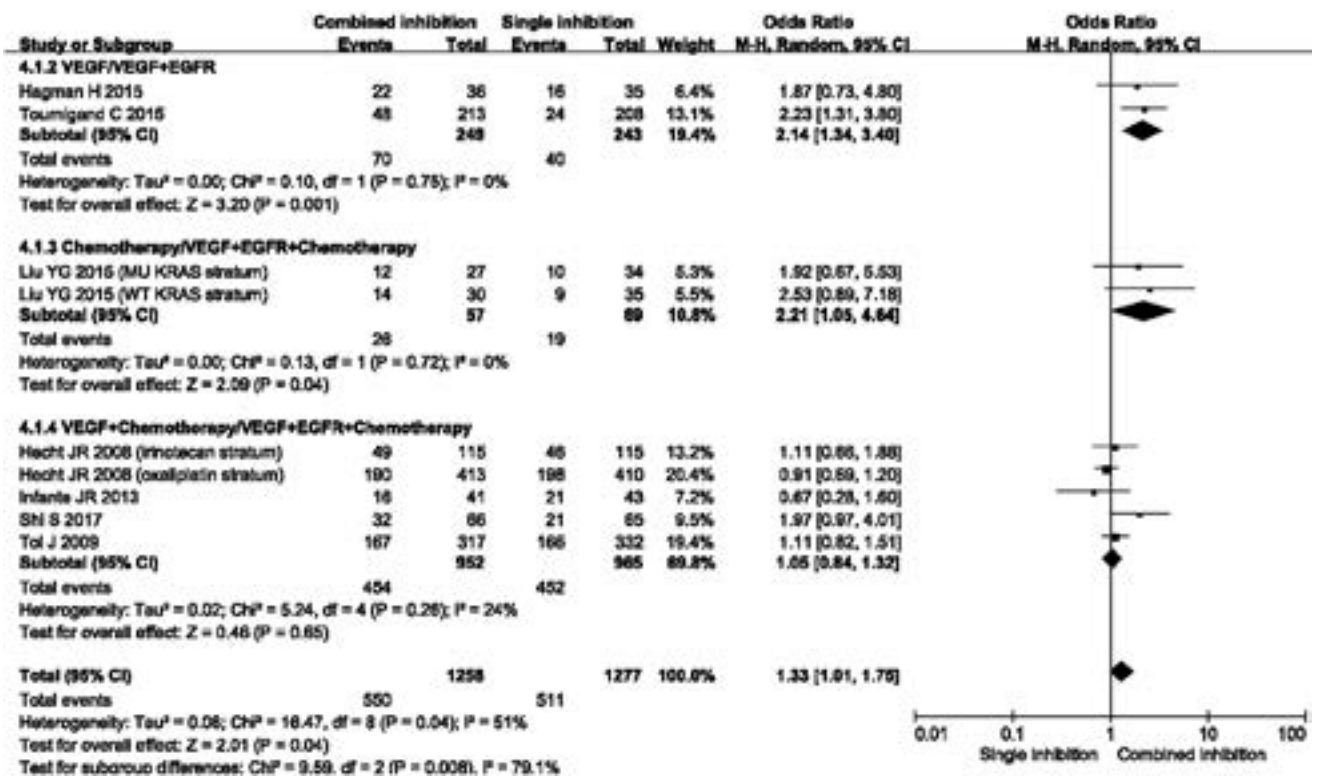

Fig. 3 Comparison of progression-free survival between combined inhibition therapy and single inhibition therapy

Table 1 (continued) Characteristics of included trials

Authors (year)	Patients status	Interventions	Jadad score	Endpoint
Tol J *et al*. (2009) [27]	Untreated mCRC[1]	Arm-1: Bevacizumab + Chemotherapy (Capecitabine, Oxaliplatin) Arm-2: Bevacizumab + Cetuximab + Chemotherapy (Capecitabine, Oxaliplatin)	4	PFS; OS; ORR
Hecht JR *et al*. (2008) (oxaliplatin stratum) [28]	Untreated mCRC[2]	Arm-1: Bevacizumab + Chemotherapy (Ox-CT: Fluorouracil, Leucovorin and Oxaliplatin) Arm-2: Bevacizumab + Panitumumab + Chemotherapy (Ox-CT: 5-Fluorouracil, Leucovorin and Oxaliplatin)	4	PFS; OS; ORR
Hecht JR *et al*. (2008) (irinotecan stratum) [28]	Untreated mCRC[2]	Arm-1: Bevacizumab + Chemotherapy (Iri-CT: 5-Fluorouracil, Leucovorin and Irinotecan) Arm-2: Bevacizumab + Panitumumab + Chemotherapy (Iri-CT: 5-Fluorouracil, Leucovorin and Irinotecan)	4	PFS; OS; ORR
Shi S *et al*. (2017) [29]	Untreated mCRC[3]	Arm-1: Bevacizumab + Chemotherapy (FOLFOX4: Oxaliplatin, 5-Fluorouracil and Leucovorin) Arm-2: Bevacizumab + Erlotinib + Chemotherapy (FOLFOX4: Oxaliplatin, 5-Fluorouracil and Leucovorin)	4	PFS; OS; ORR
Infante JR *et al*. (2013) [30]	Untreated mCRC[4]	Arm-1: Bevacizumab + Chemotherapy (FOLFOX: Oxaliplatin, 5-Fluorouracil and Leucovorin) Arm-2: Bevacizumab + Axitinib + Chemotherapy (FOLFOX: Oxaliplatin, 5-Fluorouracil and Leucovorin)	4	PFS; OS; ORR
Johnsson A *et al*. (2013) [31]	Untreated mCRC[5]	Arm-1: Bevacizumab Arm-2: Bevacizumab + Erlotinib	4	PFS; OS
Hagman H *et al*. (2015) [32]	mCRC with KRAS wild type[6]	Arm-1: Bevacizumab Arm-2: Bevacizumab + Erlotinib	4	PFS; OS; ORR
Tournigand C *et al*. (2015) [33]	mCRC[7]	Arm-1: Bevacizumab Arm-2: Bevacizumab + Erlotinib	4	PFS; OS; ORR
Hecht JR *et al*. (2011) [34]	Untreated mCRC	Arm-1: Placebo + Chemotherapy (FOLFOX4: Oxaliplatin, Fluorouracil and Leucovorin) Arm-2: (PTK/ZK: Vatalanib) + Chemotherapy (FOLFOX4: Oxaliplatin, 5-Fluorouracil and Leucovorin)	5	PFS; OS
Liu YG *et al*. (2015) (WT KRAS stratum) [35]	mCRC with WT KRAS[8]	Arm-1: Chemotherapy (Iri-CT: 5-Fluorouracil, Leucovorin and Irinotecan) Arm-2: Bevacizumab + Panitumumab + Chemotherapy (FOLFIRI: Irinotecan, 5-Fluorouracil and Leucovorin)	4	PFS; OS; ORR
Liu YG *et al*. (2015) (MU KRAS stratum) [35]	mCRC with MU KRAS[8]	Arm-1: Chemotherapy (Iri-CT: 5-Fluorouracil, Leucovorin and Irinotecan) Arm-2: Bevacizumab + Panitumumab + Chemotherapy (FOLFIRI: Irinotecan, 5-Fluorouracil and Leucovorin)	4	PFS; OS; ORR

Note: mCRC: metastatic colorectal cancer; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; WHO: World Health Organization; ECOG: Eastern Cooperative Oncology Group; PS: performance status; KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene; WT: wild-type; MU: mutant. [1] Not amenable to curative surgery, measurable tumor; no previous systemic chemotherapy; [2] Without any prior chemotherapy or biologic therapy; [3] Without any previous treatment involving bevacizumab or erlotinib; still with progression after 1st-line oxaliplatin-based or irinotecan-based chemotherapy; [4] Patients who received previous adjuvant chemotherapy were eligible if the last dose of adjuvant therapy was administered > 12 months before enrollment; [5] Without tumor progression after chemotherapy and bevacizumab as first-line treatment; [6] Without progression after first-line induction treatment with XELOX/FOLFOX or XELIRI/FOLFIRI + bevacizumab; [7] Without progression after bevacizumab-based induction therapy; [8] With unsuccessful previous oxaliplatin- or 5-FU based chemotherapy

heterogeneity between the trials (I^2 = 69%, P = 0.0003; Fig. 4). In addition, the Begg's test (Z = 0.78, P = 0.44) and Egger's test (t = –1.45, P = 0.18) showed that there was no significant publication bias.

Subgroup analysis showed that EGFR and VEGF inhibitor therapy significantly improved PFS compared with VEGF inhibitor therapy (Random-effects model, OR = 0.82; 95% CI, 0.69-0.97; P = 0.02; Fig. 5). There was no significant heterogeneity (I^2 = 0%, P = 0.87; Fig. 5).

VEGF inhibitor therapy and chemotherapy significantly improved PFS compared with EGFR and VEGF inhibitor therapy and chemotherapy (Random-effects model, OR = 1.20; 95% CI, 1.11–1.30; P = 0.00; Fig. 5) with no significant heterogeneity (I^2 = 0%, P = 0.86; Fig. 5).

However, compared with chemotherapy, there was no evidence of an improved PFS in the patients with EGFR and VEGF inhibitor therapy and chemotherapy

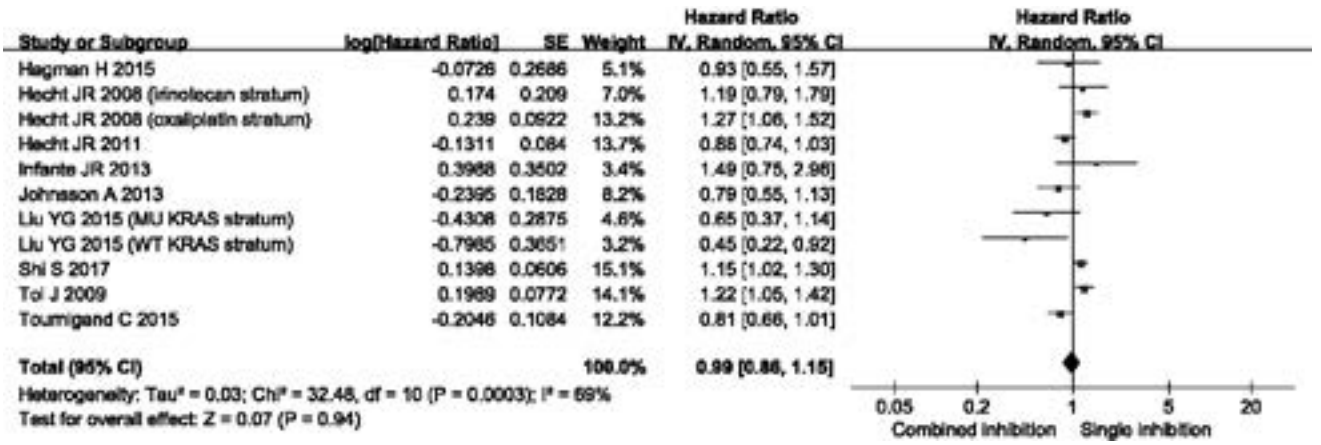

Fig. 4 Comparison of overall survival between combined inhibition therapy and single inhibition therapy

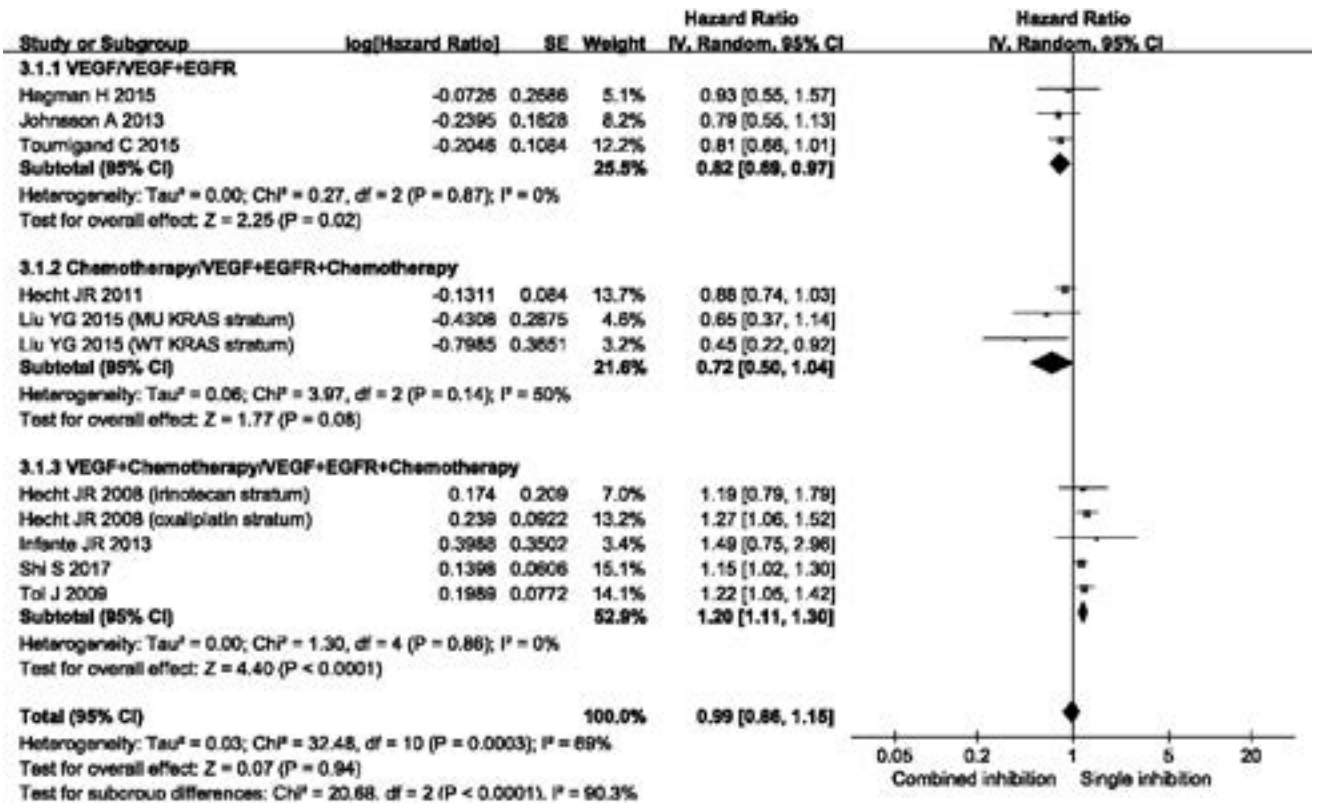

Fig. 5 Subgroup analysis of objective response rate among different groups

(Random-effects model, HR = 0.72, 95% CI: 0.50–1.04; P= 0.08; Fig. 5); there was no significant heterogeneity (Heterogeneity, I^2 = 50%, P = 0.14; Fig. 5).

OS

All trials were available for OS analysis. There was no evidence of an OS benefit in the patients with the combined inhibition therapy (Random-effects model, HR = 1.04, 95% CI: 0.88–1.23; P = 0.65) with significant heterogeneity among the individual trials (Heterogeneity, I^2 = 64%, P = 0.002, random-effect model, Fig. 6), and no evidence of significant publication bias was detected (Egger test, t = 0.53, P = 0.61; Begg test, Z = 0.00, P = 1.00).

Subgroup analysis showed that the group with EGFR and VEGF inhibitor therapy had improved OS compared with VEGF inhibitor therapy group (Random-effects

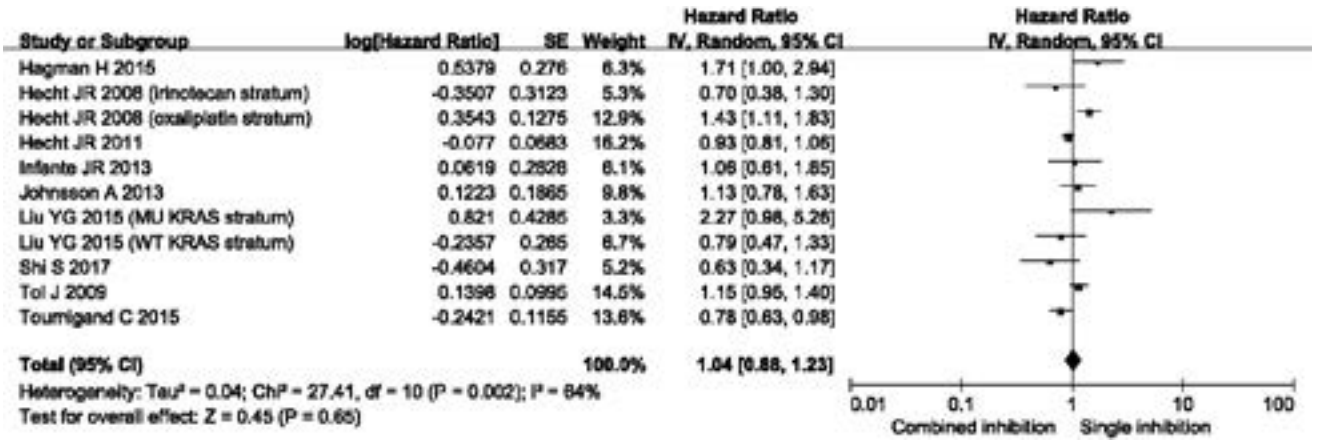

Fig. 6 Subgroup analysis of progression-free survival among different groups

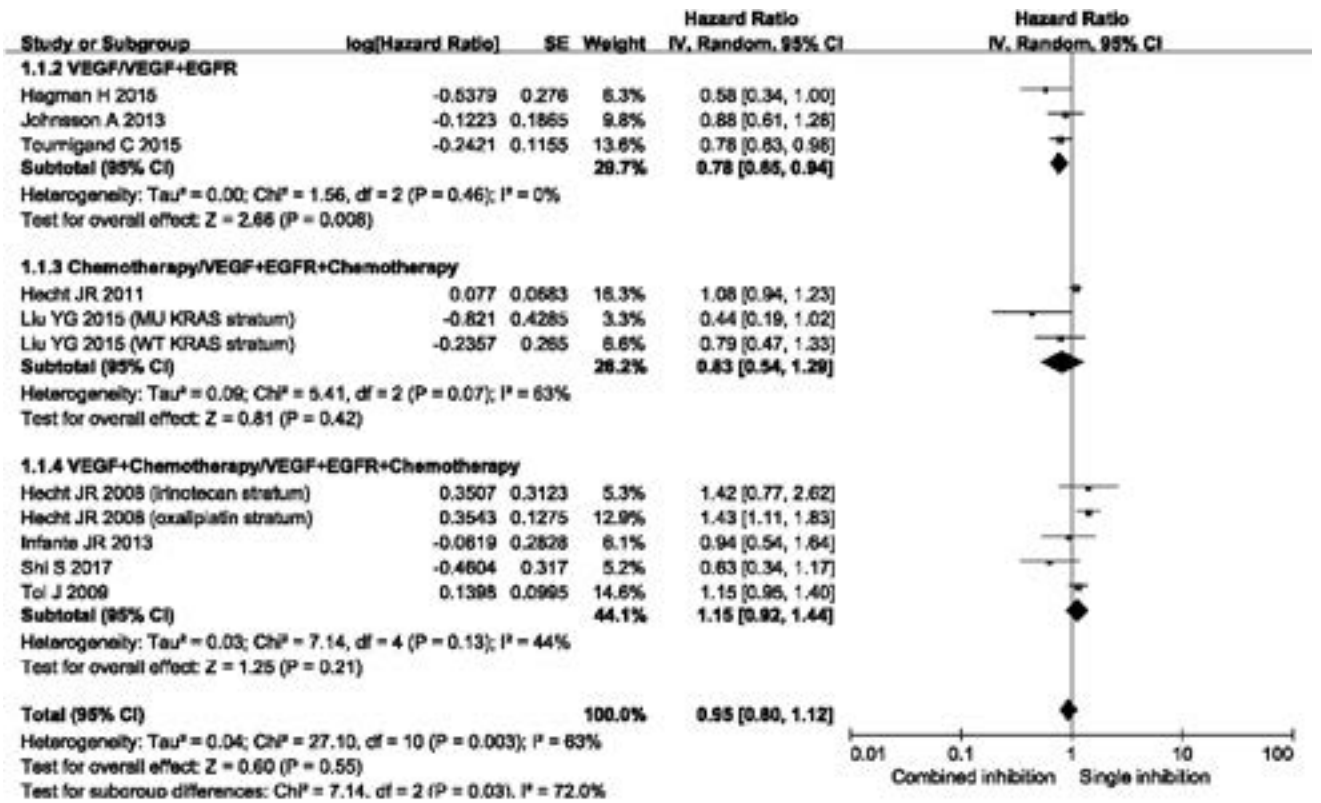

Fig. 7 Subgroup analysis of overall survival among different groups

model, HR = 0.78, 95% CI: 0.65-0.94; P = 0.008; Fig. 7) with no significant heterogeneity (Heterogeneity, I^2 = 0%, P = 0.46; Fig. 7).

No improved OS was found in the group with EGFR-VEGF inhibitor therapy and chemotherapy compared with the chemotherapy group (Random-effects model, HR = 0.83, 95% CI: 0.54–1.29; P = 0.42; Fig. 7); there was no significant heterogeneity (Heterogeneity, I^2 = 63%, P = 0.07; Fig. 7).

Moreover, there was no improved OS in the patients with EGFR-VEGF inhibitor therapy and chemotherapy compared with the chemotherapy group (Random-effects model, HR = 1.15, 95% CI: 0.92–1.44; P = 0.21; Fig. 7) with no significant heterogeneity (Heterogeneity, I^2 =

Table 2 Summary of toxicities grade 3 or greater

Adverse events	Combined inhibition arm (Events/total)	Single inhibition arm (Events/total)	Odds ratio (95% CI)	*P* value	Heterogeneity	
					I^2	*P* value
Cutaneous and mucosal effects	470/1384	109/1965	6.45 (2.71, 15.36)	**< 0.01**	89%	< 0.01
Diarrhea/abdominal pain	411/1963	252/1965	1.97 (1.45, 2.68)	**< 0.01**	60%	< 0.01
Nausea/vomiting	242/1906	179/1896	1.43 (1.00, 2.04)	0.05	58%	0.02
Fatigue/asthenia	149/1388	99/1386	1.60 (1.10, 2.32)	**0.01**	36%	0.15
Infection	143/1000	92/990	1.59 (0.99, 2.57)	0.06	54%	0.07
Neutropenia	345/1641	332/1572	1.03 (0.87, 1.23)	0.71	15%	0.31
Hypertension	211/1897	132/1900	1.44 (0.72, 2.88)	0.30	82%	< 0.01
Bleeding	62/1307	36/1313	1.81 (0.98, 3.34)	0.06	36%	0.14
Thromboembolic events	152/1820	105/1822	1.54 (0.97, 2.42)	0.07	55%	0.04
Dehydration or electrolyte disturbance	197/1231	83/1231	2.78 (1.48, 5.21)	**< 0.01**	70%	< 0.01
Neuropathy	116/1795	123/1783	0.90 (0.64, 1.28)	0.56	36%	0.14
Nail disorder	11/598	0/589	8.23 (1.52, 44.57)	**0.01**	0%	0.99
Thrombocytopenia	55/986	35/985	1.51 (1.00, 2.26)	0.05	0%	0.80
Anemia	5/327	5/332	1.06 (0.28, 4.06)	0.93	0%	0.47
Dizziness/headache	47/620	13/617	3.43 (1.89, 6.23)	**< 0.01**	0%	0.48
Renal and urinary disorders	23/500	9/515	2.34 (1.00, 5.48)	0.05	10%	0.35

44%, $P = 0.13$; Fig. 7).

AEs

For all-grade AEs, the combined inhibition therapy showed an obviously increased risk of cutaneous and mucosal effects (RR = 6.45; 95% CI: 2.71–15.36; $P < 0.01$), diarrhea/abdominal pain (RR = 1.97; 95% CI: 1.45–2.68; $P < 0.01$), fatigue/asthenia (RR = 1.60; 95% CI: 1.10–2.32; $P = 0.01$), dehydration or electrolyte disturbance (RR = 2.78; 95% CI: 1.48–5.21; $P < 0.01$), nail disorder (RR = 8.23; 95% CI: 1.52–44.57; $P = 0.01$) and dizziness/headache (RR = 3.43; 95% CI: 1.89–6.23; $P < 0.01$) in mCRC patients compared with single inhibition therapy. The detailed characteristics of AEs are summarized in Table 2.

Quality assessment of the studies

For quality assessment, Jadad scale was used to assess the quality of the included trials. Of the enrolled trials, one trial had a Jadad score of 5, while the rest trials had a Jadad score of 4 [36].

Discussion

The results of this meta-analysis showed that the combined targeted therapy of EFGR and VEGF was associated with a clinically substantial and statistically significant improvement in ORR, PFS, and OS compared with the single inhibition therapy in mCRC patients. Moreover, compared with single-targeted therapy, combined inhibition therapy might lead to higher rates of AEs.

Our data showed that the combined targeted therapy of EFGR and VEGF determined a statistically significant increase in ORR compared with the single inhibition therapy in mCRC patients. This result proved that the therapy that inhibited both VEGFR and EGFR signaling pathways improved the ORR of mCRC patients. The analyses of the trial by Shi *et al* suggested that the therapy of bevacizumab and erlotinib plus chemotherapy (FOLFOX4: oxaliplatin, 5-FU, and leucovorin) (48.5%) was associated with a statistically significant improvement in partial response and stable disease rate compared with the therapy of bevacizumab plus chemotherapy alone (32.2%) in patients without any previous treatment involving bevacizumab or erlotinib [29]. However, other previous study showed that the RRs did not differ significantly between the Capecitabine, Oxaliplatin, and Bevacizumab group and the same regimen plus cetuximab in untreated mCRC patients [32]. Moreover, ORR was not statistically improved by the combined therapy of vatalanib and chemotherapy (FOLFOX4) compared with that of placebo plus chemotherapy [34]. Our result represented the current evidence that the combined inhibition therapy of EFGR and VEGF in treatment of mCRC patients improved the ORR of mCRC patients.

Moreover, our analysis found that the treatment, which inhibited both VEGFR and EGFR signaling pathways, improved PFS and OS among patients with mCRC. Some existing evidence from RCTs maintained that PFS and OS were not statistically improved by vatalanib, a multi-targeted agent that inhibited both VEGFR and EGFR signaling pathways [32]. Median PFS was 7.7 months with vatalanib as against 7.6 months with placebo (HR = 0.88, 95% CI: 0.74–1.03; $P = 0.12$); while

median OS was 21.4 months with vatalanib as against 20.5 months with placebo (HR = 1.08, 95% CI: 0.94–1.24; P = 0.26) [32]. However, PFS and OS advantage for the therapy that inhibited both VEGFR and EGFR signaling pathways was suggested by previous studies of mCRC patients [28, 33]. Our data suggested that the addition of the combined inhibition therapy could improve PFS and OS of mCRC patients.

It seemed that the therapy that inhibited both VEGFR and EGFR signaling pathways could provide a more profound pathway inhibition, which would improve clinical outcomes of mCRC patients more significantly. The combination of anti-EGFR and anti-VEGF drugs in our study increased efficacy compared with the single inhibition therapy alone for mCRC patients.

Finally, as expected, the combined inhibition therapy did increase toxicity, and made some treatment-emergent AEs significantly more severe in mCRC patients who received it. The safety profile of the treatment that inhibited both VEGFR and EGFR signaling pathways in the current study was consistent with the outcomes of some previous studies [32–33].

In summary, the combination of anti-EGFR and anti-VEGF drugs could improve ORR, PFS, and OS compared with the single inhibition therapy. In addition, the combined inhibition therapy appeared to be somewhat less tolerable, with higher incidence of toxicity, compared with treatment with the single inhibition therapy. However, evidences of a significant difference in ORR, PFS, and OS were found to support further study of the therapy that inhibited both VEGFR and EGFR signaling pathways. Further studies with larger sample sizes of the combined inhibition therapy in mCRC patients are warranted to further explore the hypothesis of whether simultaneous inhibition of the VEGFR and the VEGF could improve ORR, PFS, and OS of mCRC patients with less AEs.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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