Systematic Review and Meta-Analysis

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Efficacy and safety of FOLFIRI and biotherapy versus FOLFIRI alone for metastatic colorectal cancer patients

A meta-analysis

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Abstract

Background: Previous randomized controlled trials (RCTs) and meta-analyses have demonstrated the useless of FOLFIRI alone for previously treated patients with metastatic colorectal cancer (mCRC). The role of FOLFIRI regimen combined with biological therapy is unknown. The purpose of this meta-analysis is to evaluate the efficacy and safety of combining biological therapy with chemotherapy in previously treated patients with mCRC.

Methods: MEDLINE, EMBASE, Web of Science, Cochrane library, and ClinicalTrials.gov were searched. Eligible studies were RCTs that evaluated the efficacy and safety of the FOLFIRI regimen with or without biological therapy for previously treated patients with mCRC. The hazard ratio (HR) or risk ratio (RR) with 95% confidence interval was estimated. The Chi-squared and *I*-squared tests were used to assess the statistical heterogeneity.

Results: The literature search identified 7 RCTs that met the inclusion criteria for the meta-analysis, and 3680 patients with mCRC were included. The meta-analysis showed that combined therapy was associated with a significant improved progression-free survival (PFS) (HR = 0.78, 95% CI = 0.72–0.85, $P < .001$), overall survival (OS) (HR = 0.84, 95% CI = 0.77–0.92, $P < .001$), and overall response rate (ORR) (RR = 1.70, 95% CI = 1.25–2.31, $P = .001$). Sensitivity analysis suggested that combined therapy versus FOLFIRI alone might increase the risk of Grade 3/4 AEs.

Conclusion: The addition of biological therapy to the FOLFIRI regimen improved the PFS, OS, and ORR compared with FOLFIRI alone for previously treated patients with mCRC. Long-term survival outcomes are warranted.

Abbreviations: CI = confidence intervals, EGFR = epidermal growth factor receptor, HR = hazard ratio, IPD = individual patient data, mCRC = metastatic colorectal cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, RR = risk ratio.

Keywords: FOLFIRI, meta-analysis, metastatic colorectal cancer, systematic review

1. Introduction

Colorectal cancer (CRC) is a serious public health concern in East Asia, South America, and Eastern Europe, accounting for more than 1360,000 new cases per year and it is the fourth leading cause of cancer death worldwide (GLOBOCAN 2012).[1] CRC is often diagnosed in an advanced stage due to hiding of clinical symptom. Like common cancers, most CRC-related deaths resulted from metastasis. It is demonstrated that approximately 25% of CRC patients with metastases are diagnosed initially and nearly 50% of them will develop metastases afterwards.[2]

The clinical management of patients with unresectable metastatic CRC (mCRC) primarily consists of combination chemotherapy with or without a targeted agent. However, it should be noted that overall survival (OS) and progression-free survival (PFS) remain relatively short when using only chemotherapy. Therefore, biological agents used against the epidermal growth factor receptor (EGFR) in combination with chemotherapy can be considered for mCRC patients because they can improve survival.

After first-line chemotherapy, approximately 70% of mCRC patients who have a good performance status and adequate organ function receive second-line chemotherapy.[3] Since the introduction of oxaliplation and irinotecan, current standard second-line chemotherapy regimens for mCRC include different oxaliplatin- and irinotecan-based chemotherapy.[4] Especially, it has been shown that second-line combination FOLFIRI chemotherapy regimen of 5-FU/LV/irinotecan may help mCRC patients who are

Editor: Weina Chen.

Funding/support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare that they have no conflict of interest.

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Medicine (2017) 96:48(e8767)

Received: 26 July 2017 / Received in final form: 19 October 2017 / Accepted: 20 October 2017

http://dx.doi.org/10.1097/MD.0000000000008767

refractory to an oxaliplatin-based regimen get a better quality of life with longer survival.[3,5,6] However, there is no consensus on the efficacy and safety of different biological agents in addition to FOLFIRI regimen when compared with FOLFIRI alone in the second-line treatment of mCRC patients.[7–11] This meta-analysis was designed to investigate whether the biological therapy combined with FOLFIRI regimen is effective for mCRC patients.

2. Materials and methods

2.1. Search strategy and selection criteria

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009.[12] An electronic literature search was performed in MEDLINE, EMBASE, Web of Science, Cochrane library, and ClinicalTrials.gov, for all studies that were published between January 2000 and December 2015 that compared FOLFIRI combined with biological therapy with FOLFIRI alone or observation for previously treated mCRC patients. The following search terms were used: "FOLFIRI [Mesh]" "metastatic colorectal cancer/carcinoma[Mesh]" "randomized/random/RCT/trial/clinical trials [Mesh]/randomized controlled trial [Mesh]." We placed no limitations on the publication language and publication status (published or in press). We also performed the manual search of the reference lists of the obtained studies.

All the obtained articles were reviewed independently by 2 authors for inclusion criteria. The studies included in the meta-analysis met the following criterion: randomized controlled trial; eligible patients histologically or cytologically diagnosed as mCRC; chemotherapy that confined to the FOLFIRI regimen and the treatment that confined to the second-line therapy; no previous treatment of irinotecan; and results reported in each trial, including PFS, OS, overall response rate (ORR), and Grade 3/4 adverse effects (AEs). Any inconsistency between these 2 authors was reevaluated and resolved by group discussion until a consensus was reached.

2.2. Data extraction and quality assessment

The following information was extracted from each study by 2 researchers (Yang-bo Jiang and Guo-quan Li): study type, year of publication, male percentage, name of the first author, number of patients in each treatment group, median PFS and 95% confidence intervals (CI), median OS and 95% CIs, ORR, and the incidence of Grade 3/4 AEs. In addition, the risk of bias (selection, detection, attrition, and reporting bias) of each study was assessed independently by 2 researchers by using the tools from the *Cochrane Handbook for Systematic Reviews of Interventions* (Table 1).[13–15]

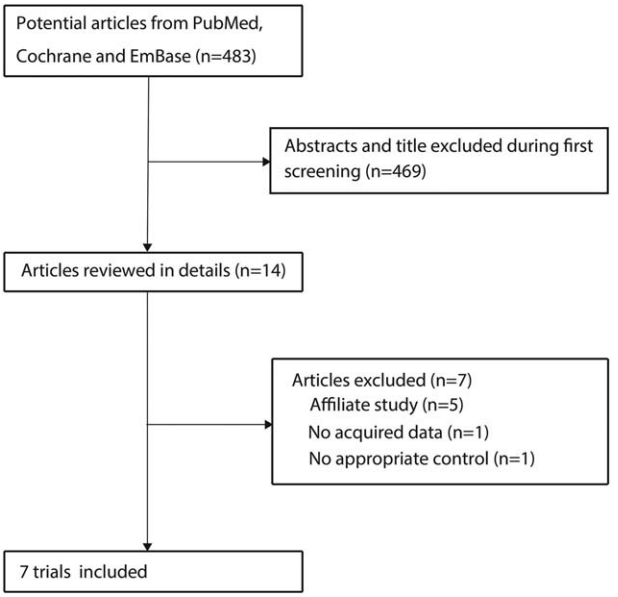

Figure 1. Flow chart for study selection assessing the efficacy and safety of biological therapy and FOLFIRI versus FOLFIRI alone in the meta-analysis.

2.3. Statistical analyses

All analyses were performed using software STATA version 12.0 (Stata Corporation, College Station, TX). We calculated the hazard ratio (HR) and 95% CI for PFS and OS. The risk ratio (RR) and 95% CI was calculated for ORR and Grade 3/4 AEs. Q statistic and *I*-squared (I^2) tests were calculated to evaluate the statistical heterogeneity between trials. If either Q statistic ($P<.1$) or I^2 (>50%) indicated substantial heterogeneity among studies, the randomized-effects model (DerSimonian–Laird method)[16] was used. Otherwise, the fixed-effects model Mantel–Haenszel method[17] was used. Sensitivity analysis was conducted by sequential removal of each trial.[18] Visual inspections of funnel plots were performed and the Egger[19] and Begg test[20] results, which were also used to quantitative to statistically assess publication bias.

3. Results

3.1. Search results and basic characteristics

A total of 483 articles were identified in the electronic searches. Of these, 469 were excluded for being duplicates and irrelevant. After reviewing 14 full-text eligible articles, 7 randomized controlled trials involving 8 comparisons satisfied the selection

Table 1

Risk of bias among included studies.

Source	Sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Other bias
Tabernero et al [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Peeters et al [8]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
Cohn et al [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Cohn et al [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Cutsem et al [10]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
Peeters et al [7]	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear	Low risk
Xie et al [14]	Low risk	Unclear	High risk	Unclear	Low risk	Unclear	Low risk
Cao et al [15]	Low risk	High risk	High risk	High risk	Low risk	Unclear	Low risk

Table 2

Basic patient characteristics.

Ref.	Study type	Comparison	Cases, n	Male sex, %	Median PFS, mo	Median OS, mo	ORR, %	Grade3/4 AEs, %
Tabernero et al[11]	Phase III RCT	Folfiri ± Ramucirumab	536 and 536	54.0%, vs 61.0%	5.7 vs 4.5	13.3, vs 11.7	13.4%, vs 12.5%	79%, vs 62%
Peeters et al[8]	Phase II RCT	Folfiri ± trebananib	95 and 49	63.0%, vs 49.0%	3.5, vs 5.2	11.9, versus 8.8	14%, vs 0	55.3%, vs 59.2%
Cohn et al[9]	Phase II RCT	Folfiri ± conatumumab	51 and 52	53.0%, vs 44.0%	6.5, vs 4.6	12.3, vs 12.0	14%, vs 2%	72%, vs 47%
Cohn et al[9]	Phase II RCT	Folfiri ± Ganitumab	52 and 52	46.0%, vs 44.0%	4.5, vs 4.6	12.4, vs 12.0	8%, vs 2%	55%, vs 47%
Cutsem et al[10]	Phase III RCT	Folfiri ± Aflibercept	612 and 614	59.6%, vs 57.5%	6.90, vs 4.67	13.50, vs 12.06	19.8%, vs 11.1%	83.5%, vs 62.5%
Peeters et al[7]	Phase III RCT	Folfiri ± panitumumab	303 and 294	62.0% vs 65.0%	5.9, vs 3.9	14.5, vs 12.5	35%, vs 10%	73%, vs 52%
Xie et al[14]	Phase II RCT	Folfiri ± panitumumab or bevacizumab	137 and 155	59.1%, vs 63.2%	5.5, vs 4.2	13.9, vs 10.7	40.1%, vs 30.1%	52.6%, vs 80.0%
Cao et al[15]	Phase II RCT	Folfiri ± bevacizumab	65 and 77	61.5%, vs 62.3%	8.5, vs 5.1	15.2, vs 11.3	9.2%, vs 6.5%	63.1%, vs 75.3%

AE = adverse effect, Folfiri = 5-fluorouracil, leucovorin, and irinotecan, NA = not available, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, RCT = randomized controlled trials.

criteria were found[7–11,14,15] (Fig. 1). A manual search of the reference lists of these studies did not yield any new eligible studies. The basic characteristics of the studies included in the meta-analysis are summarized in Table 2.

The characteristics of these trials (Tabernero et al,[11] Peeters et al,[13] Cohn et al,[9] van Cutsem et al,[10] Peeters et al,[7] Xie et al,[14] and Cao et al[17]) are summarized in Table 2. A total of 3680 patients with mCRC were included in the 7 trials. The detailed quality of included trials is summarized in Table 1. Two of the included trials with design limitations have lower study quality due to high risk for blinding of participants and researchers, and blinding of outcome assessment.[14,15]

3.2. Progression-free survival

Six trials involving 7 comparisons were assessed for PFS.[7–11,15] The HR was 0.78 (95% CI, 0.72–0.85; $P < .001$), and there was no evidence of statistically significant heterogeneity between the groups ($I^2 = 13.3\%$; $P = .328$) (Fig. 2). The result showed a PFS benefit when biological therapy was combined with FOLFIRI regimen. Sensitivity analyses were conducted for PFS; after each trial was sequentially excluded from the pooled analyses, the conclusion was not affected.

3.3. Overall survival

Six trials involving 7 comparisons were assessed for OS.[7–11,15] The HR was 0.84 (95% CI, 0.77–0.92; $P < .001$), and there was no evidence of statistically significant heterogeneity between the groups ($I^2 = 0.0\%$; $P = .817$) (Fig. 3). The result also demonstrated a significant improvement of OS from the combination chemotherapy with biological therapy. Sensitivity analyses were conducted for OS; after each trial was sequentially excluded from the pooled analysis, the conclusion was not affected.

3.4. Overall response rate

The result of the heterogeneity test for ORR was significant ($I^2 = 59.5\%$; $P = .016$); hence, the random-effects model was used. ORR significantly differed between the combined therapy and

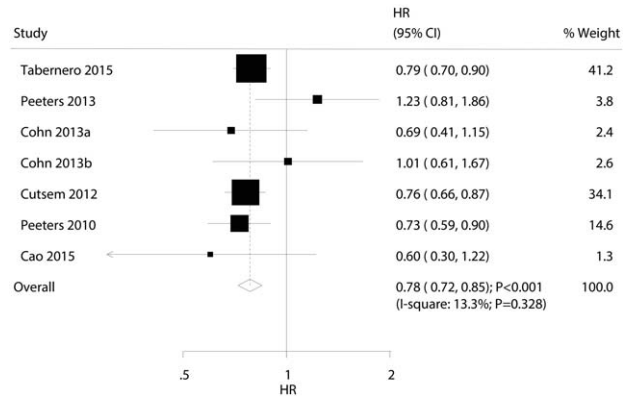

Figure 2. Forest plot of hazard ratio (HR) comparing progression-free survival (PFS) for previously treated mCRC patients who received biological therapy and FOLFIRI versus those who received FOLFIRI alone. Squares represent HR for each trial; the size of the square represents the weight of the trial in the meta-analysis and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effects based on the meta-analysis fixed-effects model for all trials. The inverse variance (IV) and fixed-effects model were used to calculate HR, 95% CIs, *P* values, and the test for overall effect; these calculations were two sided. The Chi-squared and I^2 tests were used to calculate heterogeneity. control = FOLFIRI alone group; experimental = biological therapy and FOLFIRI group; Fixed = the fixed-effects model; SE = standard error.

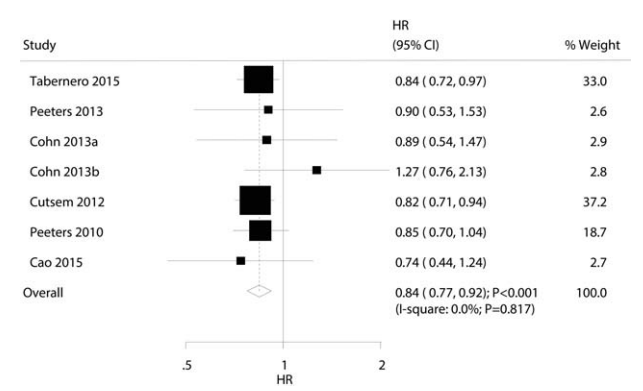

Figure 3. Forest plot of hazard ratio (HR) comparing overall survival (OS) for previously treated mCRC patients who received biological therapy and FOLFIRI versus those who received FOLFIRI alone. The squares represent HR for each trial; the size of the square represents the weight of the trial in the meta-analysis and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis fixed-effects model for all trials. The inverse variance (IV) and fixed-effects model were used to calculate HR, 95% CIs, *P* values, and the test for overall effect; these calculations were 2-sided. The Chi-squared and I^2 tests were used to calculate heterogeneity. control = FOLFIRI alone group; experimental = biological therapy and FOLFIRI group; Fixed = the fixed-effects model; SE = standard error.

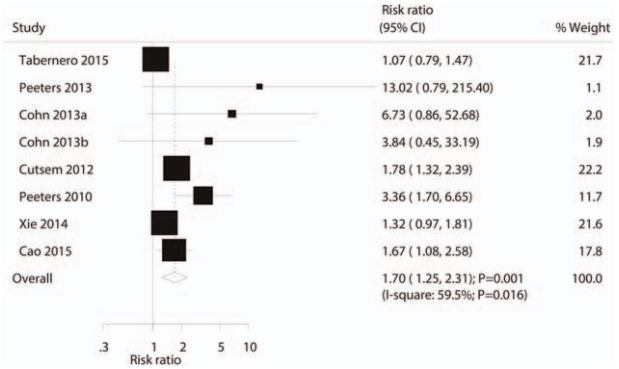

Figure 4. Forest plot of risk ratio (RR) comparing overall response rate (ORR) for previously treated mCRC patients who received biological therapy and FOLFIRI versus those who received FOLFIRI alone. The squares represent RR for each trial; the size of the square represents the weight of the trial in the meta-analysis and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis random-effects model for all trials. Mantel–Haenszel (M–H) and randomized-effects model were used to calculate RR, 95% CIs, *P* values, and the test for overall effects; these calculations were 2-sided. The Chi-squared and I^2 tests were used to calculate heterogeneity. control = FOLFIRI alone group; experimental = biological therapy and FOLFIRI group; Random = randomized-effects model.

chemotherapy alone. The combined therapy group showed a higher response rate than the chemotherapy alone group (RR = 1.70, 95% CI = 1.25–2.31, *P* = .001) (Fig. 4). Sensitivity analyses were conducted for ORR; after each trial was sequentially excluded from the pooled analysis, the conclusion was not affected.

3.5. Adverse events

Similarly, substantial heterogeneity was detected across the included trials for Grade 3/4 AEs. We used random-effects model

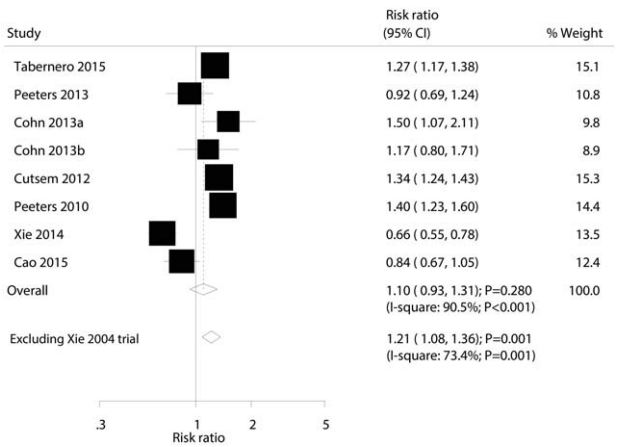

Figure 5. Forest plot of risk ratio (RR) comparing Grade 3/4 adverse events (AEs) for previously treated mCRC patients who received biological therapy and FOLFIRI versus those who received FOLFIRI alone. The squares represent RR for each trial; the size of the square represents the weight of the trial in the meta-analysis and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effects based on the meta-analysis fixed-effects model for all trials. Mantel–Haenszel (M–H) and fixed-effects models were used to calculate RR, 95% CIs, *P* values, and the test for overall effects; these calculations were 2-sided. The Chi-squared and I^2 tests were used to calculate heterogeneity. control = FOLFIRI alone group; experimental = biological therapy and FOLFIRI group; Random = randomized-effects model.

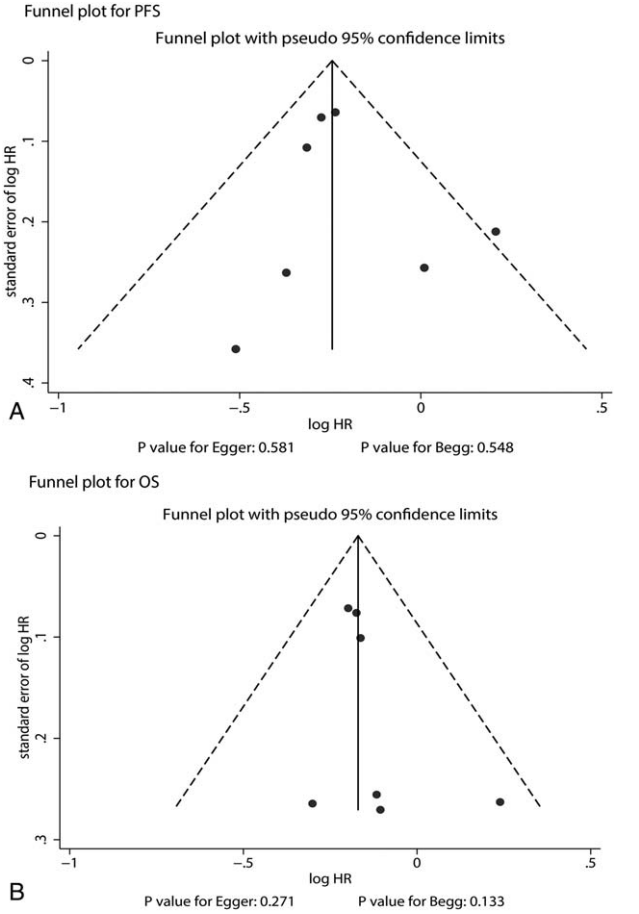

Figure 6. Funnel plots for progression-free survival (PFS), and overall survival (OS). (A) PFS: Funnel plots for standard error by log hazard ratio. (B) OS: Funnel plots for standard error by log hazard ratio.

and the results indicated that the addition of biological therapy to FOLFIRI was not associated with the risk of Grade 3/4 AEs as compared with FOLFIRI alone (RR = 1.10, 95% CI = 0.93–1.31, *P* = .280) (Fig. 5). According to sensitivity analysis, we excluded the study of Xie et al,[19] which specifically included patients received panitumumab and bevacizumab as biological therapy with FOLFIRI regimen, which may have contributed confounders. After this exclusion, combined therapy significantly increased the risk of Grade 3/4 AEs by 21% compared with FOLFIRI alone (RR = 1.21, 95% CI = 1.08–1.36, *P* = .001) (Fig. 5).

3.6. Publication bias

Publication bias was qualitative assessed by the shape of funnel plots and quantitative assessed by Egger[19] and Begg tests.[20] There was no obvious evidence of publication bias according to the symmetric funnel-shaped distribution for PFS and OS (Fig. 6). The Egger and Begg test results showed no evidence of publication bias for PFS (*P* value for Egger: .581; *P* value for Begg: .548) and OS (*P* value for Egger: .271; *P* value for Begg: .133).

4. Discussion

The main purpose of this meta-analysis was to evaluate the efficacy and safety of adding biological therapy to FOLFIRI as second-line treatment for mCRC patients. According to our

meta-analysis, the addition of biological therapy to FOLFIRI significantly improved PFS (HR = 0.78, 95% CI = 0.72–0.85, $P < .001$), OS (HR = 0.84, 95% CI = 0.77–0.92, $P < .001$), and ORR (RR = 1.70, 95% CI = 1.25–2.31, $P = .001$). Furthermore, combined therapy did not increase the incidence of Grade 3/4 AEs compared with FOLFIRI alone (RR: 1.10; 95% CI: 0.93–1.31; $P = .280$). Sensitivity analysis indicated that the combined therapy resulted in higher toxicity to mCRC patients (RR = 1.21, 95% CI = 1.08–1.36, $P = .001$).

From the findings of previous meta-analysis,[21] the use of biologic therapy in mCRC patients after first-line treatment has association with improved outcomes but increased toxicity. Although the number of trials in our study was reduced by confining the chemotherapy regimen to the FOLFIRI and the treatment to second-line therapy, our results were similar to the previous meta-analysis. And then, additional 4 randomized controlled trials were found and enrolled.[8,11,14,15] Therefore, our meta-analysis tried to explore the efficacy and safety of combined therapy with FOLFIRI in details.

Most of our included trials showed that the primary endpoint of PFS had a trend of improvement with the combined therapy. Although most investigated biological agents were different, the results from these included trials indicated that the efficacy of the combination of biological agents and FOLFIRI is robust. Moreover, several included studies detected that there was no significant difference in OS.[22,23] It is known that OS is a more objective index for an incurable disease such as mCRC. However, OS requires more cases to be enrolled and a long follow-up period, and it may be influenced by crossover and sequential therapy. Although PFS could be affected by other factors, such as the sensitivity of the imaging instrument, experience of radiographers, and the timing of tumor progression, it could be applied universally without being affected by crossover and sequential therapy.

For ORR, all 7 trials involving 8 comparisons were used in our meta-analysis. Significant heterogeneity was detected and no obvious publication bias was found. With the fixed-effects model, the sensitivity analysis for ORR suggested that 1 trial[11] would dominate the findings. With the randomized-effects model, the ORR benefit was more significant. The RR value of the combined therapy compared with FOLFIRI alone increased from 1.66 to 2.08, which has a broader 95% CI (95% CI from 1.36–2.02 to 1.23–3.51). Two factors might attribute to the result. First, the ORR of the trial by Tabernero was similar in the 2 groups only. Second, the number of patients in the trial by Tabernero et al[11]accounted for more than 33% of the total patients. In the trial by Tabernero et al,[11] the ORR results are in line with those in other trials of continuation of antiangiogenic therapy after disease progression. For example, in 1 previous trial[21] in which patients continued the same antiangiogenic therapy after disease progression, survival increased but did not have statistical significance for ORR. The specific mechanisms are not clear.

Compliance to combined therapy is recognized as a problem of studies evaluating the efficacy of combined therapy for mCRC patients. As expected, the frequency of any Grade 3/4 AE increased. The nature and incidence rate of toxicities of combined therapy had a consistence with those in other previous studies.[24,25] In the trial by Cutsem et al,[10] some of the common AEs related to FOLFIRI, including diarrhea, stomatitis, infection, neutropenia, and neutropenic complications, were more serious when using the combination therapy. This might because that biological agents likely to increase a potential overlapping toxicities. Importantly, no unexpected toxicity signals were identified; the toxicities resulting from the combination therapy were generally in accordance with those previously reported of each biological agent[24,26–30] and were manageable in each trial.[7–11]

Clinicians have already agreed on the first-line treatment strategy for mCRCs.[31] The most confusing treatment decisions are often related to second-line therapy (or failure after the first-line strategy). By identifying all relevant trials, the meta-analysis showed that the combination of FOLFIRI and biological therapy conferred a statistically significant OS and PFS compared with FOLFIRI alone or with placebo. However, whether other chemotherapy regimens combined with biological therapy could improve OS, and it is critical that predictive biomarkers that could identify mCRC patients who are most sensitive to specific targeted agents should be verified in future large-scale randomized controlled trials.

Three strengths of our study should be highlighted. First, only randomized controlled trials were included, which could avoid overestimate the effect of biological therapy and FOLFIRI regimen, which could be of concern in observational studies. Second, the large sample size allowed us to quantitatively assess the efficacy and safety of the combination of FOLFIRI and biological therapy in patients with mCRC, and thus, our findings are potentially more robust than are those of any individual study. Third, mostly summary results with no evidence of heterogeneity, and the findings of this study were stable.

The limitations of our study are as follows: first, although no publication bias was found from the results of the funnel plots and Egger or Begg test, statistical power was expected to be low because only 7 trials were used. Therefore, subgroup analysis was not performed according to multiple types of biological therapy. Second, the data were extracted from abstracted data (AD). Detailed individual patient data (IPD) were not available might indicate that the findings were not very credible. However, a preliminary correlation analysis demonstrates that AD and IPD meta-analyses are particularly relevant,[32] which means that AD is a practical alternative to IPD. Third, inevitable differences existed among the included studies, such as sample size, study design, and whether patients received first-line antivascular endothelial growth factor therapy. Fourth, the current study was based on published studies, and publication bias is an inevitable problem. All of these factors could potentially affect the treatment effect.

5. Conclusion

The addition of biological therapy to the FOLFIRI regimen improved the PFS, OS, and ORR compared with FOLFIRI alone for previously treated patients with mCRC. Long-term survival outcomes are warranted.

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