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REVIEW ARTICLE

Bevacizumab and erlotinib versus bevacizumab for colorectal cancer treatment: systematic review and meta-analysis

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Abstract

Background Improving the survival of patients diagnosed with metastatic colorectal cancer requires the use of chemotherapy to be managed with minimum adverse effects. Randomized control trials (RCTs) have shown promising results with a combination of bevacizumab and erlotinib to block two important tumor growth pathways, namely vascular endothelial growth factor and epidermal growth factor receptor. *Aim of the Review* We aimed to examine the efficacy and safety of the combination of bevacizumab and erlotinib with bevacizumab alone in the maintenance treatment of metastatic colorectal cancer, by examining PFS, OS, overall response rate (ORR), and toxicity. This study performed a systematic review meta-analysis using existing randomized clinical trial. *Methods* Randomized controlled trials were systematically reviewed from PubMed, Cochrane library, SCOPUS, CRD, and Google scholar databases. After evaluating the quality of studies through the Cochrane checklist, data of the relevant studies were extracted. This meta-analysis included outcomes of overall survival, progression-free survival of the disease through the hazard ratio, and the upper and lower confidence intervals for the third and fourth degree side effects of relative risk. To perform the meta-analysis for both types of survival, two fixed and random effect models were used. *Results* A total of three trials, providing data of 682 patients who received maintenance treatment, were included in this meta-analysis. *Conclusion* The combination of bevacizumab and erlotinib significantly increased the overall survival compared to using bevacizumab alone [HR = 0.78, 95% CI 0.66–0.93]. This combination, effectively increased progression-free survival [HR = 0.81, 95% CI 0.7–0.93] too. The side effects of diarrhea and grade III rash were more frequent in the group administered bevacizumab plus erlotinib. The combination of bevacizumab and erlotinib, in the maintenance treatment of metastatic colorectal cancer, significantly improved the overall survival and progression-free survival of patients, and the resulting side effects were easily treatable.

Keywords Bevacizumab · Colorectal neoplasms · Erlotinib hydrochloride · Maintenance chemotherapy · Meta-analysis

Impact on practice

- Maintenance therapy with combination of bevacizumab and erlotinib in mCRC can significantly increase the overal survival and the profgression free survival.
- Maintenance therapy with combination of bevacizumab and erlotinib in mCRC is well tolerated and safe.
- It is likely that the combination of erlotinib and bevacizumab, by inhibiting the VEGF and EGFR pathways, has a better effect on treating cancer than if used individually.

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Background

Colorectal Cancer (CRC) is the third most commonly occurring cancer in the world, with nearly 1.3 million cases diagnosed every year. It is also one of the leading causes of cancer death, with an annual estimate of 694,000 deaths [1–3]. Progression to metastatic colorectal cancer (mCRC) occurs in approximately half of the patients with colorectal cancer [1].

There are several options for treating CRC including surgery and chemotherapy [4, 5]. Surgery is considered the basic treatment for the primary stages of this cancer (Stages I–III) [6]. However, to treat mCRC (Stage IV), doctors prescribe chemotherapy as the first option. In terms of chemotherapy strategies, factors such as the prevention of chemotherapy-induced toxicity, maintaining the patient's quality of life, and enhanced progression-free survival (PFS), are preferred over the use of stronger drug regimens, should surgery not be an option. Therefore, doctors in such cases use maintenance therapy, i.e. using drugs with lower sensitivity and toxicity in order to control tumor growth [7, 8]. Bevacizumab and erlotinib are two such drugs used in mCRC maintenance therapy. Bevacizumab is a monoclonal antibody; its mechanism inhibits the vascular endothelial growth factor (VEGF) [9]. Erlotinib, as an anticancer drug, inhibits the epidermal growth factor receptor (EGFR), thus restricting the growth of cancer cells and preventing their spread throughout the body [10, 11]. Several trials have investigated the effects of erlotinib in colorectal cancer [10, 12–16]. Therefore, the main objective of bevacizumab and erlotinib is the inhibition of different tumor growth pathways, namely VEGF and EGFR, respectively. Furthermore, the mechanisms of these two drugs (dual inhibition of EGFR and VEGF) complement each other in the treatment of tumors [17–20] and this issue was investigated in different clinical trials [21, 22]. Therefore, it is likely that the combination of these two drugs will have a better effect on cancer treatment than each drug given alone [23, 24]. The Kirsten ras (KRAS) status of tumors is an important indicator in the management of this disease. The KRAS mutations cause poor prognosis in response to treatment with certain anti-EGFR drugs, such as panitumumab and cetuximab, that prevents these drugs from fighting the tumor. Clinical trials have been assessing the efficacy of bevacizumab plus erlotinib in patients with metastatic colorectal cancer [25–27]. Among these, two studies suggested that this particular drug combination does not have any effect on the overall survival (OS) and PFS [18–20], but the results of another study indicated that this combination had a positive effect [27].

Aim of the review

To examine the efficacy and safety of the combination of bevacizumab and erlotinib with bevacizumab alone in the maintenance treatment of metastatic colorectal cancer, by examining PFS, OS, overall response rate (ORR), and toxicity. This study performed a systematic review meta-analysis using existing randomized clinical trial (RCTs).

Method

This meta-analysis study utilized RCTs to compare the combination of bevacizumab and erlotinib versus bevacizumab alone in the maintenance treatment of metastatic colorectal cancer, without any time constraints and based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. RCTs that compared the combination of bevacizumab and erlotinib versus bevacizumab alone in the maintenance treatment of metastatic colorectal cancer, published before June 2017, were searched.

Several databases, such as PubMed, Cochrane library, SCOPUS, Centre for Reviews and Dissemination (CRD), and Google Scholar were used in this search. In addition, the abstracts sent to the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) was checked too. The manufacturer's website for the two drugs, bevacizumab and erlotinib, was searched for articles relating to the two drugs. Studies were searched with the keywords, "bevacizumab OR avastin", "erlotinib OR tarceva", "colorectal cancer", and similar words that were combined with AND OR operators. After duplicate studies removal in Endnote X5 software, all abstracts and full-text studies were reviewed. Finally, the reference list of selected articles was further reviewed for additional articles. In case of studies data overlapping (e.g. information from an identical RCT split and published in several articles), the most complete and up-to-date report was selected for inclusion in the meta-analysis. Two independent reviewers did the study selection, quality assessment and data extraction steps; any disagreement between the two reviewers was resolved through discussion and referral to a third person. The studies were included in this meta-analysis if they met the following criteria: (1) RCTs in English with full text; (2) Patients aged 18 and above, whose mCRCs were histologically or cytologically approved; (3) Patients in the intervention group received a combination of bevacizumab and erlotinib, while the control group received Bevacizimab alone; and (4) Studies that reported either PFS and OS with a hazard ratio (HR) of 95% confidence interval or data to calculate them.

Studies other than RCT that were published in a language other than English, and studies that used drugs other than bevacizumab and erlotinib in the experimental and control groups were excluded from the study. Moreover, conference abstracts that have not been published or publications for which full-text access was not available were also excluded from this meta-analysis. The methodology quality of articles was evaluated by two researchers, separately, using the standard Cochrane Collaboration risk of bias tool [29] in RevMan 5.3 software. The important criteria studied in this checklist were randomization and allocation concealment, selective reporting, and incomplete outcome data. The data was extracted in pre-designed tables and included data on the author, year of publication, sample size, age, and gender of the patients, duration of follow-up, PFS, and OS, response rate, as well as the probability of side effects. The primary characteristics of patients are briefly summarized in Table 1.

In this research, OS was the primary outcome defined as the time interval between randomization and death (from any cause). The secondary outcomes were PFS, ORR, and adverse events. PFS is referred to as the interval between the onset of maintenance therapy and relapse or patient's death without relapse. ORR is the sum of complete response rates and partial responses. For analyzing the incidence of side effects in patients, the number of patients was extracted in each complication and then odds ratio (OR) were used as an effect size. To perform meta-analysis for PFS and OS results, HR and the lower and upper limit of the articles confidence interval were extracted and analyzed using two fixed and random effects models. The heterogeneity of studies was evaluated using I^2 and Q tests.

We performed the analysis using the STATA Ver. 12 software. All reported *P* values from the two-way models were obtained from the respective tests. A *P* value ≤ 0.05 was considered as statistically significant. All confidence intervals were 95% probable.

Results

In the systematic search of all databases, 170 articles were extracted. Then, the titles and abstracts of the articles were examined to identify 94 related articles, and ultimately, by reviewing the full text of these articles and considering the inclusion and exclusion criteria, three articles were entered into the meta-analysis (Fig. 1). In total, 1183 people aged 18–80 years were included. The characteristics of the studies are summarized in Table 2. These studies were published between 2013 and 2016, and all had a multicenter design. 682 participants received maintenance treatment in these studies.

The three included articles had an open-label design, in which there was no possibility of blinding. Therefore, the items of blinding patients and personnel as well as the

Table 1 Baseline patient characteristics in the trials included in the meta-analysis

Characteristics	Johnsson et al.		Tournigand et al.		Hagman et al.		Total	
	Bevacizumab + erlotinib (*n* = 80)	Bevacizumab (*n* = 79)	Bevacizumab + erlotinib (*n* = 224)	Bevacizumab (*n* = 220)	Bevacizumab + erlotinib (*n* = 36)	Bevacizumab (*n* = 35)	Bevacizumab + erlotinib (*n* = 340)	Bevacizumab (*n* = 342)
Sex (male)	53 (66)	43 (54)	147 (66)	129 (57)	23 (64)	23 (66)	233 (65.6)	195 (57)
KRAS status (wild)	NR	NR	130 (58)	112 (49)	36 (100)	35 (100)	166 (48.8)	147 (42.9)
Primary tumor site								
Colon	44 (55)	53 (67)	166 (74)	166 (73)	27 (75)	16 (46)	237 (69.7)	235 (68.7)
Rectum	30 (38)	19 (24)	52 (23)	58 (25)	7 (19)	19 (54)	89 (26.2)	96 (28.1)
Rectum-sigmoid	6 (8)	7 (9)	6 (3)	4 (2)	2 (6)	0	14 (4.2)	11 (3.2)
Metastatic site								
Liver	62 (78)	58 (73)	192 (86)	190 (82)	NR	NR	254 (74.7)	248 (72.5)
Lung	33 (41)	37 (47)	73 (33)	83 (36)	NR	NR	106 (31.2)	120 (35.1)
Lymph nodes	35 (44)	28 (35)	49 (22)	67 (29)	NR	NR	84 (24.7)	95 (27.8)
Other	5 (6)	9 (11)	NR	NR	NR	NR	5 (1.5)	9 (2.6)
Metastatic site								
1	39 (49)	34 (43)	108 (48)	102 (45)	18 (50)	12 (34)	165 (48.5)	148 (43.3)
> 1	41 (51)	45 (57)	116 (52)	126 (55)	18 (50)	23 (66)	175 (51.5)	194 (56.7)
ECOG PS								
0	58 (73)	53 (67)	137 (61)	135 (59)	24 (67)	27 (77)	219 (64.4)	215 (62.9)
1 or 2	22 (27)	26 (33)	87 (39)	93 (41)	12 (33)	8 (23)	121 (35.6)	127 (37.1)

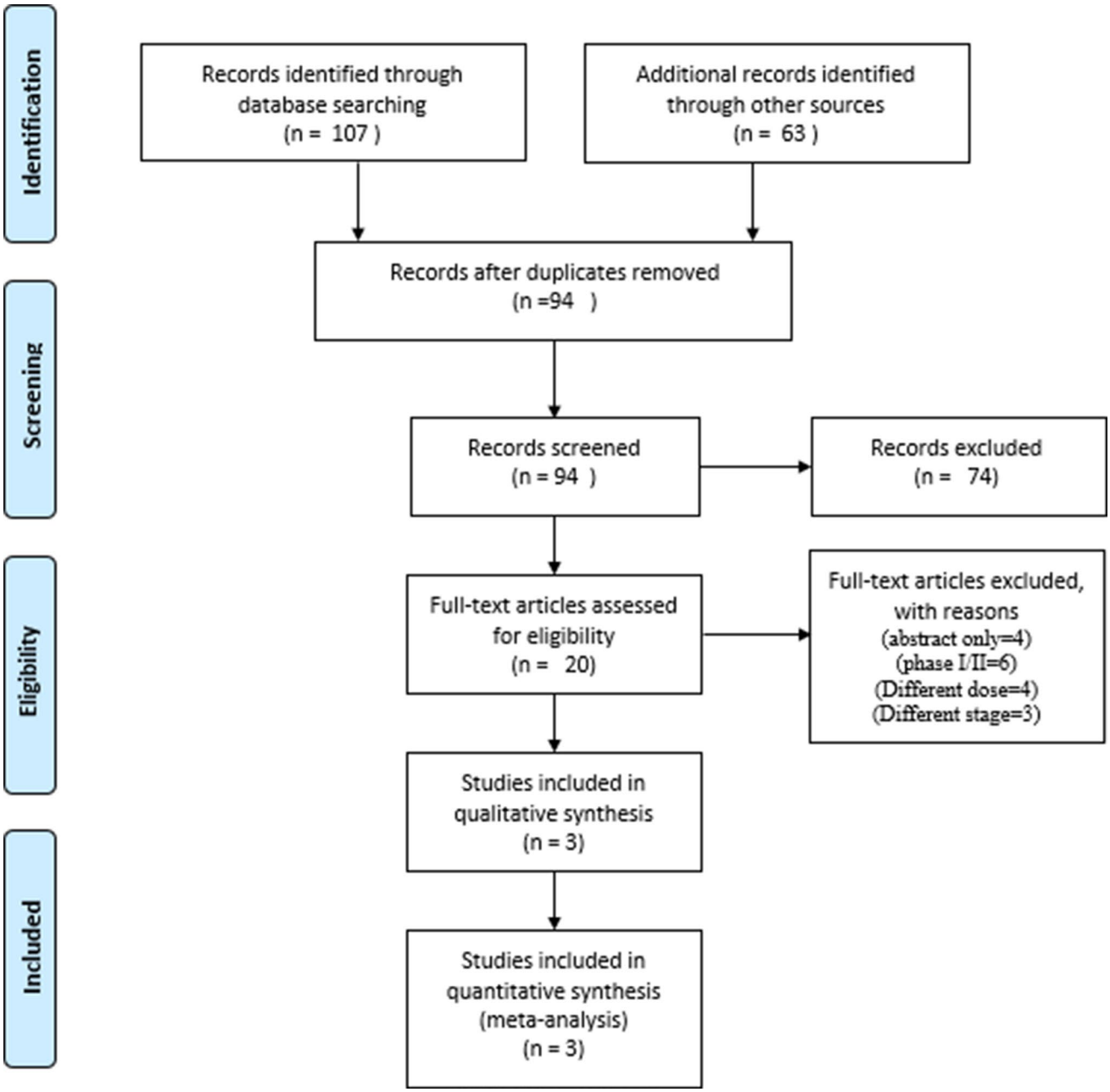

Fig. 1 Prisma flow diagram for clinical trials

allocation concealment created high bias. On the other hand, the role of pharmaceutical companies as funders probably imposed "other bias" in all included studies.

The articles quality evaluation is shown in Fig. 2. Due to the small number of studies, the test was not significant in assessing heterogeneity.

Regarding OS outcome, the figure shows that the combination of bevacizumab and erlotinib has a better effect than bevacizumab alone in maintenance therapy of mCRC. This was obtained from the Johnsson and Hagman studies, and suggests that although the drug combination resulted in a decreased death rate, it was not statistically significant. Based on the fixed effect model, the combined results of the three studies give an estimated risk ratio (RR) of 0.78 (95% CI 0.66–0.93). Finally, according to the meta-analysis of these three studies, the combined drug reduces the risk of death by 22%. (Figure 3)

Regarding PFS, the Johnsson and Hagman studies show a risk ratio of less than one and suggest that, although using a combination of the two drugs reduced mortality, it was not statistically significant. By combining the results of the three studies based on the fixed effect model, the

Table 2 Characteristics of studies included in the meta-analysis

Study	Number of patients	Age	Treatment (number of patients received)	ORR (%)	*P* value	OS (month)	*P* value	PFS (month)	*P* value
Johnsson et al.	249	≤18	Bevacizumab 7.5 mg/kg every 3 weeks (80)	NR	NR	22.8	0.51	4.23	0.19
			Bevacizumab 7.5 mg/kg every 3 weeks + erlotinib 150 mg daily (79)	NR	NR	21.5		5.73	
Tournigand et al.	700	18–80	Bevacizumab 7.5 mg/kg every 3 weeks(224)	11.53	0.0029	22.1	0.036	4.9	0.059
			Bevacizumab 7.5 mg/kg every 3 weeks + erlotinib 150 mg daily (220)	22.53		24.9		5.4	
Hagman et al.	233	≤18	Bevacizumab 7.5 mg/kg every 3 weeks (36)	NR	NR	30.7	0.0510	3.7	0.867
			Bevacizumab 7.5 mg/kg every 3 weeks + erlotinib 150 mg daily (35)	NR	NR	20.6		5.7	

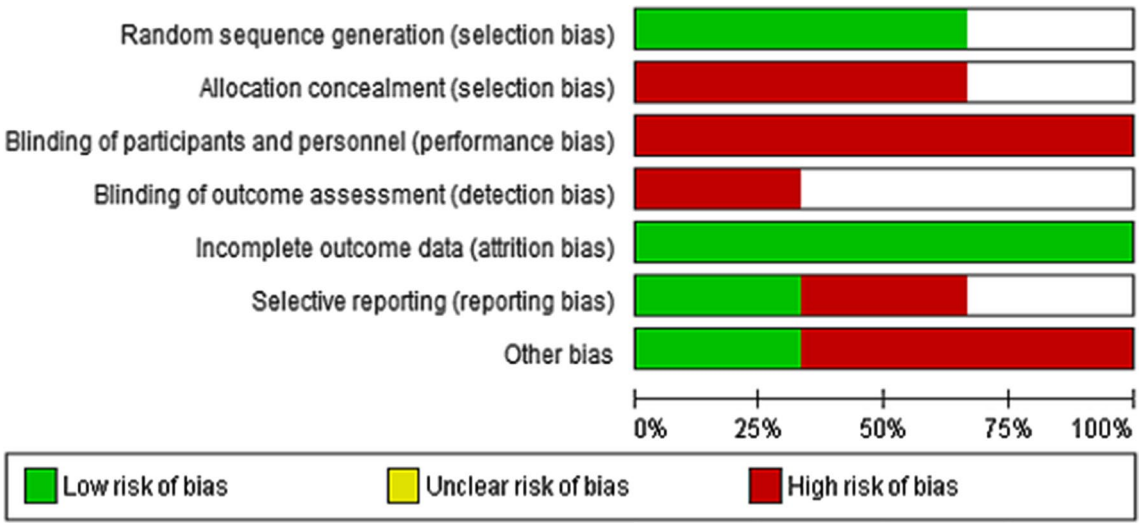

Fig. 2 Quality of included trials

risk ratio was 0.81 (95% CI 0.7–0.93). Finally, according to the meta-analysis of these three studies, it can be asserted that the combination of the two drugs reduces the risk of death by 19% (Fig. 4).

The ORR was reported only in Tournigand et al. study; bevacizumab plus erlotinib showed a significant effect in improving ORR ($P = 0.0029$). Finally, due to lack of data pertaining to this outcome, meta-analysis could not be performed.

Among grade 3 severity level side effects, the asthenia complication was not significant between the two treatment groups. Overall, according to the results of meta-analysis and Fig. 5, no significant difference was observed between the two groups (RR = 3.6, 95% CI 0.9–14.40).

In terms of hypertension, as a complication, it was not significant in any of the studies (Fig. 6), suggesting that there was no significant difference between the two treatment groups (RR = 0.99, 95% CI 0.42–2.36).

As it is shown in Table 3, the incidence of complications for asthenia, hypertention, hand-foot syndrome, anorexia proteinuria, nausea, and/or vomitting were not significant in the three studies. On the other hand, the range of their confidence intervals was high, which showed a low accuracy in measuring these complications. Overall, according to the

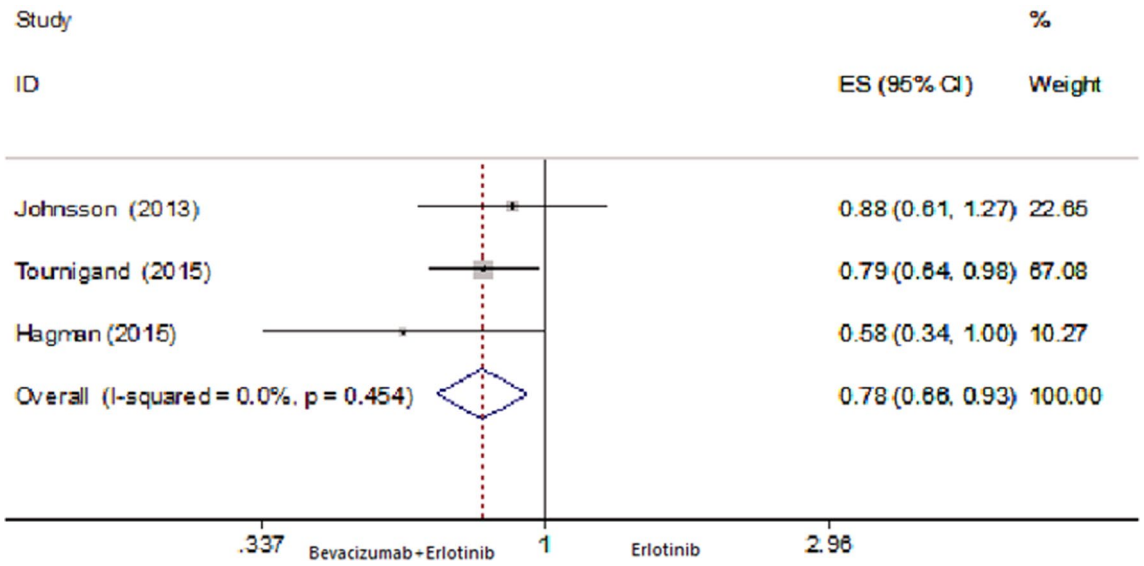

Fig. 3 Forrest Plot for of overall survival associated with the bevacizumab plus erlotinib group compared with the bevacizumab group. Fixed-effects model of HR (95% CI) of overall survival associated with the bevacizumab plus erlotinib group compared with the bevacizumab group. *CI* confidence interval, *HR* hazard ratio

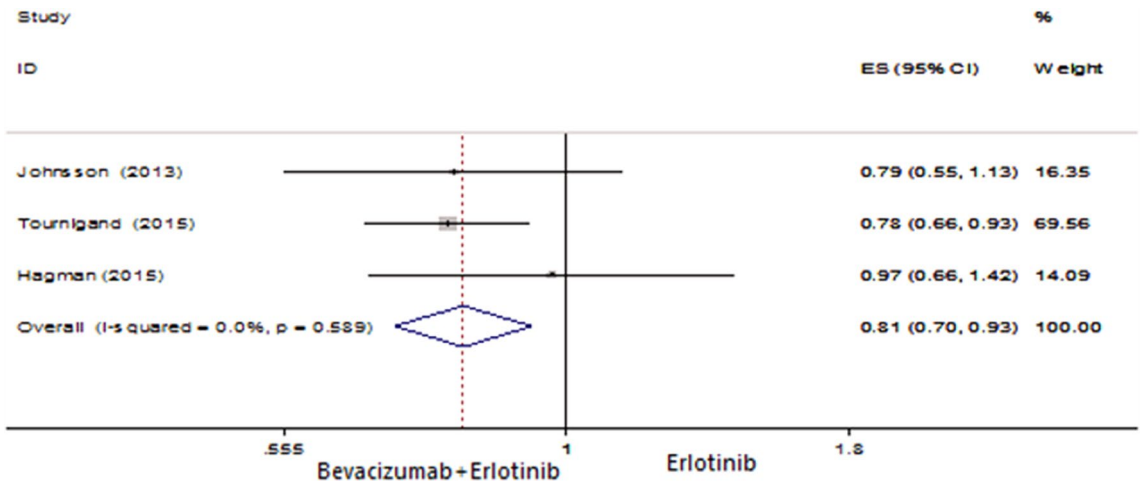

Fig. 4 Forrest plot for progression free survival associated with the bevacizumab plus erlotinib group compared with the bevacizumab group. Fixed-effects model of HR (95% CI) of progression-free survival associated with the bevacizumab plus erlotinib group compared with the bevacizumab group. *CI* confidence interval, *HR* hazard ratio

meta-analysis results, the incidence of complications in the three studies was not significant, and given the wide range of confidence intervals, the results had low accuracy.

The rash complication was significant in the Johnsson and Tournigand studies, but not significant in the Hagman study. The meta-analysis results showed a significant difference in the incidence of this side effect between the two groups, but due to the wide confidence interval, the results had low accuracy (22.652, 95% CI 5.528–92.824).

The diarrhea complication was significant in the Johnsson and Hagman studies, and the meta-analysis results indicated a significant difference between the two groups, but due to the wide confidence interval, the results had low accuracy (8.956, 95% CI 2.74–29.270).

The meta-analysis of the complications for thrombosis, epistaxis, and mucositis neutropenia also showed an insignificant difference between the two treatment groups.

The results of meta-analysis of grade 4 severity level of side effects indicated that these side effects were not significant between the two treatment groups (Table 4). In addition to insignificant results, the extent of the

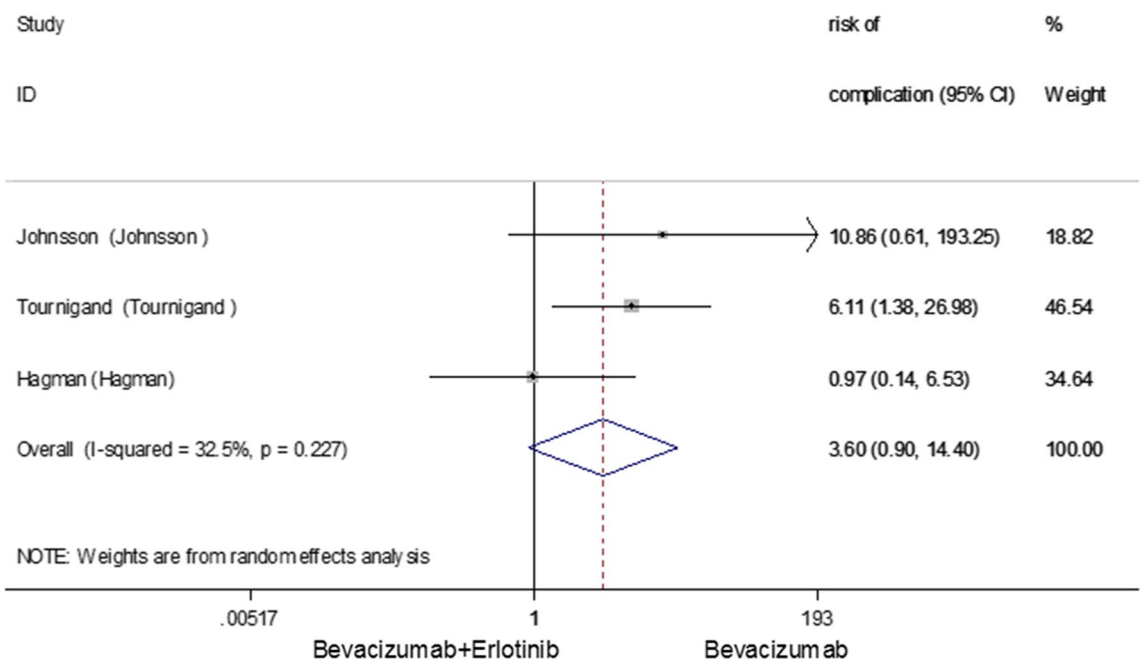

Fig. 5 Forrest plot for grade 3 Asthenia with the bevacizumab plus erlotinib group compared with the bevacizumab group. *CI* confidence interval, *RR* relative risk

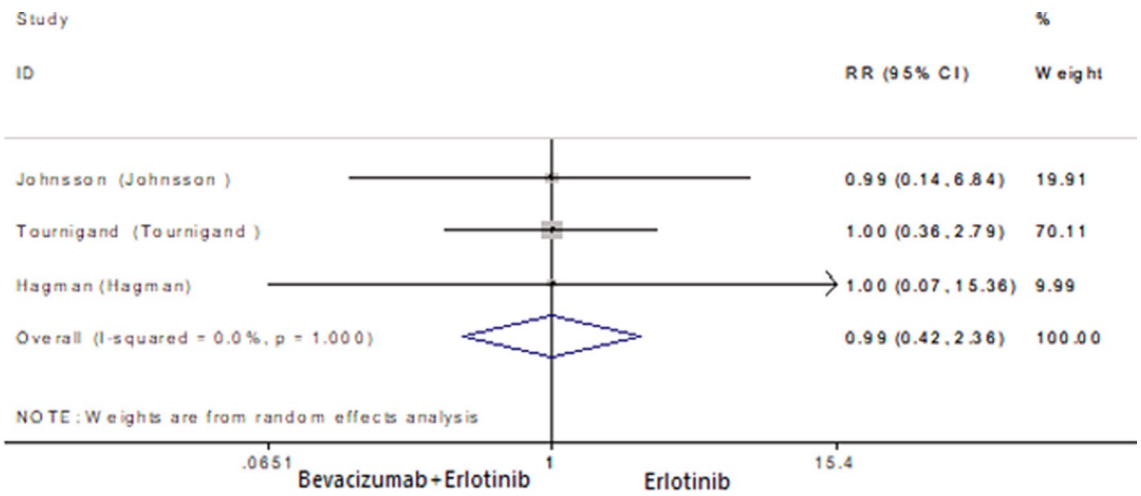

Fig. 6 Forrest plot for grade 3 hypertension with the bevacizumab plus erlotinib group compared with the bevacizumab group. *CI* confidence interval, *RR* relative risk

confidence interval ranges also showed that the difference between the two groups had low accuracy.

Discussion

Several pathways in cells can affect tumor growth and metastasis. A combination of treatments that can block several signaling pathways in the tumor seems to have a greater impact on the tumor growth than a single therapy alone [30]. Due to the association of VEGF and EGFR and their potential role in the growth and metastasis of tumors, their simultaneous obstruction can lead to greater antitumor effects [31, 32]. Of course, targeted therapies that can simultaneously influence both factors through drugs such as irinotecan, bevacizumab, and cetuximab, are known to be clinically valid in various cancers, including non-small cell lung cancer and solid tumors [32, 33]. On the other hand, the effect of simultaneous occlusion of these two factors in colorectal cancer was investigated in an animal-phase study,

Table 3 Grade 3 adverse effects

Study	Adverse effect	Incidence of adverse effect (%)		RR	95% confidence interval
		Bevacizumab + erlotinib	Bevacizumab		
Johnsson et al.	Asthenia	6.25	0	10.864	0.611–193.253
Tournigand et al.		5.45	0.9	6.109	1.383–26.981
Hagman et al.		5.56	5.71	0.972	0.145–6.526
				Pooled = 3.602	0.901–14.405
Johnsson et al.	Hypertention	2.5	2.54	0.988	0.143–6.839
Tournigand et al.		8.75	3.125	0.996	0.355–2.792
Hagman et al.		2.78	2.85	1	0.065–15.362
				Pooled = 0.994	0.419–2.358
Johnsson et al.	Hand foot syndrome	1.25	0	2.963	0.123–71.654
Tournigand et al.		0	0.45	0.339	0.014–8.286
				Pooled = 1.006	0.105–9.602
Johnsson et al.	Rash	20	1.27	15.8	2.146–116.307
Tournigand et al.		20.45	0	92.647	5.743–1494.586
Hagman et al.		13.89	0	10.703	0.614–186.599
				Pooled = 22.652	5.528–92.824
Johnsson et al.	Diarrhea	3.75	0	6.914	0.363–131.7
Tournigand et al.		9.09	0.9	10.182	2.409–43.043
Hagman et al.		8.33	0	6.811	0.365–127.225
				Pooled = 8.956	2.74–29.270
Johnsson et al.	Anorexia	1.25	0	2.963	0.123–71.654
Hagman et al.		2.78	2.85	0.972	0.063–14.944
				Pooled = 1.559	0.196–12.406
Johnsson et al.	Proteinuria	2.5	5.06	0.494	0.093–2.619
Tournigand et al.		1.81	0.45	4.073	0.459–36.151
Hagman et al.		2.8	0	2.919	0.123–69.322
				Pooled = 1.376	0.323–5.862
Johnsson et al.	Thrombosis	1.25	0	2.963	0.123–71.654
				Pooled = 2.963	0.123–71.654
Tournigand et al.	Epistaxis	0.45	0	3.054	0.125–74.572
				Pooled = 3.054	0.125–74.572
Tournigand et al.	Mucositis	0.45	0	3.054	0.125–74.572
				Pooled = 3.054	0.125–74.572
Johnsson et al.	Neutropenia	5	3.8	1.317	0.304–5.694
				Pooled = 1.317	0.304–5.694
Johnsson et al.	Nausea/vomiting	1.25	0	2.963	0.123–71.654
Tournigand et al.		1.37	0.45	3.055	0.320–29.141
Hagman et al.		0	2.86	0.333	0.014–7.920
				Pooled = 1.733	0.014–8.512

where this mechanism was confirmed in mice [34]. Clinical trials have confirmed that the combined use of bevacizumab and cetuximab in patients with colorectal cancer increases PFS [35, 36].

The present study, which was a systematic review and meta-analysis of RCTs, aimed at evaluating the efficacy and safety of a combination of bevacizumab and erlotinib compared to bevacizumab alone, in the maintenance therapy of metastatic colorectal cancer, by examining PFS, OS, overall response rate (ORR), and toxicity. Three RCTs with 682 patients receiving maintenance therapy included in this study. This research showed that the combination of bevacizumab and erlotinib is effective in increasing OS and PFS about 22% and 19% respectively. There was a low number of patients with grade 3 and 4 severity level of side effects and the results of the included clinical trials and this

Table 4 grade 4 adverse effects

Study	Advese effect	Incidence of adverse effect (%)		RR	95% confidence Interval
		Bevacizumab + erlotinib	Bevacizumab		
Johnsson et al.	Asthenia	1.25	0	2.963	0.123–71.654
Tournigand et al.		0	0	Excluded	
Hagman et al.		0	0	Excluded	
				Pooled = 2.963	0.123–71.654
Johnsson et al.	Rash	0	0	5.090	0.246–105.431
Tournigand et al.		0.91	0	Excluded	
Hagman et al.		0	0	Excluded	
				Pooled = 5.090	0.246–105.431
Johnsson et al.	Diarrhea	0	0	3.054	0.125–74.572
Tournigand et al.		0.45	0	Excluded	
Hagman et al.		0	0	Excluded	
				Pooled = 3.054	0.125–74.572
Johnsson et al.	Proteinuria	1.25	0	2.963	0.123–71.654
Tournigand et al.		0	0	Excluded	
Hagman et al.		0	0	Excluded	
				Pooled = 2.963	0.123–71.654
Johnsson et al.	Thrombosis	1.25	0	2.963	0.123–71.654
Tournigand et al.		0	0	Excluded	
Hagman et al		0	0	Excluded	
				2.963	0.123–71.654

meta-analysis revealed that these complications were manageable and treatable. In this study, the quality assessment of the included studies was done by standard Cochrane Collaboration risk of bias tool that is a validated tool [29]. The results of quality assessment showed high risk of selection and performance bias due to open-label design of studies. As outcomes of cancer trials, like PFS and OS, are not influenced by lack of blinding, the results of these open-label RCTs are acceptable [37].

Although there was no significant difference in the two treatment groups of the two studies in terms of the OS and PFS results, the meta-analysis results showed that the combination of bevacizumab and erlotinib, as maintenance therapy in metastatic colorectal cancer, could dramatically increase both OS and PFS compared to using bevacizumab alone. Despite the fact that the combination of the two drugs can lead to complications such as weakness and fatigue, skin rash and hand-foot syndrome as well as nausea and vomiting, they do not cause concern and are manageable and treatable. Furthermore, the number of people who discontinued maintenance therapy due to side effects were very limited.

Investigating the efficacy of FOLFOX4 plus bevacizumab with erlotinib as second-line chemotherapy in treatment of mCRC showed that the combination of erlotinib with FOLFOX4 plus bevacizumab was successful in increasing the PFS, but the combinational chemotherapy did not improve patients' OS [38]. Although this Phase II randomized double blind clinical study was not included in our meta-analysis, the PFS outcomes were consistent. The difference in OS results may be due to the chemotherapy setting, which was second-line treatment, whereas all the included studies in our meta-analysis were maintenance chemotherapy.

In another study the safety and efficacy of using erlotinib plus bevacizumab in the treatment of non-small-cell lung cancer as a meta-analysis was investigated; its results were consistent with the present study. Furthermore, it showed that the combination of these two drugs in the second line of treatment compared with bevacizumab or erlotinib alone, greatly improves PFS and OS [39]. Still another meta-analysis investigating safety and efficacy of adding bevacizumab to adjuvant therapy agents in cancer patients showed that combination of bevacizumab and adjuvant therapy could improve OS in colorectal cancer, NSCLC, renal cancer and melanoma cancer. Nevertheless, this combination was successful to improve PFS except in patients with melanoma, mesothelioma, and cervical cancers [40].

Zhao's meta-analysis, which considered different maintenance strategies for treating metastatic colorectal cancer with inclusion of six RCTs, has shown that the maintenance therapy with bevacizumab-based doublets was effective in

increasing PFS, but the effect of these compounds was not significant for OS. The meta-analysis result as mentioned for the outcomes of PFS was consistent with the findings of the present study. However, our study showed that the combination of bevacizumab and erlotinib was effective in increasing OS. This difference in results could be because in the present study, only bevacizumab plus erlotinib has been studied, whereas Zhao's meta-analysis included all studies that have been conducted on two-drug maintenance-based treatment with bevacizumab [41].

A different meta-analysis examined the combination of bevacizumab and erlotinib in the maintenance treatment of metastatic colorectal cancer. The results of that study and our study were consistent in terms of the PFS and OS outcomes. Moreover, in both studies, the side effects were similar, but different methods were used to study them. In the meta-analysis, the side effects were calculated using the odds ratio (OR), but this study used relative risk (RR) [42]. Since all the included studies in this meta-analysis had RCT design, the use of RR was preferred to OR. There is stronger rational to use RR instead of OR. RR is intuitive and easier to interpret and understand by researchers, physicians, and policy makers [43, 44]. The odds ratio is suitable for statistical reasons to combine the effect size in a meta-analysis. However, it is useful to convert the odds ratio into a risk ratio because it is easier to interpret [43–45].

Recent studies have shown that the status of KRAS tumors, as wild and mutant types, can be effective in maintenance therapy. Among the meta-analysis studies, two studies reported the results according to the KRAS status [25–27]. Tournigand showed that unlike other anti-EGFR drugs that are not active in KRAS mutant tumors, the efficacy of erlotinib is not dependent on the KRAS status [27]. Hagman study [25], which cumulatively analyzed the data from the KRAS status of tumors in the Johnsson study [26], considered the efficacy of bevacizumab plus erlotinib independent of the KRAS state. Some studies suggest that patients with metastatic colorectal cancers and KRAS mutant tumors show less efficacy towards certain anti-EGFR anti-drugs like cetuximab or panitumumab [46–48]. Due to limited research in this field, meta-analysis for this parameter was not possible in the present study. Therefore, further clinical research is required to investigate the impact of KRAS on the efficacy of these drugs in treatment of metastatic colorectal cancer.

The limitations of this study should be considered. First, the study of the combination of bevacizumab and erlotinib compared to bevacizumab alone was investigated in only three RCTs. The number of articles was too low for obtaining a high degree of precision in the meta-analysis. Secondly, the clinical trial sample size entered for their studies was very limited, which in turn reduced the accuracy of the present study results. The third limitation was the lack of access to patients' data, resulting in the use of the studies result summary. Fourthly, blinding was not performed in the included studies causing the quality of studies to reduce; hence, their results should be carefully studied.

Conclusion

Overall, the results of this meta-analysis indicated that the combination of bevacizumab and erlotinib, can significantly affect the maintenance treatment of metastatic colorectal cancer, with regard to the patients' PFS and OS, particularly since their grade 3 and 4 severity level of side effects are low compared to using bevacizumab alone. According to the results of the clinical trials and this meta-analysis, the side effects for both chemotherapy strategies can be managed and treated. Finally, it should be noted that the decision to use a combination of these two drugs will depend on the doctor's opinion and the patient's condition, and should be done carefully. Indeed, given the impact of KRAS tumor status on the response to treatment, it is advisable for researchers to explore this issue through additional trials.

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