Clin Drug Investig (2017) 37:155–165
DOI 10.1007/s40261-016-0465-0

ORIGINAL RESEARCH ARTICLE

Survival Benefit and Safety of Bevacizumab in Combination with Erlotinib as Maintenance Therapy in Patients with Metastatic Colorectal Cancer: A Meta-Analysis

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Published online: 24 September 2016

Abstract

Background Recently, the need for maintenance chemotherapy arose as a result of the significantly improved survival of patients with metastatic colorectal cancer (mCRC) without increasing adverse events. Currently used maintenance regimens are fluoropyrimidines, bevacizumab, and the combination of fluoropyrimidine with bevacizumab. A new combination with bevacizumab and erlotinib, a tyrosine kinase inhibitor of the epithelial growth factor receptor, has shown synergistic effects in preclinical tests and promising results in some clinical trials. Whether bevacizumab combined with erlotinib vs. bevacizumab alone as maintenance therapy will further improve the clinical outcomes in patients with mCRC is controversial. We conducted this meta-analysis to compare the survival benefit and safety of these two regimens in patients with mCRC.

Methods We searched PubMed, EMBASE, and the Central Registry of Controlled Trials of the Cochrane Library up to August 2016. We also searched the Proceedings of the American Society of Clinical Oncology (1986 to August 2016). Abstracts were manually searched to identify relevant trials. A total of three randomized controlled trials with 682 patients met the inclusion criteria.

Results Our results demonstrated that bevacizumab combined with erlotinib significantly improved overall survival (hazard ratio 0.78; 95 % confidence interval 0.66–0.93; $p = 0.006$) and progression-free survival (hazard ratio 0.79; 95 % confidence interval 0.68–0.92; $p = 0.002$). Significantly more grade 3 rash, diarrhea, infection total, and fatigue were observed in the bevacizumab combined with erlotinib arm, which were controllable and reversible.

Conclusions Based on current evidence, the addition of erlotinib to bevacizumab as maintenance therapy significantly increases overall survival and progression-free survival with an increased but manageable toxicity in patients with mCRC. It should be considered as a treatment option for these patients under the premise of a reasonable selection of the target population.

Key Points

The addition of erlotinib to bevacizumab as maintenance therapy significantly increases overall survival and progression-free survival with an increased but manageable toxicity in patients with metastatic colorectal cancer.

The effectiveness of erlotinib was independent of the KRAS status of the tumors.

It should be considered as a new non-chemotherapy-based maintenance option for patients with metastatic colorectal cancer.

W. Xu and Y. Gong contributed equally to this work and share first authorship.

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1 Introduction

Colorectal cancer is the third most commonly diagnosed cancer, after lung and breast cancers, and the fourth highest cause of cancer-related death worldwide [1]. Along with recent improvements in diagnostic and therapeutic modalities, the incidence and the mortality of cancer have been declining over the past 20 years. However, it is still the main cause of increasing morbidity and mortality [2, 3].

Early diagnosis is very important for improving treatment outcomes. However, most patients who have localized disease lose the chance to receive curative (R0) surgical resection, when being diagnosed. Almost 50 % of those with local disease ultimately develop metastases. In addition, a considerable proportion of patients (40–50 %) experience disease recurrence after surgical resection or develop metastatic disease. The current treatment for metastatic colorectal cancer (mCRC) continues to favor the use of chemotherapy. Chemotherapy remains the primary therapeutic option. With the introduction of drugs targeting vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) in clinical practice, patients with mCRC have increased overall survival (OS) compared with cytotoxic chemotherapy [4–7].

During palliative therapy, patients will adjust or interrupt treatment because of the development of adverse effects or cumulative treatment-related toxicities, e.g., oxaliplatin-related neurosensory toxicity. The main objectives of treatment are to prolong a patient's life and improve the quality of life for as long as possible. In fact, we always have to face the situation of improving survival at the cost of toxicity, which is unacceptable. There are two main methods to control this situation: stopping chemotherapy, after induction or switching to maintenance therapy to delay tumor progression and reduce side effects. Interruption of chemotherapy has been reported to have a disadvantageous effect on OS compared with continuation of chemotherapy [8, 9]. Some related trials reported that maintenance therapy was better than complete treatment cessation after induction chemotherapy in terms of survival and safety [9–14]. It would be clinically practical to find a maintenance treatment that could extend the progression-free interval without serious side effects. Currently used maintenance regimens are fluoropyrimidines, bevacizumab, and the combination of fluoropyrimidine with bevacizumab. The anti-EGFR monoclonal antibodies cetuximab and panitumumab have been shown to be effective in patients with *KRAS* and *NRAS* wild-type metastatic colorectal cancer [15, 16]. Erlotinib is a rarely investigated EGFR tyrosine kinase inhibitor in mCRC [17].

In recent years, some trials suggested that the combination of erlotinib and bevacizumab might have synergistic activity [18, 19]. Whether the addition of erlotinib to bevacizumab was more or less effective than bevacizumab alone as maintenance therapy is not completely consistent. Accordingly, we undertook this meta-analysis to compare the survival benefit and safety of bevacizumab plus erlotinib with that of bevacizumab alone in patients with mCRC.

2 Materials and Methods

2.1 Search Strategy

We conducted a systematic assessment following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria [20]. Any article (as English language full paper or abstract) that compared bevacizumab plus erlotinib with bevacizumab alone as maintenance therapy in mCRC patients was eligible for inclusion in our assessment. We searched PubMed, EMBASE, and the Central Registry of Controlled Trials of the Cochrane Library for original articles that were published and unpublished till August 2016. We also searched the Proceedings of the American Society of Clinical Oncology (1986 to August 2016). To minimize the risk of selection or information bias, only prospective studies were identified in our study. We used various combinations of the following key words: "erlotinib", "bevacizumab", "randomized controlled trial", "metastatic colorectal cancer", "colon cancer", and "rectal cancer". References of selected articles and previous systematic reviews were also checked in case any studies were potentially missed.

2.2 Selection of Trials

The included trials had to fulfill the following criteria: (1) subjects were patients, and histological or cytological confirmation was required; (2) prospective phase II and III randomized controlled trials (RCTs); (3) control arm patients received bevacizumab alone (collectively referred to as the bevacizumab group) and experimental arm patients received bevacizumab plus erlotinib (collectively referred to as the bevacizumab plus erlotinib group) as maintenance therapy; (4) bevacizumab plus erlotinib and bevacizumab alone were compared without confounding by additional agents or interventions (i.e., in the maintenance therapy, the control and experimental arms had to differ only by with or without erlotinib component); and (5) reported hazard ratios (HRs) with 95 % confidence intervals (CIs) for OS and/or progression-free survival (PFS), or data to calculate these.

The eligibility of all abstracts identified by the search was evaluated by two independent reviewers (W. X. and Y. G.). If only one reviewer considered an abstract eligible, the full text of the article was retrieved, and both reviewers reviewed it in detail. All publications were included, but only the most recent and the most informative data were used.

2.3 Quality Assessment

We used the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the quality of included trials according to the report on the methods and results from the studies [20].

2.4 Data Extraction

To avoid bias in the data extraction process, the data were independently extracted from the eligible trials, and results were compared by the same two reviewers (W. X. and Y. G.). The following information was extracted from each article: (1) publication details such as the type of cancer, first author, year of publication, country, and form of publication (full/abstract); (2) information on the treatment such as maintenance therapy, median OS, median PFS, overall response rate (ORR), and toxicity; and (3) characteristics of the patients such as the number of patients, age, sex, prior chemotherapy history, and Eastern Cooperative Oncology Group performance status. Before performing the analyses, data of each published study were carefully double-checked by another reviewer (M.K.), and any disagreements were resolved by group discussion or the reviewers contacted the authors of the original study. Whenever possible, we tried to obtain the updated results from the researchers via email.

2.5 Statistical Analysis

The primary outcome measure was OS, which was defined as the time from randomization to death from any cause. Secondary outcome measures were PFS, defined as the interval from the date of randomization to the date of progression, or the date of death for patients without progression, whichever came first; ORR, defined as the sum of partial and complete response rates; with regard to toxicity events, data on the proportion of participants with severe (grade 3–4) adverse events for each group were extracted and analyzed. Cochran's χ^2-based Q statistic was used to test for heterogeneity among the trials [21]. $P_{\text{heterogeneity}} \leq 0.1$ or $I^2 > 50$ % indicated heterogeneity existed. We applied a random-effects model to calculate the pooled estimations of the HR and risk ratio (RR) for each study. Otherwise, a fixed-effects model was used because of a lack of significant heterogeneity. The existence of publication and selection bias was assessed through funnel plots using the Begg's and Egger's tests [22, 23]. We conducted this systematic assessment using the STATA version 10.0 software (Stata Corporation, College Station, TX, USA). All reported p values are from two-sided versions of the respective tests. A p value <0.05 was considered significant. All CIs had two-sided probability coverage of 95 %.

3 Results

3.1 Characteristics of Included Trials

According to our search strategy, three eligible trials [24–26] were identified (Fig. 1). The analysis was conducted with the data of 682 mCRC patients; they were randomly assigned to receive maintenance therapy with bevacizumab plus erlotinib (340 patients) or bevacizumab alone (342 patients) after induction chemotherapy. All trials were population-based RCTs to guarantee the methodological quality of our article. All trials were experimentally controlled. The characteristics of the three included trials are summarized in Table 1.

3.2 Quality Assessment

The results of the quality assessment are shown in Table 2. Among three RCTs, two trials [24, 26] were assigned B level whereas one trial [25] had a high risk of allocation concealment and blinding, so we ranked them as C level. All of the three trials included in this study could be identified as having adequate random sequence generation, and the trials addressed incomplete outcome data, selective reporting, and other bias. It was unclear whether two trials [24, 26] used allocation concealment and incomplete outcome data.

3.3 Efficacy and Safety

All trials provided OS and PFS data directly or indirectly (682 patients, Table 3). Pooled analysis indicated that bevacizumab plus erlotinib was associated with a clinically substantial and statistically significant reduction of 22 % in the hazard for death and 21 % in the hazard for progression when compared with bevacizumab alone (HR 0.78; 95 % CI 0.66–0.93; $p = 0.006$, Fig. 2; HR 0.79; 95 % CI, 0.68–0.92, $p = 0.002$; Fig. 3). There was no significant heterogeneity (OS: $I^2 = 0.0$ %, $P_{\text{heterogeneity}} = 0.458$; PFS: $I^2 = 0.0$ %, $P_{\text{heterogeneity}} = 0.816$), and the pooled HRs for OS and PFS were performed using fixed-effects models. ORR was extracted in only the Tournigand et al. trial, which reported a statistically significant improvement

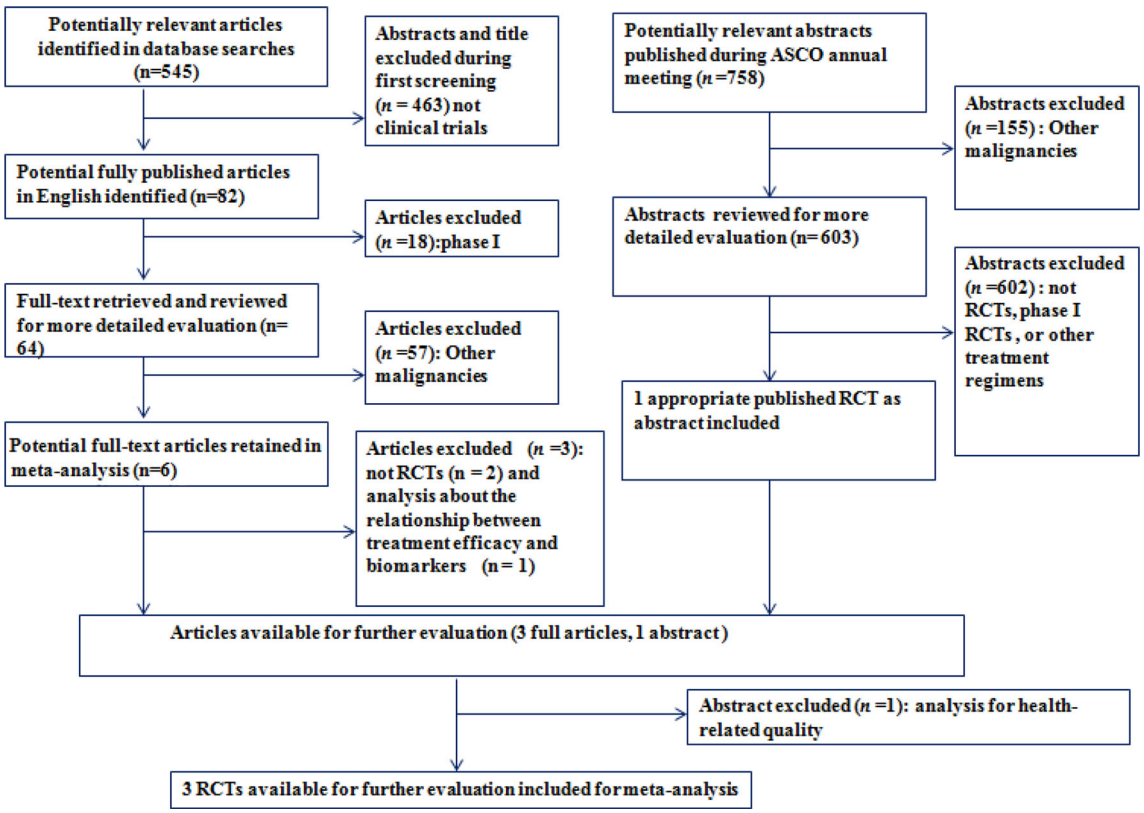

Fig. 1 Trials flow chart. *ASCO* American Society of Clinical Oncology, *RCTs* randomized controlled trials

($p = 0.0029$). We could not conduct a pooled analysis owing to the limited published data. Three trials including 674 patients provided toxicity-profile results (Table 4). Both grade 3 and 4 adverse effects are analyzed and reported in Table 4. The most commonly recorded adverse event was rash, accounting for 19.94 %, with the second most common event being diarrhea (8.33 %), and fatigue and infection total accounted for 6.25 and 3.27 %, respectively. Relevant to this, patients in the bevacizumab plus erlotinib group had a significantly higher incidence of the above-mentioned adverse effects (OR 58.97, 10.58, 5.01, and 8.25, respectively) compared with the bevacizumab group. The incidences of other adverse events, including hypertension, thrombocytopenia, hand and foot syndrome, skin ulceration, nausea or vomiting, proteinuria and neuropathy, were lower than the above findings in the bevacizumab plus erlotinib group. No significant difference in each of these adverse events was observed between the two groups (OR 1.01, 3.03, 1.0, 7.38, 1.67, 1.35, and 1.26 respectively). In total, most adverse events were tolerated and manageable. With regard to treatment-related death, no significant difference was observed. No heterogeneity existed for all of above-mentioned adverse effects among the studies.

3.4 Publication Bias

We performed Begg's funnel plot and Egger's test to assess the publication bias of the literature. The shapes of the funnel plots (Fig. 4) indicated the absence of publication bias. Furthermore, Egger's test was used to statistically confirm the funnel plot symmetry ($p = 0.655$ for OS; $p = 0.372$ for PFS). The results still did not suggest any evidence of publication bias, although the number of included trials was relatively small.

4 Discussion

As EGFR and VEGF inhibitors exert their anti-tumor effects through different mechanisms, their combination should theoretically lead to greater effects. Preclinical trials also demonstrated that the combination of more than one targeted agent led to a stronger inhibition of the downstream signaling pathways compared with single-drug treatment [27, 28]. In addition, some research reported that the anti-EGFR monoclonal antibodies cetuximab and panitumumab had been shown to be effective in patients with *KRAS* and *NRAS* wild-type mCRC [15, 16, 29].

Table 1 Characteristics of the patients included in the meta-analysis

Characteristic	Johnsson et al. [24]		Tournigand et al. [25]		Hagman et al. [26]		Total	
	Bevacizumab + erlotinib group ($n = 80$)	Bevacizumab group ($n = 79$)	Bevacizumab + erlotinib group ($n = 224$)	Bevacizumab group ($n = 228$)	Bevacizumab + erlotinib group ($n = 36$)	Bevacizumab group ($n = 35$)	Bevacizumab + erlotinib group ($n = 340$)	Bevacizumab group ($n = 342$)
Sex								
Male	53 (66)	43 (54)	147 (66)	129 (57)	23 (64)	23 (66)	223 (65.6)	195 (57)
Female	27 (34)	36 (46)	77 (34)	99 (43)	13 (36)	12 (34)	117 (34.4)	147 (50.0)
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)	94 (41)	12 (33)	8 (23)	121 (35.6)	128 (37.4)
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)
Both	6 (8)	7 (9)	6 (3)	4 (2)	2 (6)	0 (0)	14 (4.1)	11 (3.2)
Primary tumor in situ								
Yes	31 (39)	26 (33)	NR	NR	21 (58)	15 (43)	52 (15.3)	41 (12.0)
Previous adjuvant therapy								
Yes	13 (16)	15 (19)	24 (11)	20 (9)	2 (6)	7 (21)	39 (11.5)	42 (12.3)
Previous oxaliplatin								
Yes	4 (5)	3 (4)	201 (90)	205 (90)	2 (6)	6 (17)	207 (60.9)	214 (62.8)
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		
Liver only	29 (36)	18 (23)	NR	NR	14 (39)	7 (20)	43 (12.6)	25 (7.3)
Number of metastatic sites								
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 (51)	126 (56)	18 (50)	23 (66)	175 (51.5)	194 (56.7)
KRAS status								
Wild-type	26 (32.5)	29 (36.7)	130 (58)	112 (49)	36 (100)	35 (100)	192 (56.5)	176 (51.5)

Values are expressed as *n* (%)

ECOG PS Eastern Cooperative Oncology Group performance status, *NR* none or not reported

Table 2 Quality of the three included trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Rank
Johnsson et al. [24]	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	A
Tournigand et al. [25]	Yes	No	Yes	No	Yes	Yes	Yes	C
Hagman et al. [26]	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	A

Erlotinib is a less widely investigated EGFR tyrosine kinase inhibitor in mCRC [17]. One study stated that the combination of erlotinib and chemotherapy had limited tolerability in patients with mCRC [30]. However, some studies showed promising results when adding erlotinib to bevacizumab as maintenance therapy [18, 19]. The feasibility and safety of the addition of erlotinib to bevacizumab as maintenance therapy continues to be controversial compared with bevacizumab alone as maintenance therapy. To the best of our knowledge, this is the first meta-analysis to compare the feasibility and safety of erlotinib plus bevacizumab as maintenance therapy with bevacizumab alone.

Although without significantly longer median OS and PFS in two trials, our meta-analysis still demonstrated that bevacizumab plus erlotinib as maintenance treatment was associated with superior OS, PFS compared with bevacizumab-alone patients. Patients in the bevacizumab plus erlotinib arm were more likely to experience frequent adverse events including rash, diarrhea, infection total, and fatigue. However, all above-mentioned adverse events appeared uncommonly and were predictable, manageable, and acceptable. The proportions of patients that stopped maintenance treatment because of side effects were limited. Accordingly, the bevacizumab plus erlotinib group-based therapy was associated with longer OS, PFS, and almost equivalent safety compared with bevacizumab-alone therapy.

Some previous studies suggested that prolonged bevacizumab exposure beyond first-line chemotherapy may improve patients' survival [14, 31]. In our included trials, the treatments of the experimental group and controlled group both contained bevacizumab. In addition, the differences in the basic characteristics of the patients enrolled, such as age, Eastern Cooperative Oncology Group performance status, primary tumor location, number of metastatic sites, and history of adjuvant treatment, which may have affected the outcome, were not obvious. The proportion of total patients with performance status = 0 accounted for over 60 %. Whether the promising and positive conclusion in our meta-analysis was the result of the treatment or a positive patient selection is unknown.

The proportion of wild- and mutation-type KRAS may be an influencing factor. In our meta-analysis, the Hagman et al. [26] and Tournigand et al. trials [25] displayed the relationship between KRAS status and curative effect of the addition of erlotinib to bevacizumab. Because of a low sample size, Hagman et al.'s trial conducted a preplanned pooled analysis with data from KRAS wild-type patients in the preceding Johnsson et al. trial [24] to increase the power. The preclinical trials mentioned that anti-EGFR monoclonal antibodies were not active in patients with KRAS and NRAS mutation-type tumors, but the Hagman et al. and Tournigand et al. trials stated that the effect on PFS and OS of bevacizumab plus erlotinib was independent of the KRAS status of the tumors. This is in contrast to non-small-cell lung cancer in which KRAS wild-type patients in the ATLAS trial were more likely to benefit from the addition of erlotinib to bevacizumab, at least in terms of PFS [32]. Future research should concentrate on exploring other possible biomarkers to identify the benefit of the addition of erlotinib in this clinical setting.

In addition, the following issues may confound the assessment of survival and are worthy of further discussion. First, the inconsistency of systemic therapy before and after the study among the three trials may have affected the endpoints. All trials did not consider the different induction drugs and sequential treatment used. This aspect of the design could affect the clinical outcomes, but to demonstrate it requires more statistical power. Second, different induction chemotherapy intervals may also affect the result. In the Johnsson et al. and Hagman et al. trials, the induction chemotherapy intervals of patients were 18 weeks. In the Hagman et al. trial, patients were randomized to 3 months of induction therapy at the beginning. Then, after a post-protocol amendment, patients were no longer randomized at induction and the duration of induction therapy was increased to 6 months. Third, platinum is toxic and is not well tolerated for some patients, almost half of the patients used oxaliplatin-containing

Table 3 Characteristics of enrolled trials, including treatment regimens and survival data

Study	Country	Phase	Age (years)	Number	Treatment	Median OS (months)	*P* value	Median PFS (months)	*P* value	ORR (%)	*P* value	ECOG PS
Johnsson et al. [24]	Sweden	III	≥18	249	Bevacizumab 7.5 mg/kg every 3 weeks + erlotinib 150 mg daily	21.5	0.51	5.73	0.19	NR	NR	0–1
					Bevacizumab 7.5 mg/kg as a single agent every 3 weeks	22.8		4.23		NR		
Tournigand et al. [25]	France	III	≥18 and ≤80	452	Bevacizumab 7.5 mg/kg every 3 weeks + erlotinib 150 mg daily	24.9	0.035	5.4	0.023	22	0.0029	0–2
					Bevacizumab 7.5 mg/kg as a single agent every 3 weeks	22.1		4.9		11		
Hagman et al. [26]	Sweden	III	≥18	233	Bevacizumab 7.5 mg/kg every 3 weeks + erlotinib 150 mg daily	20.6	0.051	5.7	0.787	NR	NR	0–1
					Bevacizumab 7.5 mg/kg as a single agent every 3 weeks	30.7		3.6				

ECOG PS Eastern Cooperative Oncology Group performance status, *NR* not reported, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival

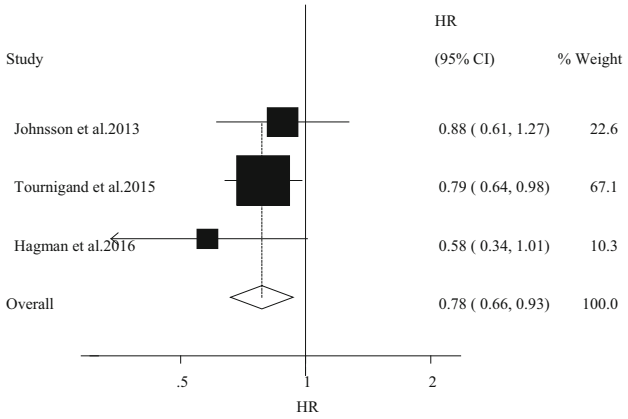

Fig. 2 Fixed-effects model of HR (95 % CI) of overall survival associated with the bevacizumab plus erlotinib group compared with the bevacizumab group. Heterogeneity Chi-squared = 1.56 (*df* = 2); $p = 0.458$. *I*-squared (variation in ES attributable to heterogeneity) = 0.0 %. Test of ES = 1: $z = 2.73$; $p = 0.006$. *CI* confidence interval, *HR* hazard ratio

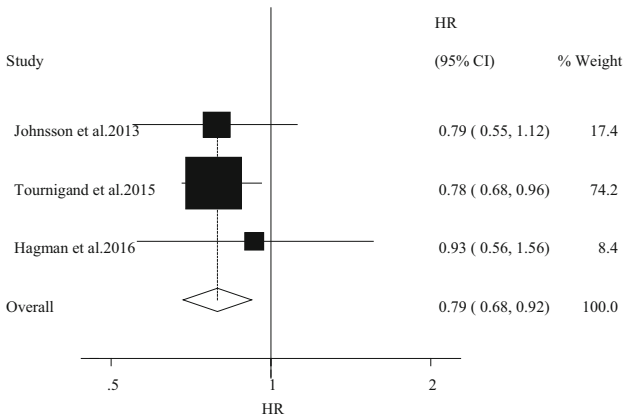

Fig. 3 Fixed-effects model of HR (95 % CI) of progression-free survival associated with the bevacizumab plus erlotinib group compared with the bevacizumab group. Heterogeneity Chi-squared = 0.41 (*df* = 2); $p = 0.816$. *I*-squared (variation in ES attributable to heterogeneity) = 0.0 %. Test of ES = 1: $z = 3.06$; $p = 0.002$. *CI* confidence interval, *HR* hazard ratio

chemotherapy as induction therapy in our trials, which may also potentially affect the results.

We also explored whether adding erlotinib to bevacizumab would be more effective than standard therapy. Some studies suggest that activation of the EGFR pathway increases tumor-derived VEGF expression, which acts on endothelial cells in a paracrine manner to promote angiogenesis [33, 34]. Exposure to EGFR inhibitors leads to attenuation of VEGF expression, and resistance to EGFR inhibitors is often associated with increased VEGF expression [35]. Their combination should theoretically lead to greater effects. Two clinical trials showed that a combination of bevacizumab with either cetuximab or panitumumab was disadvantageous [29, 36]. The trial by

Table 4 Most common grade 3 or 4 adverse events

AEs (%)	Johnsson et al. [24]		Tournigand et al. [25]		Hagman et al. [26]		Total		*P* value
	Bevacizumab + erlotinib group ($n = 80$)	Bevacizumab group ($n = 79$)	Bevacizumab + erlotinib group ($n = 220$)	Bevacizumab group ($n = 224$)	Bevacizumab + erlotinib group ($n = 36$)	Bevacizumab group ($n = 35$)	Bevacizumab + erlotinib group ($n = 336$)	Bevacizumab group ($n = 338$)	
Hypertension	3.75	3.79	3.18	3.13	2.78	2.86	3.27	3.25	0.99
Fatigue	8.75	0	5.45	0.89	5.56	5.71	6.25	1.18	0.002
Infection total	10	1.27	NR	NR	8.3	0	3.27	0.3	0.016
Hand-and-foot syndrome	1.25	0	0	0.46	NR	NR	0.3	0.3	0.998
Rash	25	1.27	21.36	0.89	NR	NR	19.94	0.3	0.0001
Skin ulceration	1.25	0	NR	NR	13.89	0	1.79	0	0.063
Diarrhea	5	0	9.56	0.89	8.33	0	8.33	0.59	0.0001
Nausea or vomiting	1.25	0	1.36	0.5	0	2.86	1.19	0.59	0.484
Proteinuria	5	6.33	1.82	0.5	NR	NR	2.38	1.78	0.59
Thrombocytopenia	1.25	0	0.45	0	NR	NR	0.6	0	0.338
Neuropathy	5	0	2.27	2.68	0	2.86	2.68	2.07	0.627

AEs adverse events, *NR* none or not reported

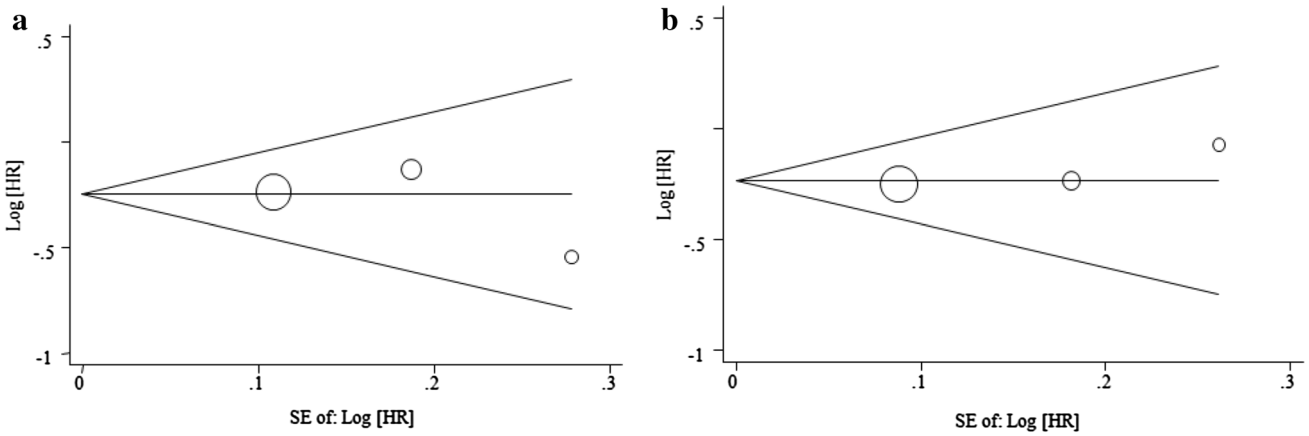

Fig. 4 Begg's funnel plots of publication bias test: overall survival (**a**) and progression-free survival (**b**). *HR* hazard ratio, *SE* standard error

Tournigand et al. implied that some of the signaling events were autocrine and intracellular and are not easily accessible to monoclonal antibodies. By contrast, erlotinib, as a small-molecule tyrosine kinase inhibitor, binds to the intracellular adenosine triphosphate-binding site of the receptor, which could explain this mechanism.

The limitations of these studies also need attention. First, as we all know, the results of any meta-analysis were affected by the quality of the individual studies. All the trials were RCTs, no updated or confirmed results could be obtained from the authors. Therefore, our results should be interpreted with care. Second, our meta-analysis was based on summary data and not on individual patient data. Meta-analyses based on individual patient data tend to give a more robust estimation for the association compared with published data analyses. Third, the difference in treatment schedules among the trials (data not shown) might contribute to increase the clinical heterogeneity of the meta-analysis. Fifth, a comparatively low sample size may lack sufficient statistical power to make a conclusion. The total sample size of our included patients was 682. Among three trials, the number of patients in the Hagman et al. and Johnsson et al. trials was obviously lower than that in the Tournigand et al. trial. It may explain the reason for the lack of significance in the Hagman et al. and Johnsson et al. trials. Sixth, we applied a random-effects model or a fixed-effects model to calculate the pooled estimations of HR and RR for each study according to the $P_{\text{heterogeneity}}$ value and I^2 value. When heterogeneity existed, we applied the random-effects model for a pooled analysis. At the same time, we need to find the reason from clinical aspects and evaluated the feasibility of merged data including the homogeneity, the design, and statistical methods. Otherwise, we should conduct a subgroup analysis to find out the essence of the problem. We found that no heterogeneity existed in the pooled estimations of HR (OS: $I^2 = 0.0\ \%$, $P_{\text{heterogeneity}} = 0.458$; PFS: $I^2 = 0.0\ \%$, $P_{\text{heterogeneity}} = 0.816$), thus we applied the fixed-effects model. Only one trial refers to RR; therefore, we could not conduct the pooled analysis. Finally, lack of blinding, which could be inevitable in all these included studies, might have resulted in an overestimation of the effects. Because the two treatment methods studied were quite different (two-drug combination vs. single drug), the treatment allocation could not be blinded from the investigators or patients.

The design of our inclusion trials may be criticized owing to a lack of comparison with a 'standard maintenance' arm. Currently used maintenance regimens are fluoropyrimidines, bevacizumab, and the combination of fluoropyrimidine with bevacizumab. Recently, some studies showed that maintenance treatment with bevacizumab alone in mCRC was of limited value [10, 37]. The combination of capecitabine or fluoropyrimidine and bevacizumab has shown to be an active maintenance strategy [10, 11]. Against this background, our included trials selected bevacizumab alone as a controlled group. The reasons were as follows: before the results of the CAIRO3 trial were known [11], the Tournigand et al. and Johnsson et al. trials had been conducted. As a continuation of the Johnsson et al. trial, the Hagman et al. trial still selected bevacizumab alone as a controlled group of the patients with the KRAS wild type. In contrast to the pre-planned trial, the trial added a subgroup to research the effects of bevacizumab alone vs. capecitabine in patients with the KRAS mutation type. Tournigand et al. proposed a hypothesis that interrupting chemotherapy before it produced resistance would provide benefit to second-line therapy, thus the trial used bevacizumab alone as a controlled group. Further research should explore the efficiency of the different maintenance regimens as the controlled group with bevacizumab plus erlotinib as the experimental group.

5 Conclusion

Bevacizumab plus erlotinib as a new non-chemotherapy-based maintenance therapy was not only superior to bevacizumab alone in terms of OS, but also led to increased PFS. All of these results confirmed that bevacizumab plus erlotinib could be a good choice in the treatment of patients with advanced mCRC with almost equivalent tolerance. More predictive biomarkers of erlotinib and the superiority of different maintenance regimens as the controlled group vs. bevacizumab plus erlotinib as the experimental group need to be further evaluated and confirmed through larger trials with longer observation periods.

Compliance with Ethical Standards

Funding This study was supported by a grant from The Project of Plans for the Development of Science and Technology of Nanjing, China (Grant No. 201208020).

Conflict of interest Wei Xu, Yang Gong, Meng Kuang, Peng Wu, Chunxiang Cao, Jinfei Chen, and Cuiju Tang declare no conflicts of interest.

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