International Journal of Clinical Pharmacy (2022) 44:843–851
https://doi.org/10.1007/s11096-022-01415-6

REVIEW ARTICLE

The effectiveness and safety of bevacizumab versus cetuximab in the treatment of colorectal cancer: a systematic review and meta-analysis

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Received: 10 March 2022 / Accepted: 16 April 2022 / Published online: 24 June 2022

Abstract

Background Despite available meta-analyses, comparative efficacy and safety between bevacizumab and cetuximab-containing therapies in treating advanced colorectal cancer (CRC) still need to be elucidated.

Aim This meta-analysis aimed to investigate the efficacy and grade 3–5 treatment-related adverse events (TRAE3-5) of bevacizumab versus cetuximab in treating advanced CRC.

Method Randomized controlled trials (RCTs) and observational cohort studies were searched from electronic databases. Data on overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and TRAE (3-5) were synthesized.

Results Five RCTs and four observational cohort studies (2970 patients) were included. The bevacizumab-containing group was associated with a significantly lower ORR (risk ratio RR 0.91, 95% confidence interval CI 0.85–0.97, $P=0.006$) than the cetuximab group. Bevacizumab was associated with significant superior DCR (RR 1.05, 95% CI 1.01 to 1.10, $P=0.02$) than cetuximab. No significant differences were observed for PFS (HR 0.96, 95% CI 0.91–1.02, P = 0.17) and OS (HR 1.10, 95% CI 0.90–1.34, P = 0.96) between the groups. Bevacizumab showed a lower rate of skin disorders (RR 0.10, 95% CI 0.02–0.43, $P=0.002$) than cetuximab. There were no significant differences between the groups in the overall rate of TRAE3-5 (RR 0.92, 95% CI 0.84–1.01, $P=0.08$). Subgroup analysis found a lower TRAE3-5 rate in the bevacizumab group in RCTs (RR 0.91, 95% CI 0.83–1.00, $P=0.04$).

Conclusion Bevacizumab could increase DCR and lower the skin disorder rate to treat patients with advanced CRC.

Keywords Bevacizumab · Cetuximab · Colorectal cancer · Effectiveness · Meta-analysis · Safety

Impact statements

- When added to chemotherapy regimens, bevacizumab or cetuximab improves overall survival in patients with advanced colorectal cancer.
- Bevacizumab and cetuximab-containg regimens appears to have different efficacy and adverse event profiles and these differences should be considered when selecting treatment options.

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide, accounting for 10.2% of new cases and 9.2% of the deaths in 2018 [1]. Many CRCs can be prevented by regular screening, and early detection of CRC has emerged as a significant global issue to reduce its high mortality. Fluoropyrimidine-based chemotherapy has been the primary treatment for CRC, with demonstrated benefits in overall survival in patients after complete resection of CRC metastases [2]. Irinotecan and oxaliplatin are widely used in combination with 5-fluorouracil (5-FU) and leucovorin (folinic acid) as first or second-line treatment for CRC patients [3].

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With the increasing use of targeted therapies, including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) antibodies, the median overall survival (OS) of CRC has increased from approximately 20 months to 30 months in the last ten years [4]. In particular, targeted agents such as cetuximab, bevacizumab, and panitumumab have been considered standard choices, combined with chemotherapy, based on their encouraging results. Cetuximab, a chimeric monoclonal antibody targeting EGFR, can inhibit cancer cell growth and induce apoptosis [5]. Bevacizumab is a recombinant humanized monoclonal antibody targeting VEGF and inhibiting tumor-driven angiogenesis [6, 7]. Since they were approved, increasing numbers of clinical trials have been conducted with cetuximab or bevacizumab to treat patients with CRC [8, 9].

A systematic review and meta-analysis was performed based on 21 observational cohort studies published in journals up to November 2017 to assess the comparative effectiveness and safety of three monoclonal antibodies (bevacizumab, cetuximab, and panitumumab) associated with fluoropyrimidine-based chemotherapy regimens and compared to fluoropyrimidine-based chemotherapy alone in patients with metastatic CRC (mCRC). The results pointed to advantages in favor of bevacizumab for OS, progression-free survival (PFS), post-progression survival (PPS), and metastasectomy [10]. There were serious adverse events associated with its use, especially severe hypertension and gastrointestinal perforation. Another systematic review and meta-analysis was performed based on two randomized controlled trials (RCTs) and three observational cohort studies published in databases up to March 2018 to determine the efficacy of first-line cetuximab versus bevacizumab for RAS and BRAF wild-type mCRC. The meta-analysis reported that cetuximab was associated with a longer OS [hazard rato HR 0.89, 95% confidence interval CI 0.81–0.98, $P=0.02$], a higher overall response rate (ORR) [relative risk 1.11, 95% CI 1.03–1.19, $P=0.006$], a greater complete response [relative risk 3.21, 95% CI 1.27–8.12; $P=0.01$], and a greater median depth of response than bevacizumab. However, no significant differences were observed between the cetuximab and bevacizumab groups for PFS, disease control rate (DCR), partial response, progressive disease, curative intent metastasectomy, and incidence of grade 3 or higher adverse events [11]. Current evidence indicates that first-line biologic treatment is still controversial between cetuximab and bevacizumab in ORR, DCR, OS, and adverse events for advanced CRC. We aimed to summarize the most up-to-date evidence and perform a timely meta-analysis to assess the efficacy and safety of bevacizumab versus cetuximab in patients with advanced CRC.

Aim

The objective of the analysis was to compare the relative efficacy (ORR, DCR, OS, and PFS) and adverse events in advanced CRC patients treated with bevacizumab and cetuximab-containing regimens.

Method

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study was not a human or animal experiment; thus, ethical approval was not required.

Search strategy

We systematically searched electronic databases including PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception up to January 8, 2022. Search terms were ("epidermal growth factor receptor inhibitor" or "EGFR inhibitor" or cetuximab) and ("targeted agent" or "targeted therapy of vascular endothelial growth factor inhibitor" or "VEGF inhibitor" or bevacizumab) and "metastatic colorectal cancer." Additionally, to check for potentially eligible studies, we also performed a hand search by reviewing the reference lists of the included studies and searching Google Scholar. All records retrieved from the electronic databases were imported into Endnote X9 (Thomson Reuters, New York, USA) to remove duplicate documents.

Inclusion criteria and study selection

We included studies that met the following inclusion criteria: (1) RCT, prospective cohort study, or retrospective cohort study; (2) studies included patients diagnosed with metastatic colorectal cancer aged ≥ 18 years; (3) studies that compared bevacizumab-containing regimens and cetuximab-containing regimen; (4) studies reported at least the following outcomes: OS, PFS, ORR, DCR, and treatment-related adverse events (TRAE) grade 3 or higher including overall events, skin disorders, diarrhea, fatigue, stomatitis, and neutropenia. Two reviewers independently screened the titles, abstracts, and full texts based on the above inclusion criteria.

Quality assessment and data extraction

Two reviewers independently assessed the risk of bias of trials based on the Cochrane risk of bias tool. The risk of bias was judged as "low risk of bias," "high risk of bias," or "unclear risk of bias" in the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other biases [12]. We also assessed the quality of observational cohort studies according to the Newcastle–Ottawa Scale (NOS) [13].

We extracted the following data: first author, year of publication, country of the study performed, sample size, and the outcomes of interest (ORR, DCR, OS, PFS, and TRAE3-5). Two authors independently performed the data extraction using a pre-designed data extraction form. Any disagreements were resolved by discussion.

Statistical analysis

To estimate the treatment effects between bevacizumab and cetuximab, we calculated a pooled risk ratio (RR) with 95%CI for ORR, DCR, and TRAE, and a pooled HR with 95%CI for OS and PFS. We pooled the data from RCTs and cohort studies and then performed a subgroup analysis by study design (RCTs *versus* cohort studies). We also tested the difference in treatment effects between the above subgroups ($P_{interaction}$). The heterogeneity between studies was assessed using the I^2 test. If $I^2 < 50\%$, we considered heterogeneity between studies as low, and a fixed-effects model was employed to pool the data. Otherwise, a random-effects model using DerSimonian and Laird [14] would be selected. We also assessed the publication bias using a visual inspection of the funnel plot. All statistical analyses were performed using RevMan software (version 5.1; Cochrane Collaboration, Copenhagen, Denmark). A $P < 0.05$ was considered statistically significant.

Results

Search results and characteristics of included studies

Four studies were excluded due to inappropriate intervention methods, and two studies were excluded due to inappropriate outcomes. Five RCTs [4, 15–18] involving 2022 patients and four observational cohort studies [19–22] involving 948 patients met the inclusion criteria and were included in this meta-analysis (Fig. 1). The basic information of the included studies is presented in Table 1. The risk of the bias of included trials and the quality of the cohort studies are shown in Fig. 2 and Supplemental Table 1, separately.

Efficacy outcomes

Overall survival

A total of 8 studies reported OS [4, 15–20, 22]. The results of the meta-analysis showed that no significant difference was observed for OS (HR 1.10, 95% CI 0.90–1.34, P = 0.96, Fig. 3A). Subgroup analysis indicated similar outcomes both in RCT group and OCS group (RCT:HR 1.02, 95% CI 0.81–1.28, P = 0.87, OCS: HR 1.36, 95% CI 0.83–2.24, P = 0.23, Fig. 3A). There was no difference between the above subgroups ($P_{interaction} = 0.30$). There was significant heterogeneity

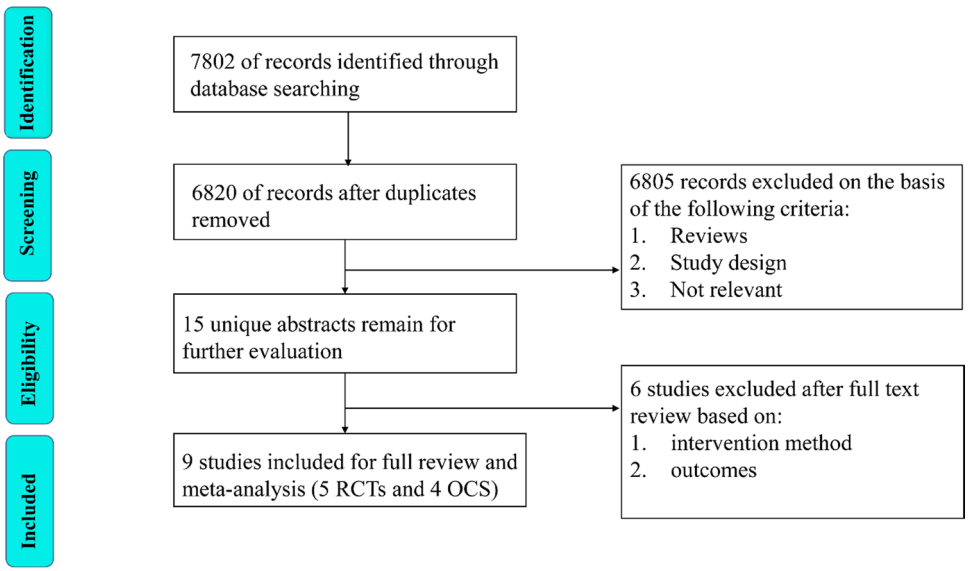

Fig. 1 Flow chart and results of literature screening. *RCT* randomized controlled trial, *OCS* observational cohort study

Table 1 Basic characteristics of included studies

Author, year	Study period	Country	Study design	Line therapy	Combination drug	Number of patients (B/C)	Age (years)	Male sex: n (B/C)	Follow-up (months) (median, range)
Bennouna, J. 2018 [16]	2010.12–2015.05	France	RCT; phase II; open-label; multicenter	Second-line treatment	mFOLFOX6 or FOLFIRI	65/67	61 (33–83) /63 (37–84)	41/44	37.4 (1–48)
Cremolini, C. 2018 [17]	2011.10–2015.03	Italy	RCT; phase II; open-label; multicenter	Second-line treatment	Induction with mFOLFOXIRI plus cetuximab	57/59	59 (53-67) /61 (52-67)	42/40	44.0 (30.5–52.1)
Heinemann, V. 2014 [4]	2007.03–2012.09	Germany	RCT; phase III; open-label; multicenter	First-line therapy	FOLFIRI	295/297	65 (27–76) /64 (38–79)	214/196	39.0 (22.5–56.9)/33.0 (19.0–55.4)
Nishizawa, Y. 2021 [18]	2012.02–2016.10	Japan	RCT; phase II; open-label; multicenter	First-line therapy	SOX	22/23	67 (49–79) /66 (40–79)	14/15	19.9 (1.5–55.4)/12.0 (0.8–59.4)
Venook, A.P. 2017 [15]	2005.11–2012.03	USA	RCT	First-line therapy	mFOLFOX6 or FOLFIRI	559/578	59.0 (21.8–85.0) /59.2 (20.8–89.5)	349/348	47.4 (0–110.7)
Bai, L. 2016 [20]	2009.0–2013.12	China	Observational cohort study	First-line therapy	mFOLFOX-6, FOLFIRI, or XELOX	188/101	50 (24–79) /55 (21–83)	68/120	NR
Houts, A.C. 2017 [21]	2005.04–2012.03	USA	Observational cohort study	First-line therapy	FOLFOX or FOLFIRI	254/146	61.7 ± 11.77 /61.8 ± 12.65	93/140	NR
Liu, S. 2020 [22]	2008.10–2016.01	China	Observational cohort study	First or second -line therapy	Chemotherapy	50/51	≥ 52: 46%/48%	33/33	NR
Yang, Y.H. 2014 [19]	2005.04–2012.03	China	Observational cohort study	First-line therapy	FOLFOX or FOLFIRI	95/63	> 60: 54.7%/39.7%	34/63	NR

mFOLFOX6 leucovorin, fluorouracil, and oxaliplatin; *FOLFIRI* leucovorin, fluorouracil, and irinotecan; *SOX* S-1 and oxaliplatin; *B* bevacizumab; *C* cetuximab; *NR* not report

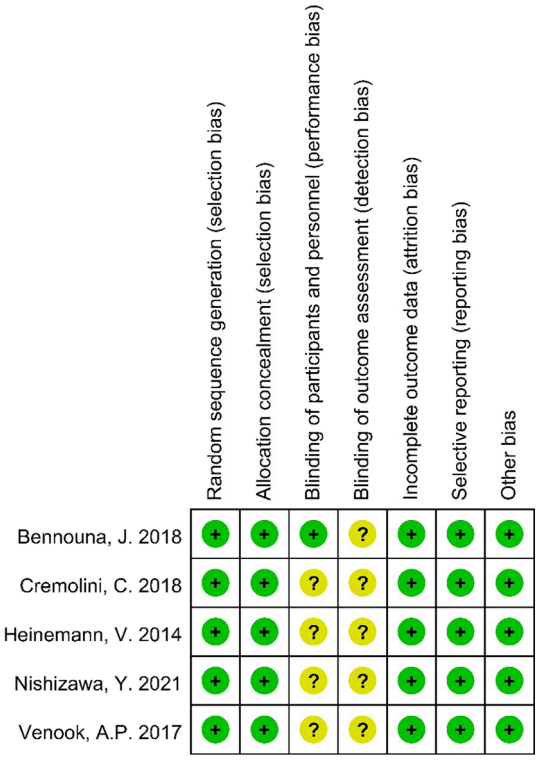

Fig. 2 The Cochrane risk of bias evaluation of randomized controlled trials

between the studies ($I^2 = 61\%$) (Fig. 3A). There was no publication bias (Supplemental Fig. 1A).

Progression-free survival

We included a total of 8 studies that reported PFS [4, 15–21]. The results of the meta-analysis found no significant differences in PFS between the bevacizumab-containing regimens and the cetuximab-containing regimens (HR 0.96, 95% CI 0.91 to 1.02, P =0.17, Fig. 3B). We found a difference in PFS between bevacizumab-containing regimens and cetuximab-containing regimens in the subgroup analysis of RCTs (HR 0.91, 95% CI 0.83–1.00, P = 0.05, Fig. 3B) but not in the subgroup analysis of observational cohort studies (HR 0.99, 95% CI 0.92–1.06, P = 0.82, Fig. 3B). Furthermore, there were no significant differences between RCTs and observational cohort studies ($P_{interaction} = 0.14$).There was significant heterogeneity between the studies ($I^2 = 52.2\%$) (Fig. 3B) but no publication bias (Supplemental Fig. 1B).

Overall response rate

When combining data from 8 RCTs and observational studies [4, 15–20, 22], bevacizumab- containing regimens were significantly associated with lower ORR than cetuximab-containing regimens (RR 0.91, 95% CI 0.85–0.97, $P = 0.006$, Fig. 4A). Our subgroup analysis by study design showed that bevacizumab-containing regimens were not significantly associated with a lower ORR than cetuximab-containing regimens when combining RCT data (RR 0.95, 95% CI 0.88–1.02, $P = 0.14$, Fig. 4A). In comparison, bevacizumab-containing regimens were significantly associated with a lower ORR than cetuximab-containing regimens when pooling data from observational cohort studies (RR 0.75, 95% CI 0.63–0.89, $P = 0.001$, Fig. 4A). We observed a significant difference between the RCTs and the observational cohort subgroups ($P_{interaction} = 0.02$) (Fig. 4A). No significant heterogeneity was observed between studies ($I^2 < 50\%$) (Fig. 4A) and no publication bias (Supplemental Fig. 2A).

Disease control rate

Seven studies reported the outcome of DCR [4, 16–20, 22]. The meta-analysis results showed that bevacizumab-containing regimens were significantly associated with an increase in DCR compared to cetuximab-containing regimens (RR 1.05, 95% CI 1.01–1.10, $P = 0.02$, Fig. 4B). We did not find a significant difference between RCTs (RR 1.08, 95% CI 1.02–1.14, $P = 0.008$, Fig. 4B) and observational cohort studies (RR 1.01, 95% CI 0.95–1.07, $P = 0.76$, Fig. 4B) with a *P*-value of 0.12. No significant heterogeneity was observed between studies ($I^2 < 50\%$) (Fig. 4B) and no publication bias (Supplemental Fig. 2B).

Safety outcomes

The results of the meta-analysis for the safety outcomes are presented in Table 2. There were no significant differences between the bevacizumab-containing regimens and the cetuximab-containing regimens in terms of overall TRAE 3–5 (RR 0.92, 95% CI 0.84–1.01, $P = 0.08$), diarrhea (grade 3–5) (RR 0.86, 95% CI 0.68–1.09, $P = 0.22$), fatigue (grade 3–5) (RR 1.01, 95% CI 0.75–1.37, $P = 0.92$), neutropenia (grade 3–5) (RR 1.11, 95% CI 0.85–1.46, $P = 0.43$), anemia (grade 3–5) (RR 0.37, 95% CI 0.13–1.06, $P = 0.06$), and stomatitis (grade 3–5) (RR 1.01, 95% CI 0.50–2.04, $P = 0.97$). Bevacizumab-containing regimens were significantly associated with a decreased risk of skin disorders (grade 3–5) compared to cetuximab-containing regimens (RR 0.10, 95% CI 0.02–0.43, $P = 0.002$). The results of subgroup analysis found a lower risk of overall TRAE 3–5 in bevacizumab-containing regimens than cetuximab-containing regimens in RCTs (RR 0.91, 95% CI 0.83–1.00, $P = 0.04$) but not in observational cohort studies (RR 0.98, 95% CI 0.74–1.31, $P = 0.92$). No significant differences in the treatment effects

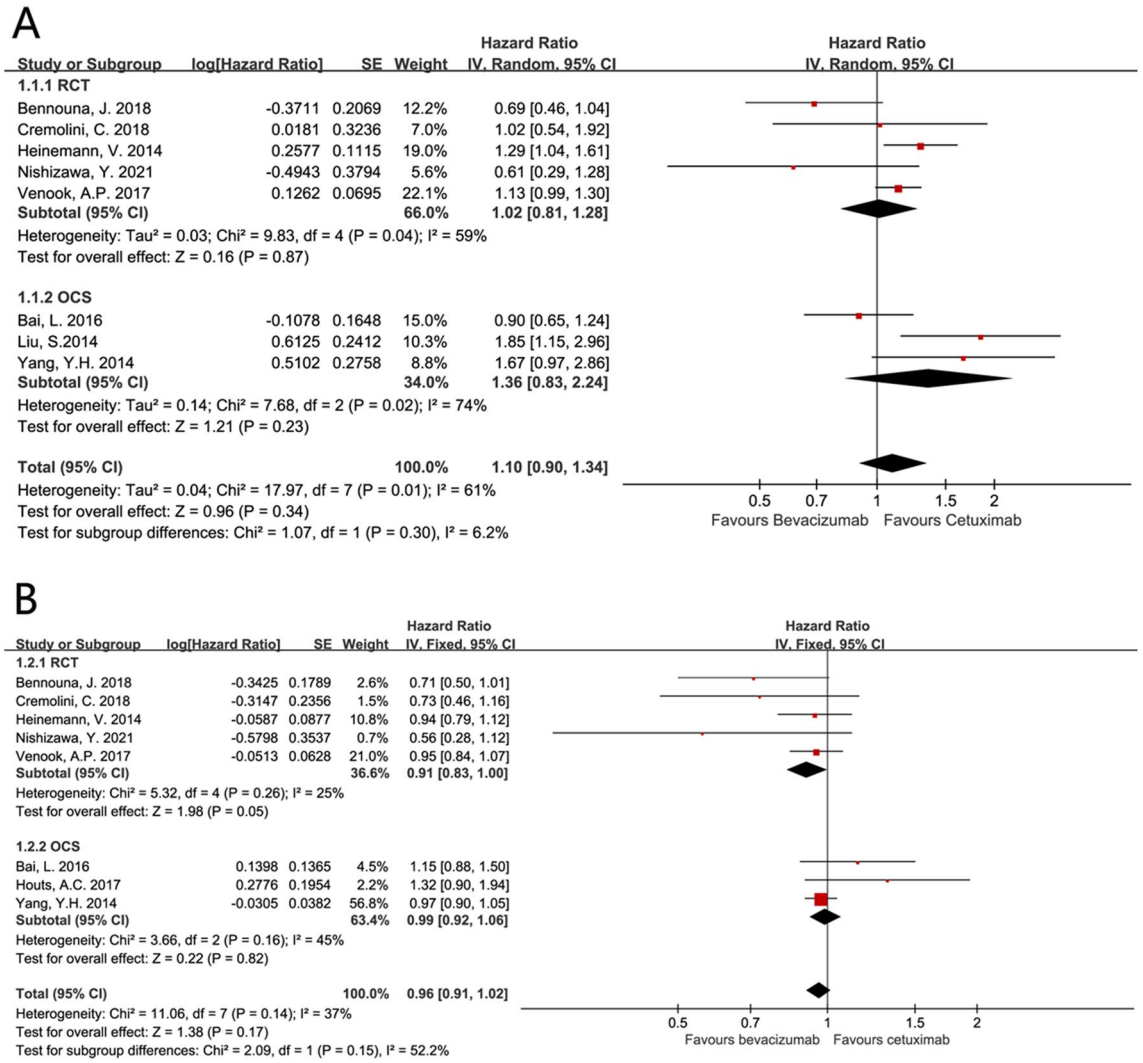

Fig. 3 Comparison of overall survival (3A) and progression-free survival (3B) between bevacizumab-based regimen (experimental) and cetuximab-based regimens (control)

of bevacizumab-containing regimens *versus* cetuximab-containing regimens were observed between RCT and observational cohort studies were observed ($P_{interaction} > 0.05$). The forest plots of these safety outcomes are shown in Supplemental Fig. 3.

Discussion

In the present meta-analysis of bevacizumab versus cetuximab for patients with advanced CRC, bevacizumab was associated with higher DCR. On the contrary, cetuximab was associated with a higher ORR than bevacizumab. No significant differences were observed between the bevacizumab and cetuximab groups for PFS and OS. Regarding safety data, no significant differences were observed in the incidence of overall grade 3 or higher adverse events and other specific adverse events (diarrhea, fatigue, neutropenia, anemia, and stomatitis) between the bevacizumab and cetuximab groups. However, bevacizumab resulted in a lower incidence of grade 3 or higher skin adverse events. To our knowledge, this meta-analysis report provides the most up-to-date evidence of differences in bevacizumab-containing regimens efficacy and safety compared with cetuximab-containing regimens in patients with advanced CRC.

The guidelines recommend chemotherapy combined with targeted drug therapy to treat advanced CRC. Fluorouracil-based therapies, FOLFOX6 (leucovorin, fluorouracil, and oxaliplatin) and FOLFIRI (leucovorin, fluorouracil, and irinotecan), are frequently used chemotherapy regimens for the first-line treatment of mCRC. When added to chemotherapy regimens, the VEGF antibody bevacizumab or the EGFR antibody cetuximab improved overall survival in patients with mCRC [4, 6]. Previous meta-analyses pointed out differences in comparative efficacy data (OS, PFS, PPS,

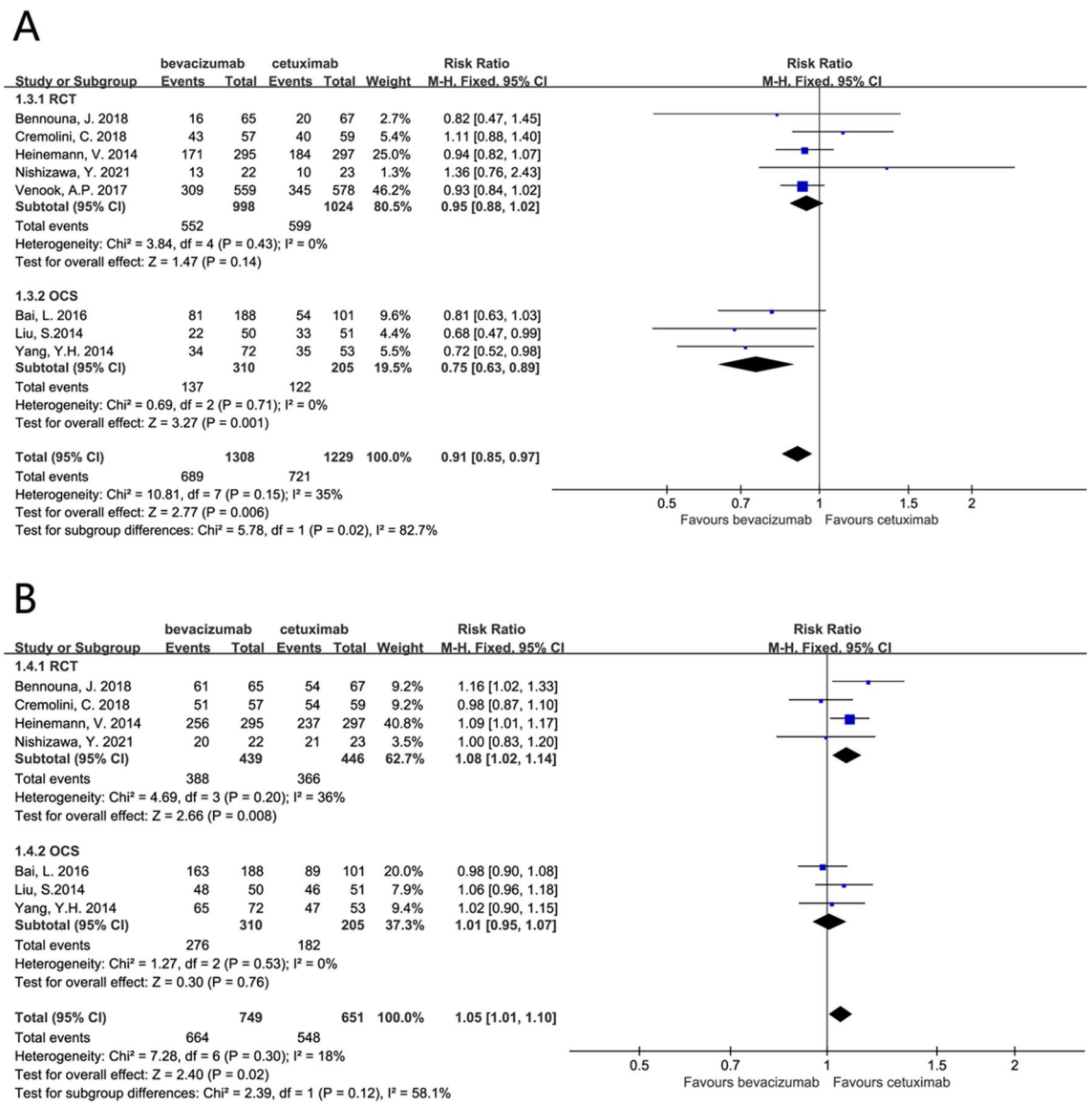

Fig. 4 Comparison of overall response rate (4A) and disease control rate (4B) between bevacizumab-based regimen (experimental) and cetuximab-based regimens (control)

and DCR) and adverse event profiles between the bevacizumab and cetuximab-containing regimens [10, 11]. Our meta-analysis with five RCTs and four observational cohort studies involving a total of 2,970 patients provided further evidence on the therapeutic efficacy and adverse events of bevacizumab and cetuximab-containing regimens for advanced CRC patients. The cetuximab-containing regimen was associated with significantly superior ORR than the bevacizumab-containing regimen. No significant differences were observed in PFS between the two groups. The findings of ORR, PFS and OS are similar to the previous meta-analysis report [11]. In our analysis, the bevacizumab group was associated with a significantly superior DCR than the cetuximab group. The findings of DCR is different from those of meta-analysis [11]. The potential reasons could be that the previous report only included five studies, and only two were RCTs.

In terms of adverse events, the bevacizumab and cetuximab-containing groups had similar safety profiles except for skin disorders (grade 3–5). The results are quite similar to the previous meta-analysis [11]. A previous trial found no significant differences in the incidence of adverse events of any grade and grade 3–4 [23]. A systematic review and meta-analysis published in 2018 compared the toxicity profiles of cetuximab and panitumumab in mCRC treatment [24]. Cetuximab was associated with fewer grade 3–4 skin toxicities (OR = 0.62, 95% CI 0.53–0.62; $P < 0.001$), slightly more frequent grade 3–4 acne-like rash (OR = 1.24, 95%

Table 2 Meta-analysis of the effects of bevacizumab versus cetuximab on safety outcomes

Outcomes	Subgroup	No. of patients (studies)	No. with event/No. in the group (%)		RR [95% CI]	P	p for heterogeneity	I^2(%)
			Bevacizumab	Cetuximab				
Overall TRAE3-5	All	1058 (4)	327/570	321/488	0.92 [0.84, 1.01]	0.08	0.92	0
	RCT	769 (3)	250/382	279/387	0.91 [0.83, 1.00]	0.04	0.88	0
	OCS	289 (1)	77/188	42/101	0.98 [0.74, 1.31]	0.92	NA	NA
Skin disorders (grade 3–5)	All	1332 (6)	13/722	120/610	0.10 [0.02, 0.43]	0.002	0.001	78
	RCT	885 (4)	13/439	101/446	0.15 [0.02, 1.00]	0.05	0.0005	87
	OCS	447 (2)	0/283	19/164	0.03 [0.00,0.22]	0.0006	0.88	0
Diarrhea (grade 3–5)	All	2469 (7)	122/1281	132/1188	0.86 [0.68, 1.09]	0.22	0.74	0
	RCT	2022 (5)	101/998	114/1024	0.91 [0.70, 1.17]	0.45	0.66	0
	OCS	447 (2)	21/283	18/164	0.65 [0.36, 1.18]	0.16	0.69	0
Fatigue (grade 3–5)	All	2311 (6)	85/1186	76/1125	1.01 [0.75, 1.37]	0.92	0.63	0
	RCT	2022 (5)	61/998	67/1024	0.94 [0.68, 1.31]	0.72	0.67	0
	OCS	289 (1)	24/188	9/101	1.43 [0.69, 2.96]	0.33	NA	NA
Neutropenia (grade 3–5)	All	1287 (5)	103/700	66/587	1.11 [0.85, 1.46]	0.43	0.69	0
	RCT	840 (3)	31/417	28/423	1.14 [0.74, 1.77]	0.52	0.74	0
	OCS	447 (2)	72/283	38/164	1.10 [0.78, 1.54]	0.59	0.20	38
Anemia (grade 3–5)	All	769 (3)	4/382	12/387	0.37 [0.13, 1.06]	0.06	0.69	0
Stomatitis (grade 3–5)	All	753 (3)	15/374	15/379	1.01 [0.50, 2.04]	0.97	0.68	0

RCT randomized controlled trial, *OCS* observational cohort study, *TRAE* treatment-related adeverse event, *RR* risk ratio, *CI* confidence interval

CI 1.04–1.48; $P = 0.04$) and paronychia (OR 1.36, 95% CI 1.1–1.7), but fewer cases of skin fissures (OR = 0.64, 95% CI 0.44–0.93; $P = 0.02$) and pruritus (OR = 0.45, 95% CI 0.35–0.58; $p < 0.001$) than panitumumab. The present meta-analysis indicated that the group showed a lower rate of skin disorders (grade 3–5) than the cetuximab group. However, the subgroup analysis found a lower TRAE3-5 rate in the bevacizumab group than in the cetuximab group.

This meta-analysis has some limitations: (1) we did not perform a subgroup analysis as it will result in limited available articles, (2) various chemotherapeutic regimens are involved in different RCTs and observational cohort studies leading to a certain degree of heterogeneity, (3) the primary tumor location is different between the two groups, and this may have a potential impact on the results. A recent systematic review illustrated that patients with left-sided CRC might benefit more from anti-EGFR therapy than patients with right-sided CRC [25].

Conclusion

Our meta-analysis showed that bevacizumab-containing regimens could increase DCR, and lower the rate of grade 3–5 skin disorders for the treatment of advanced CRC patients. The cetuximab regimen was associated with superior ORR.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-022-01415-6.

Acknowledgements None.

Funding This research was funded by Heilongjiang Provincial Key Laboratory of New Drug Development and Pharmacotoxicological Evaluation (kfkt2021-08) Yingxue Guo

Conflicts of interest The authors declare that they have no conflict of interest.

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