

Original Article

The efficacy and toxicity of anti-VEGFR agents in the treatment of advanced colorectal cancer: a meta-analysis of randomized controlled trials

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Abstract: Aim: The aim of present study was to pool all published data on the efficacy and toxicity of anti-vascular epithelial growth factor receptor (VEGFR) agents in the treatment of advanced colorectal cancer (CRC). Methods: We performed asystematic review of all published studies exploring the efficacy and toxicity of anti-VEGFR agents in advanced CRC patients. The pooled hazard ratio (HR) or relative risk (RR), and 95% confidence intervals (CI) were calculated. Results: Seven randomized controlled trials were included with a total of 4,904 patients. Our results demonstrated that anti-VEGFR agents-containing regimens significantly improved PFS (HR 0.70, 95% CI: 0.55-0.88, $P=0.002$), but not for ORR (RR 1.29, 95% CI: 0.91-1.83, $P=0.151$), and OS (HR 0.88, 95% CI: 0.77-1.01, $P=0.069$). Sub-group analysis according to treatment lines showed that the addition of anti-VEGFR agents to second therapies significantly improved OS, PFS and ORR. However, no significant survival benefits had been observed in anti-VEGFR agents plus first-line treatment for advanced CRC. Additionally, more incidences of grade 3 or 4 hypertension and proteinuria were observed in anti-VEGFR agents-containing regimens, while equivalent frequencies of grade 3 or 4 thrombosis events, GI perforation, congestive heart disease, and hemorrhage were found between the two groups. Conclusions: The findings of this study support the addition of anti-VEGFR agents to second-line therapies in advanced CRC patients due to its survival benefits, while no significant survival benefits have been observed in anti-VEGFR agents plus first-line regimens.

Keywords: Advanced colorectal cancer, anti-VEGFR agents, randomized, meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors throughout the world with over 1.2 million new cases and 608700 deaths estimated to occur annually [1]. Nearly 50% of all patients with colorectal carcinoma will develop metastatic disease, and are therefore incurable with surgery alone. The prognosis for metastatic CRC patients is dismal with 5-year survival of 13% [2]. Obviously, it is necessary to develop novel agents to achieve greater survival benefits for CRC patients.

During the past decades, many studies have been conducted to clarify the underlying mechanism of tumor angiogenesis in CRC, accompanied by efforts directed at the development of molecular-targeted drugs for the treatment of this cancer. Indeed, previous research have

shown that angiogenesis is mainly driven by vascular epithelial growth factor (VEGF), thus angiogenesis inhibitors targeting the VEGF signal pathway is a potentially effective strategy for the treatment of metastatic CRC [3, 4]. Currently, bevacizumab, a humanized monoclonal antibody targeting VEGF-A, has been approved for use in advanced CRC cancer due to its potential survival benefits [5, 6]. Another VEGF targeted agent aflibercept has been approved for use in combination with 5-fluorouracil, leucovorin, and irinotecan for the treatment of patients with metastatic CRC that is resistant to or has progressed following treatment with an oxaliplatin-containing regimen [7]. Recently, other novel angiogenesis inhibitors targeted VEGF receptor (VEGFR) such as ramucirumab, sorafenib, and cediranib, are currently being under investigation [8, 9]. However, to our best knowledge, there is no specific systematic

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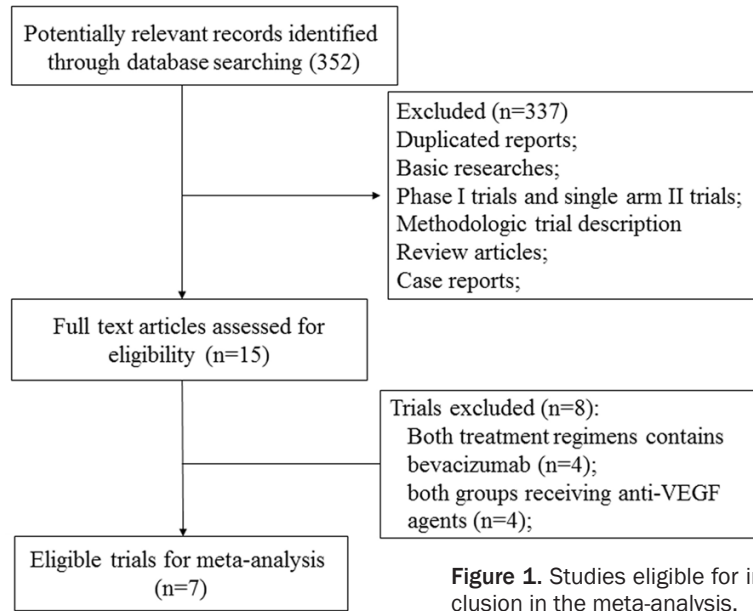


Figure 1. Studies eligible for inclusion in the meta-analysis.

trolled trails; (2) Designed to compare therapies combined with an anti-VEGFR agent versus chemotherapy for the treatment of advanced CRC patients; and (3) The study had sufficient efficacy and toxicity data for extraction. Exclusion criteria: (1) single arm prospective trials or respective studies; (2) both treatment regimens included anti-VEGFR agents; (3) insufficient data could be extracted from the study; We used the 5-item Jadad scaletto roughly assess the quality of included trials [11].

Data extraction

review and meta-analysis focusing on the efficacy and toxicities of VEGFR-targeted agents in advanced CRC patients. We therefore conduct this comprehensive meta-analysis of randomized controlled trials to assess the overall efficacy and toxicities of anti-VEGFR agents in advanced CRC patents.

Method and materials

Study design

We conducted this meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [10].

Search strategy and selection of trials

We performed an extensive research in these four databases (Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews) for relevant trials up to March 2016. Our search strategy included the following terms: “colorectal neoplasms”, “colorectal cancer”, “colorectal carcinoma”, “sorafenib”, “sunitinib”, “pazopanib”, “axitinib”, “cediranib”, “regorafenib”, “ramucirumab”, “vandetanib”, “anti-VEGFR agents” and “randomized controlled trials”.

Trials met the following inclusion criteria were included: (1) Phase II and III randomized con-

Information recorded for each study included the author, publication year, study design, interventions (anti-VEGFR agents and dose), sample size and outcomes of interest [overall survival (OS), progression free survival (PFS), objective response rate (ORR) and grade 3-4 toxicities]. Data were independently extracted by two authors using a standardized pilot-tested form, and any discrepancies were solved by consensus with a third expert.

Statistical analysis

The pooled estimates of hazard ratio (HR) for OS and PFS, the risk ratio (RR) for overall response rate, and grade 3 or 4 AEs was calculated using comprehensive meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA). We used the χ^2 -based Q statistic test to detect the heterogeneity across the different studies [12]. The level of significance was set at 5%. If heterogeneity existed, data was analyzed using a random effects model according to the method of DerSimonian and Laird. In the absence of heterogeneity, a fixed effects model was used. HR>1 reflects more deaths or progression in anti-VEGFR agents group, and RR>1 indicates more toxicities and overall response rate in anti-VEGFR agents group; and vice versa. We also performed sub-group analysis according to treatment lines. Publication bias was evaluated according to the Begg and Egger tests [13, 14]. All *p*-values were two-sided.

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Table 1. Baseline characteristics of seven included trials

Author/year	Phase	Total patients	Treatment line	Treatment regimen	No. for analysis	Median age	Median PFS	Median OS	Jadad Score
Tabernero J. et al/2015	III	1072	Second-line	Ramucirumab 8 mg/kg	536	62	5.7	13.3	5
				Placebo	536	62	4.5	11.7	
Li J. et al/2015	III	204	Second-line	Regorafenib 160 mg qdpo	136	57.5	3.2	8.8	5
				Placebo	68	55.5	1.7	6.3	
Tabernero J. et al	IIB	198	First-line	Sorafenib 400 mg bid po + FOLFOX6	97	59.2	9.1	17.6	5
				placebo + FOLFOX6	101	60.3	8.7	18.1	
Siu L.L. et al/2013	III	750	Second-line	Brivanib 800 mg qdpo + cetuximab	376	64.1	5	8.8	5
				Placebo + cetuximab	374	63.4	3.4	8.1	
Grothey A. et al/2013	III	1052	Second-line	Regorafenib 160 mg qdpo	505	61	1.9	6.4	5
				Placebo	255	61	1.7	5	
Carrato A. et al/2013	III	768	First-line	Sunitinib 37.5 mg qdpo + FOLFIRI	386	59	7.8	20.3	5
				Placebo + FOLFIRI	382	58	8.4	19.8	

Abbreviation: PFS, progression-free survival; OS, overall survival; FOLFOX6, oxaliplatin plus leucovorin plus fluorouracil; FOLFIRI, irinotecan plus fluorouracil plus leucovorin.

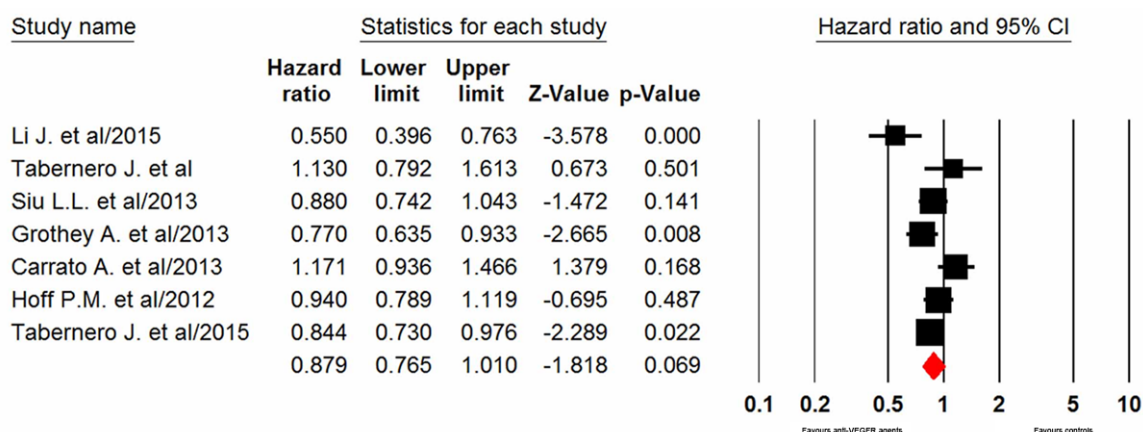


Figure 2. Comparison of overall survival in CRC patients between therapies with or without anti-VEGFR agents.

Results

Search results

The process of searching and evaluating the publications for inclusion in the meta-analysis was shown in the **Figure 1**. A total of 352 publications were identified from the database search, of which 15 reports were retrieved for full-text evaluation. Eight additional studies were excluded for the reasons showed in **Figure 1**. Finally, a total of seven RCTs with 4,094 patients were included for the meta-analysis [10, 15-20]. The baseline characteristics of each trial were presented in **Table 1**. Three reports were from first-line studies, and four were from a second-line trial. The quality of each included study was roughly assessed according to Jadad scale, all seven trials were

placebo-controlled, double-blinded randomized trials, thus had Jadad score of 5.

Overall survival

HR data for OS could acquire from all included trials. Our pooled results for OS favored anti-VEGFR agents group (HR 0.88, 95% CI: 0.77-1.01, $P=0.069$, **Figure 2**).

As there was significant heterogeneity among included trial ($I^2=68.1$, $P=0.005$), we then performed sub-group analysis according to treatment lines, and found that anti-VEGFR agents as second-line therapy significantly improved OS when compared to controls (HR 0.79; 95% CI: 0.68-0.91, $P=0.001$), while the use of anti-VEGFR agents as first-line therapy did not improve OS (HR 1.04; 95% CI: 0.91-1.12, $P=0.60$).

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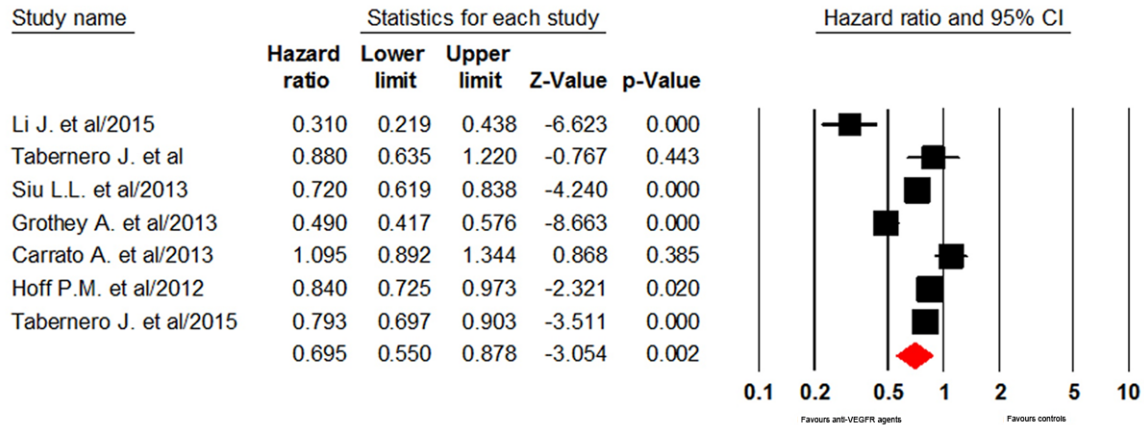


Figure 3. Comparison of progression-free survival in CRC patients between therapies with or without anti-VEGFR agents.

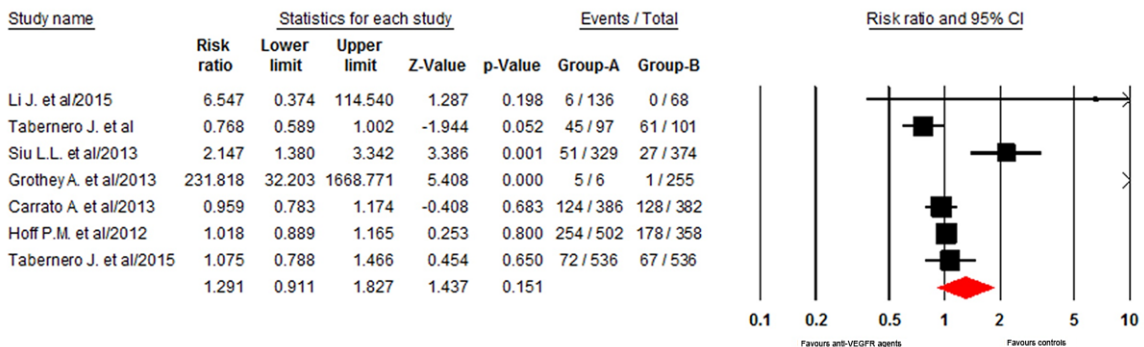


Figure 4. Comparison of ORR in CRC patients between therapies with or without anti-VEGFR agents.

Progression-free survival

HR data for OS could acquire from all included trials. Our results demonstrated that the addition of anti-VEGFR agents to therapies significantly improved PFS (HR 0.70, 95% CI: 0.55-0.88, $P=0.002$, **Figure 3**) by using a random-effect model due to its significant heterogeneity among included trials ($I^2=91.2\%$, $P<0.001$). Sub-group analysis according to treatment lines found that the use of anti-VEGFR agents as second-line treatment significantly improved PFS (HR 0.65; 95% CI: 0.60-0.70, $P<0.001$) when compared to controls, while there was a tendency to improve PFS in trials using anti-VEGFR agents as first-line therapy (HR 0.92; 95% CI: 0.82-1.02, $P=0.12$).

Overall response rate

All seven trials reported ORR data, and the pooled RR for overall response rate showed that there was a tendency to improve ORR in

anti-VEGFR groups with RR (RR 1.29, 95% CI: 0.91-1.83, $P=0.151$ **Figure 4**). There was significant heterogeneity between the trials ($I^2=87.1\%$, $P<0.001$), and the pooled RR for overall response was performed using random-effects model. Sub-group according to treatment lines also showed that the use of anti-VEGFR agents as second-line treatment significantly improve ORR (RR, 1.49; 95% CI: 1.16-1.91, $P=0.002$) when compared to controls in advanced CRC patients, but not for first-line therapy (RR, 0.96; 95% CI: 0.86-1.07, $P=0.44$).

Toxicity

We also pooled the grades 3 or 4 adverse events (AEs) of interest associated with anti-VEGFR agents. More incidences of grade 3 or 4 hypertension (RR 4.76; 95% CI: 3.34-6.80, $P<0.001$) and proteinuria (RR 4.44, 95% CI: 1.29-15.3, $P=0.018$) was observed in anti-VEGFR containing groups. As for grade 3 or 4 hemorrhage (RR 1.55, 95% CI: 0.69-3.47, $P=0.29$),

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Table 2. Outcome of grade 3 or 4 anti-VEGF toxicities associated with anti-VEGFR agents in advanced CRC

Grade 3-4 Toxicities	Trials	Anti-VEGFR agents	Non-anti-VEGFR agents	Heterogeneity		RR (95% CI)	P value
				P value	I ²		
Hemorrhage	2	16/1041	9/791	0.57	0	1.55 (0.69-3.47)	0.29
Hypertension	7	219/2538	35/2074	0.61	0	4.76 (3.34-6.80)	<0.001
VTEs	3	50/1427	37/1173	0.10	57.2	1.25 (0.62-2.50)	0.54
ATEs	3	6/1058	6/986	0.65	0	0.88 (0.29-2.63)	0.82
GI perforation	1	9/536	3/536	1	0	3.0 (0.82-11.0)	0.10
CHF	2	4/672	4/604	0.25	24.9	0.92 (0.24-3.55)	0.90
Proteinuria	3	25/1177	3/859	0.21	35.5	4.44 (1.29-15.3)	0.018

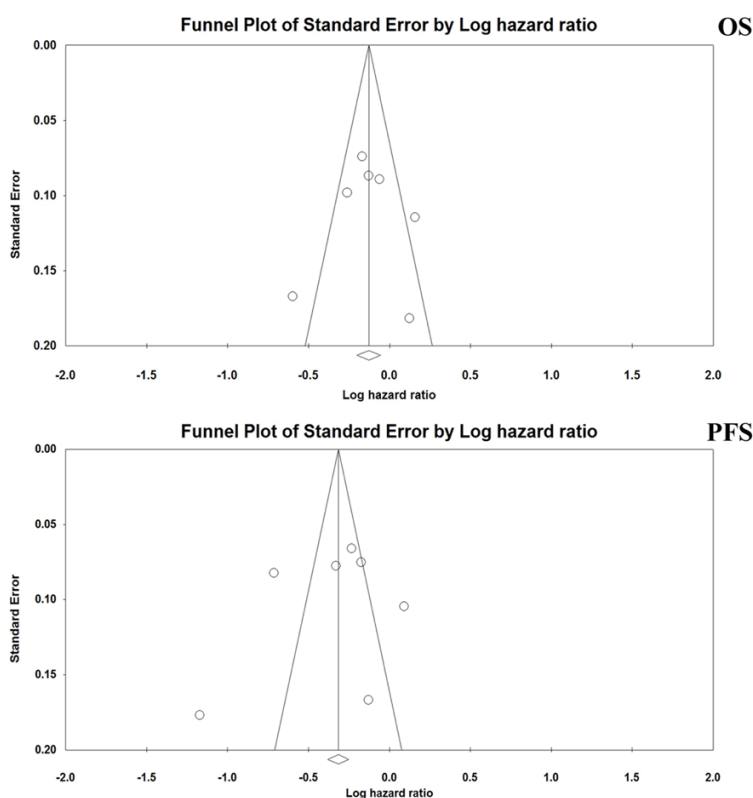


Figure 5. Begg's funnel plot of publication bias in the meta-analysis.

VTEs (RR 1.25, 95% CI: 0.62-2.50, $P=0.54$), ATEs (RR 0.88, 95% CI: 0.29-2.63, $P=0.82$), GI perforation (RR 3.0, 95% CI: 0.82-3.55, $P=0.90$) and CHF (RR 0.92, 95% CI: 0.24-3.55, $P=0.90$), there were no significant difference between the two groups (Table 2).

Publication bias

We performed the publication bias analysis by using Begg's funnel plot and Egger's test. The Begg's funnel plots did not detect any publication bias ($P=0.65$ for OS, $P=0.45$ for PFS, res-

pectively, Figure 5). Similarly, Egger's test also did not detect publication bias ($P=0.96$ for OS, $P=0.58$ for PFS, respectively).

Discussion

Increased vascularity has been reported in many solid tumors including colorectal cancer. Angiogenesis, especially VEGF signal pathway, plays a pivotal role in tumor growth, progression, and metastasis [21, 22]. Thus, the VEGF signal pathway has been targeted as a therapeutic option for colorectal cancer. During the past decades, several novel angiogenesis inhibitors targeting VEGFR have been under investigation in colorectal cancer patients, but the results are controversial. Therefore, the role of anti-VEGFR agents in advanced CRC patients remains unknown.

To our best knowledge, this is the first meta-analysis specifically focusing on the efficacy and toxicities of anti-VEGFR agents in advanced CRC patients. Our study includes a total of 4,904 patients from seven RCTs. The pooled results demonstrate that anti-VEGFR agents-containing regimens significantly improve PFS (HR: 0.70, 95% CI: 0.55-0.88, $P=0.002$), but not for ORR, and OS. Due to the significant heterogeneity among included trials, we also perform sub-group analysis according to treatment lines and shows that the addition of anti-VEGFR

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agents to second therapies significantly improve OS, PFS and ORR. However, no significant survival benefits has been observed in anti-VEGFR agents plus first-line treatment for advanced CRC. With available evidence, the use of anti-VEGFR agents as second-line treatment of advanced CRC could be recommended but not for first-line therapy.

Safety of systematic treatments is of particular importance in palliative setting in metastatic CRC patients, given the potential negative impact on benefit ratio and quality of life. Finding of our study indicates that there are more incidences of grade 3 and 4 hypertension and proteinuria, while equivalent frequencies of grade 3 or 4 thrombosis events, GI perforation, congestive heart disease, and hemorrhage are found between the two groups. Based on our results, we could conclude that the use of anti-VEGFR agents is generally tolerable.

There are several limitations of our study needed to be note from this analysis. Firstly, our study is a meta-analysis of published data, and we could not get individual patient data, which might prevents us to investigate the treatment efficacy based on patient characteristic variables. Second, our study only include prospective randomized controlled trials. According the inclusion criteria of these trials, patients with poor renal, hematological, and hepatic functions might be excluded from the study. Therefore, the pooled results of present study may not apply to patients with organ dysfunctions and in the overall community. Finally, publication bias is another important issue in the meta-analysis, because trials with positive results are more likely to be published than those trials with null results. However, we does not detects publication bias using Begg and Egger tests in present study.

Conclusion

In summary, we observe that the addition of anti-VEGFR agents to second-line therapies provides substantial survival benefits for advanced CRC patients, while no significant survival benefits have been detected in anti-VEGFR agents plus first-line regimens. Additionally, anti-VEGFR agents significantly increases the risk of developing high-grade hypertension and proteinuria. These observations may aid medical oncologists in weighing up the risks

and benefits associated with anti-VEGFR agents in treating advanced colorectal cancer patients.

Disclosure of conflict of interest

None.

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