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The role of angiogenesis inhibitors re-challenge in colorectal cancer previously treated with bevacizumab: a meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: The potential usefulness of angiogenesis inhibitors (AIs) re-challenge in the treatment of metastatic colorectal cancer (CRC) who previously treated with bevacizumab has not been established yet.

MATERIALS AND METHODS: We identified relevant clinical studies through searching databases up to October 2016. Prospective clinical trials investigating AIs re-challenge in metastatic CRC were included for analysis. The primary endpoint was overall survival with secondary endpoint progression-free survival. Estimates of treatment effect from individual trials were combined using standard techniques.

RESULTS: A total of 2.686 patients with metastatic CRC who previously received bevacizumab were identified for analysis. The meta-analysis results demonstrated that AI re-challenge significantly improved progression-free survival (hazard ratio: 0.63, 95% confidence interval: 0.52-0.76, $p < 0.001$) and overall survival (hazard ratio: 0.82, 95% confidence interval: 0.76-0.89, $p < 0.001$) when compared to non-AI containing regimens. No publication bias was detected by Begg's and Egger's tests for PFS ($p = 0.09$ and $p = 0.32$) and OS ($p = 0.85$ and $p = 0.50$).

CONCLUSIONS: Our pooled analysis shows that AIs re-challenge offers an improved PFS and OS in the treatment of metastatic CRC patients who relapsed after a first-line bevacizumab-containing therapy. Further prospective clinical trials are still needed to confirm our findings.

Key Words:
Angiogenesis inhibitors, Colorectal cancer, Second-line, Meta-analysis.

Introduction

Colorectal cancer (CRC) is the third commonly malignancy with approximately 1.2 million new cases and 600,000 deaths estimated to occur worldwide every year[1,2]. Currently, surgical resection remains the cornerstone treatment for early-stage CRC (stage I-III)[3,4]. Unfortunately, the majority of CRC patients are diagnosed with locally advanced or metastatic disease. As a result, most of the patients are ultimately treated in the advanced disease setting where systematic chemotherapy is used to improve quality of life and prolong survival[3]. Although the introduction of relatively new cytotoxic agents irinotecan and oxaliplatin has significantly prolonged survival and has provided symptomatic benefit, the prognosis of patients with metastatic CRC remains poor[5,6]. Angiogenesis, the formation of new blood vessels from pre-existing vessels, has been validated as a target in several tumor types through randomized trials, incorporating vascular endothelial growth factor (VEGF) pathway inhibitors into the therapeutic armory[7-9]. Currently, several antiangiogenic agents such as bevacizumab[10-12], aflibercept[13,14], ramucirumab[15] and regorafenib[16] have been approved as second-line treatment for metastatic CRC patients by the US Food and Drug Administration. Also, bevacizumab has been approved as a first-line treatment for metastatic CRC[17]. As a result, more and more CRC patients have been treated with bevacizumab-containing regimen. However, whether continuously anti-angiogenetic agents by using bevacizumab or switch other an-

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ti-angiogenetic agents would improve survival remains undetermined. In this study, we assess the effect on OS and PFS of angiogenesis inhibitors (AIs) rechallenge in advanced CRC patients, who had previously been given bevacizumab-containing regimens.

Materials and Methods

Selection of Studies

We conducted a computer-based literature search of PubMed, Embase and the Cochrane Library electronic databases up to October 2016, by using the following search terms: "colorectal cancer", "colorectal neoplasm", "antineoplastic agents", "vascular endothelial growth factor", and specific names of anti-angiogenic agents in clinical use. We also manually searched for abstracts from major conferences from 2004-2014. Each publication was reviewed by two authors and in cases of duplicate publication we used the most recent and updated report of that trial.

Data Extraction and Clinical end Point

We performed this systematic review and meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline[18]. The name of the first author and the year of publication were used to identify the study. The main measurement outcome was OS (time from random assignment to death). The second was PFS (the time from random assignment to the first documentation of progression for disease, or death from any cause). HR and its 95% confidence intervals (CI) of OS and PFS were directly collected from each selected study. For each study, the following information was extracted: year of publication, trial phase, number of patients, treatment regimens, median age, and so forth. To be included in the meta-analysis, a study had to satisfy the following requirements: (1) prospective randomized controlled trails comparing therapies with or without AIs (bevacizumab, aflibercept, sorafenib, sunitinib, vandetanib, pazopanib, axitinib, regorafenib, apatinib, cediranib, ramucirumab, nintedanib, thalidomide, lenalidomide); (2) patients were pathologically confirmed of colorectal cancer; (3) the study had sufficient survival data of patients who previously received bevacizumab. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included. We used the 5-item Jadad scale including randomization, double-blinding, and withdrawals to assess the quality of included clinical trials[19].

Statistical Analysis

The data were analyzed using Version 2 of the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA). Survival data of OS and PFS were reported as hazard ratios (HRs). The corresponding 95% confidence intervals (CIs) were calculated. A statistical test with a p-value less than 0.05 was considered significant. HR greater than 1 favored the standard arm, whereas a HR less than 1 favored the experimental treatment (AIs-containing regimens). Between-study heterogeneity was estimated using the χ^2-based Q statistic[20]. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials (25% was considered low-level heterogeneity, 25-50% moderate-level heterogeneity, and 50% high-level heterogeneity). If heterogeneity existed, data were analyzed using a random-effects model, which provided a more conservative analysis. In the absence of heterogeneity, a fixed-effects model according to the inverse-variance was performed. To assess the possibility of publication bias, the funnel-plot test described by using the Begg and Egger tests were performed[21]. All p-values were two-sided. All *CI*s had two-sided probability coverage of 95%.

Results

Search Results

As shown in Figure 1, a total of 205 potentially relevant citations were reviewed, and 196 of which were excluded. Finally, six published RCTs assessing the efficacy of AIs re-challenge in CRC patients were included. The baseline characteristics of these studies were listed in Table I. A total of 2.686 patients were available for the meta-analysis. All patients included in the trials were required to have an adequate renal, hepatic and hematologic function. The quality of each included study was roughly assessed according to Jadad scale, and five trials had Jadad score of 5, and one trial had Jadad scores of 3.

Overall Survival

Six trials reported OS data of AIs re-challenge in CRC patients. The pooled results demonstrated

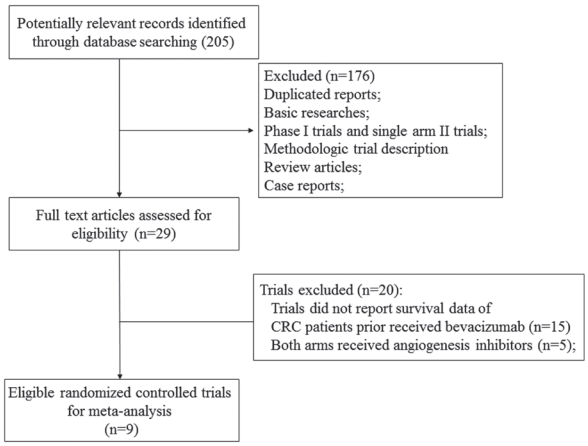

Figure 1. Studies eligible for inclusion in the meta-analysis.

that AIs re-challenge significantly improved OS in comparison with non-AIs containing therapies (HR 0.82, 95% CI: 0.76-0.89, $p < 0.001$, Figure 2) using a fixed-effects model ($I^2 = 0\%$, $p = 0.96$).

Progression-Free Survival

Six trials reported PFS data. The pooled hazard ratio for PFS demonstrated that AIs re-challenge also significantly improved PFS giving HR 0.63 (95% CI: 0.52-0.76, $p < 0.001$, Figure 3), compared with non-AIs containing regimens. There was significant heterogeneity between trials ($I^2 = 79.6\%$, $p < 0.001$), and the pooled HR for PFS was performed by using a random-effects model.

Publication Bias

We did not observe significant asymmetry by using funnel plots (data not shown). Additionally, no evidence of publication bias was detected by using Begg's and Egger's linear regression tests (OS: $p = 0.85$, and $p = 0.50$; PFS: $p=0.09$ and $p = 0.32$; 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[8,9]. Thus, the VEGF signal pathway has been targeted as a therapeutic option for colorectal cancer[22,23]. In fact, several novel angiogenesis inhibitors targeting VEGF pathway have been approved for the treatment of advanced CRC patients. However, the efficacy of AIs re-challenge in CRC patients previously treated with bevacizumab remains undetermined. Previous preclinical research finds that the angiogenesis continues throughout the lifespan of the tumor. It has been assumed that persistent VEGF suppression, along with secondary and tertiary cytotoxic regimens, may result in continued clinical benefit. Based on this hypothesis, we conduct the current meta-analysis to evaluate whether AIs re-challenge could obtain clinical benefits in CRC patients who have progressed after first-line treatment with bevacizumab-containing chemotherapy. To the best of our knowledge, this study is the first meta-analysis with a focus on investigating the value of AIs re-challenge in pretreated CRC patients. A total of 2.686 patients with metastatic CRC who previously received bevacizumab was

Table I. Baseline characteristic of the six trials included for analysis.

Authors	Total patients	No. of patients who received AIs already	Treatment arms	Primary endpoint	Median follow-up	Jadad score
Van cutsem et al/2012	1226	373	Aflibercept + FOLFIRI Placebo + FOLFIRI	OS	22.28	5
Bennouna et al/2013	820	820	Bevacizumab +chemotherapy chemotherapy	OS	9.6	3
Grothey et al/2013	760	760	Regorafenib placebo	OS	NR	5
Siu et al/2013	750	152	Brivanib + cetuximab Placebo + cetuximab	OS	18.7	5
Li et al/2015	204	45	Regorafenib Placebo	OS	7.4	5
Tabernero et al/2015	1072	1072	Ramucirumab + FOLFIRI Placebo + FOLFIRI	OS	21.7	5

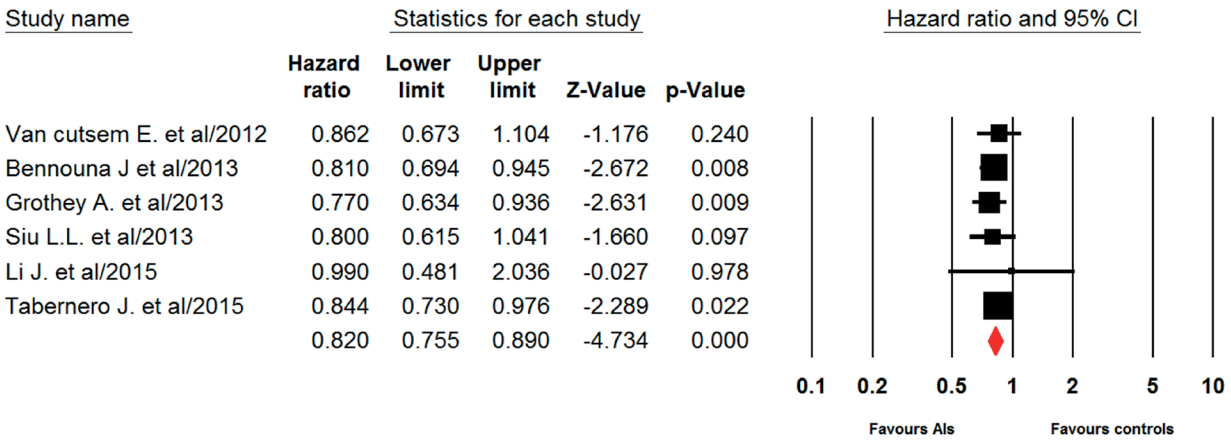

Figure 2. Fixed-effects model of hazard ratio (95% CI) of OS associated with therapies with or without AIs.

identified for analysis. The meta-analysis results demonstrate that AI re-challenge significantly improved progression-free survival (hazard ratio: 0.63, 95% confidence interval: 0.52-0.76, $p < 0.001$) and overall survival (hazard ratio: 0.82, 95% confidence interval: 0.76-0.89, $p < 0.001$) when compared to non-AI containing regimens. Based on our findings, angiogenesis inhibitors could be recommended in patients with advanced CRC who previously received bevacizumab, AIs re-challenge in combination with standard treatment could be a preferable treatment option over standard second-line therapy alone, although this recommendation cannot be conclusive because the overall comparisons are not based on randomization. Furthermore, the toxicity outcome is not assessed. Several limitations need to be concerned in the present work. Firstly, most of the included trials are conducted to assess the role of AIs in CRC patients, but not specifically for patients who previously received bevacizumab, which might lead to the imbalance of patient characteristics between the two treatment groups. Secondly, our study is a study-level meta-analysis, confounding variables at the patient level could not be incorporated into the analysis. Thirdly, different AIs are included for analysis, which would increase the clinical heterogeneity among included trials. Finally, a possible publication bias might have been introduced because trials with positive results are more likely to be published. Our research detects no publication bias using Begg and Egger tests for OS and PFS.

Conclusions

This is the first meta-analysis assessing the efficacy of AIs re-challenge in metastatic

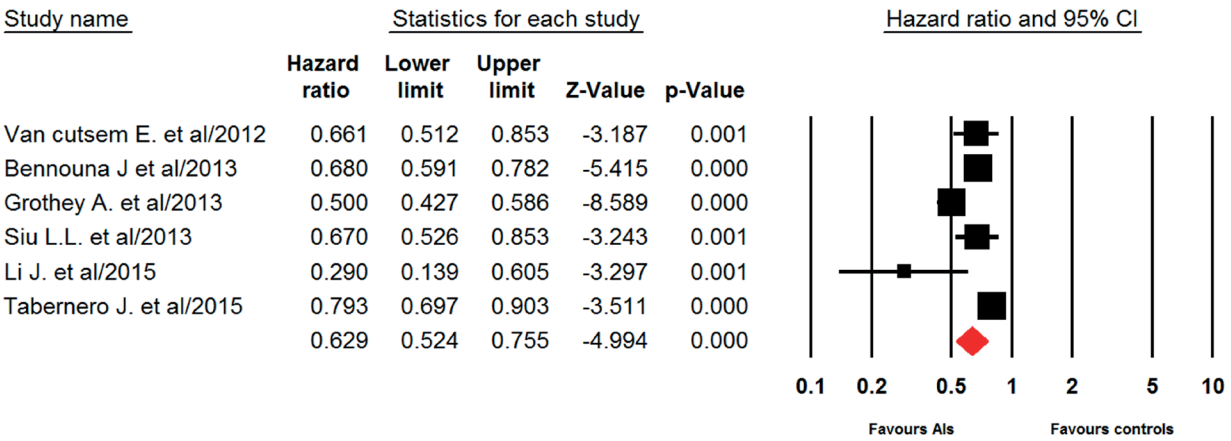

Figure 3. Fixed-effects model of hazard ratio (95% CI) of PFS associated with therapies with or without AIs.

CRC patients. Our results indicate that AIs re-challenge offers an improved PFS and OS in metastatic CRC patients when compared to non-AIs containing regimens. Thus, AIs could be recommended for metastatic CRC patients who previously treated with bevacizumab.

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Conflict of Interest
The Authors declare that they have no conflict of interests.

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