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ORIGINAL ARTICLE

Hypertension as a predictive biomarker for efficacy of bevacizumab treatment in metastatic colorectal cancer: A meta-analysis

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Summary

Purpose: *Bevacizumab has demonstrated survival benefit in patients with metastatic colorectal cancer (mCRC) when combined with chemotherapy. However, no validated predictors currently exist for its efficacy. Hypertension has been evaluated as a surrogate marker for efficacy of bevacizumab, although analyses, to date, have yielded conflicting results. The aim of this meta-analysis was to dissect the association between hypertension and efficacy of bevacizumab treatment in mCRC.*

Methods: *We searched PubMed, EMBASE, Chinese Biomedical Database (CBM), and Wan Fang Digital Journals before September, 2013. The primary clinical outcomes included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Relative risk (RR) or summary hazard ratio (HR) were calculated using a fixed-effects or random-effects model, depending on the heterogeneity of the included studies. Studies meeting our search criteria were assessed.*

Results: *Nine studies were considered eligible, with 1674 mCRC patients included. Six (308 patients, 104 with hypertension), 8 (1661 patients, 431 with hypertension) and 5 (1512 patients, 408 with hypertension) studies were eligible for the ORR, PFS and OS meta-analysis, respectively. Bevacizumab-related hypertension was associated with increased ORR (RR= 1.63; 95% CI 1.26–2.12; p=0.0002), improved PFS (HR=0.68; 95% CI 0.58–0.79; p<0.00001) and OS (HR=0.52; 95% CI 0.42–0.66; p<0.00001). There was no statistically significant difference between-study heterogeneity.*

Conclusion: *These analyses suggest that hypertension may be a potential biomarker for efficacy of bevacizumab treatment in mCRC. Additional large prospective trials are required to confirm its predictive role.*

Key words: *bevacizumab, hypertension, metastatic colorectal cancer, meta-analysis*

Introduction

Colorectal cancer (CRC) is one of the most frequent human malignant diseases and a serious public health problem. Despite advances in pharmacotherapy of CRC in recent years, the 5-year survival rate for mCRC remains poor [1].

Bevacizumab, a humanized monoclonal antibody (MAB) that binds to and neutralizes vascular endothelial growth factor (VEGF), has been shown to prolong PFS and OS when combined with chemotherapy for mCRC in both the first- and second-line setting [2-6]. However, unlike the anti-EGFR MABs cetuximab and panitumumab, for which the presence of KRAS mutation is now known to predict response, no validated predictors currently exist for the efficacy of bevacizumab [7]. As bevacizumab is closely related with increased toxicities and costs, it is important to identify those patients who are more likely to respond and make the treatment more cost-effective.

Arterial hypertension is one of the common side-effects during bevacizumab therapy. A recent meta-analysis demonstrated that the RR of CRC

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patients developing hypertension was significantly increased when treated with bevacizumab [8]. The pathogenesis of bevacizumab-induced hypertension is not completely clear. It has been suggested that bevacizumab inhibits VEGF signalling to endothelial cells, which reduces the amount of endothelial cell-derived nitric oxide and prostacyclin, causing vascular smooth muscle constriction, increased vascular resistance, and elevated blood pressure [9,10]. Additionally, the number of capillary beds, which could cause the rise in vascular resistance, decreases along with the chronic treatment with bevacizumab [11]. Thus, hypertension might be a valuable predictor of VEGF activity, thereby possibly predicting the efficacy of bevacizumab. However analyses, to date, have yielded conflicting results.

For example, Scartozzi et al. reported a correlation between hypertension and PFS and tumor response rate in a retrospective study of 39 CRC patients [12]. On the contrary, development of hypertension was not predictive of outcome in Dewdney's study [13]. The reasons for this difference could be merely a result of chance, or heterogeneity between studies, or the limit of sample size. We thus conducted this meta-analysis to dissect the associations between hypertension and clinical outcomes of mCRC patients in relation to bevacizumab.

Methods

Literature search

Systematic computerized searches were performed in the following search engines: PubMed, EMBASE, Chinese Biomedical Database (CBM), and Wan Fang Digital Journals. The following search items were variably combined: metastatic colorectal cancer (e.g. 'metastatic colon cancer', 'metastatic rectal cancer', 'mCRC'), hypertension (e.g. 'arterial hypertension', 'bevacizumab-induced hypertension', 'bevacizumab-related hypertension', 'HTN'), and clinical outcomes (e.g. 'objective response rate', 'progression-free survival', 'overall survival'). No limits were set for this search. The cutoff date for trial inclusion was September 30, 2013. We also scanned references of selected articles and previous systematic reviews for any other relevant trials. Literature search and study selection and results in each step were depicted in the form of flow chart (Figure 1). Two independent investigators conducted the search. Each study was reviewed for eligibility and quality by two investigators. A third investigator helped make a judgement if disagreements existed.

Inclusion and exclusion criteria

The aim was to evaluate the correlation between the modifications of arterial blood pressure and clinical outcomes, including ORR, PFS and OS, in patients with mCRC treated with bevacizumab.

Studies meeting all the following two inclusion criteria were eligible and included in the review: (i) those exploring the relationship between hypertension and clinical outcomes in patients with mCRC treated with bevacizumab; (ii) those using one or more of the following as outcomes to assess tumor response and prognosis: ORR, PFS and OS.

Excluded were studies without adequate statistical analysis information, studies still in progression, and those without full text articles online.

Data extraction

The following data were collected from each study: first author's name, year of publication, study design, patient baseline characteristics, total number of patients included in the study, proportion of hypertension, line of treatment, study treatment protocols, chemotherapy regimens, response criteria, the method of recording and definition of hypertension, ORR, PFS, and OS. In addition, we collected the number of responders for calculating RRs and 95% confidence intervals (95% CI) for ORR. HRs and their variance for the relevant survival outcomes comparing patients with increased and normal arterial blood pressure receiving treatment with bevacizumab were also extracted. The methods developed by Parmaret et al. [14] were used to calculate the HR and/or its variance if they were not provided by the eligible studies. When the data was not shown in articles directly, we extracted it from survival curves by the Engauge Digitizer version 4.1 and then estimated the log HR and its variance using the previously described methods [14,15] .

Statistics

The software packages Review Manager V. 5.1 (Nordic Cochran Centre, Copenhagen, Denmark) were used to calculate the pooled estimates.

The association between bevacizumab-related hypertension and ORR was expressed as RR, namely the overall response rate in those who developed hypertension divided by that in those who did not. The association between bevacizumab-related hypertension and PFS or OS was expressed as HR. Summary HRs with their 95% CI were calculated using an inverse variance method. A fixed-effects model using the Mantel–Haenszel method [16] or a random-effects model using the DerSimonian–Laird method [17] were adopted depending on the heterogeneity of the included studies. Heterogeneity was evaluated using Q statistics and quantified by the I^2 statistic [18,19]. If p value was less than 0.10 or I^2 was not less than 50%, there was statistically significant between-study heterogeneity. Forest plots were visually applied for displaying odds ratios within individual trials and overall. Publication bias was investigated with funnel plots. All p values were two-sided.

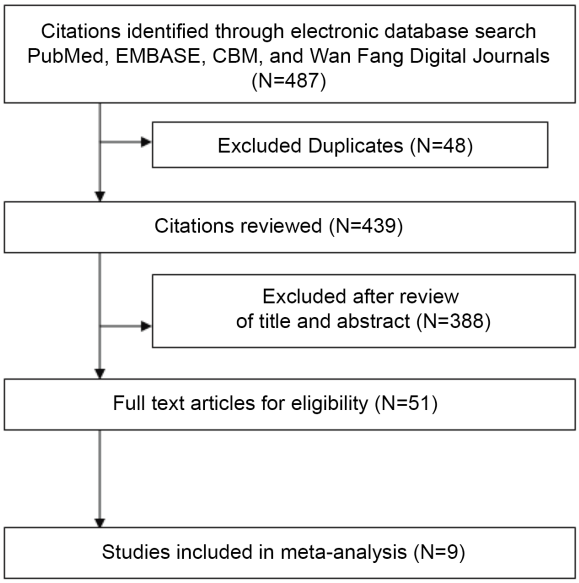

Figure 1. Flow chart of study selection.

Results

Study characteristics

Figure 1 is the flow chart of literature search and study selection. The search in bibliographic databases yielded 487 citations, of which 51 were classified as potentially relevant and subjected to full text assessment. A total of 9 studies met the inclusion criteria.

Table 1 shows the main characteristics of the 9 studies for patients treated with bevacizumab, all of which were retrospective cohort studies. The studies were published between 2009 and 2013. As shown in Table 1, arterial hypertension was graded by NCI—CTCAE 3.0 in most studies. Two of the studies employed NCI—CTCAE 2.0 for evaluation. Only one study employed NCI—CTCAE 4.0. The studies showed slight variation in the cut-off level for hypertension definition. Overall, the eligible studies reported on 1674 patients, of whom 440 (26.3%) developed hypertension. Their median age ranged from 58 to 66 years and the frequency of bevacizumab-related hypertension ranged from 15.5 to 56.4% across different studies. Bevacizumab in combination with chemotherapy were used in all studies. Bevacizumab was given as first-line treatment in 5 studies and as first-line or subsequent lines in 3 studies. In several studies, the patients were treated within phase II or III clinical trials. In the study by Hurwitz [34], mCRC patients treated within two phase III studies, AVF2107g and NO16966, were analyzed separately.

Hypertension and ORR

Regarding ORR, 6 studies [12,13,20-23] involving 308 patients (104/33.8% with hypertension) provided data for the meta-analysis. The ORR ranged from 30 to 85% for the hypertensive group and from 20 to 79% for the non hypertensive group. There was no statistically significant between-study heterogeneity (p =0.11; I^2=44%).

Figure 2 is the forest plot of the analysis on the relative risk according to the status of hypertension. The fixed-effect pooled estimate showed an increased ORR for the hypertensive group (risk ratio [RR] =1.63; 95% CI 1.26–2.12; p=0.0002). The result suggests that patients with bevacizumab-induced hypertension had a better prognosis in terms of objective response compared to patients who did not develop hypertension.

Hypertension and survival

Data for hypertension and PFS in mCRC patients treated with bevacizumab were reported in 8 studies [12,13,21-26] involving 1661 patients (431/25.9% with hypertension).No between-study heterogeneity was observed (p=0.7; I^2=0%) and hypertension was significantly associated with improved PFS among patients treated with bevacizumab (HR=0.68; 95% CI 0.58–0.79; p<0.00001) (Figure 3).

For OS, 5 studies [13,23-26] involving 1512 patients (408/27% with hypertension) provided data for the meta-analysis. There was no statistically significant between-study heterogeneity (p=0.12; I^2=43.0%) and OS was significantly longer in patients who developed hypertension than in those who did not (HR= 0.52; 95% CI 0.42–0.66; p<0.00001) (Figure 4).

Publication bias

Funnel plots were performed to assess publication bias (Figures not shown). The results suggested that there was no evidence of publication bias for the study's primary outcome, ORR, PFS and OS.

Discussion

Bevacizumab has demonstrated survival benefit in combination with chemotherapy for treatment of mCRC [2-6,12]. However, patients who truly benefit from the treatment remain limited, making it of particular importance to identify effective markers that can help select patients who will gain greater benefit from bevacizumab.

Table 1. Main characteristics of 9 included studies

Author (year) [ref]	*Patients analysed (N)*	*No. of patients with HTN (%)*	*Median age, years, (range)*	*Gender (M/F)*	*Line of treatment*	*Chemotherapy regimens*	*HTN criteria*	*Cut-off level*	*Outcome reported*
Scartozzi M (2009) [12]	39	8 (20.5)	58 (30-70)	25/14	1st	FOLFIRI	CTC AE v 2.0	grade ≥2	ORR,PFS
Ryanne Wu R (2009) [25]	84	36 (42.9)	NR	42/42	NR	NR	CTC AE v 3.0	grade ≥1	OS,PFS
De Stefano A (2011) [22]	74	13 (17.6)	57 (31-80)	42/32	1st	FOLFIRI,-FOLFOXIRI,-FOLFOX, XELOX,XE-LIRI	CTC AE v 3.0	grade ≥1	ORR,PFS
Osterlund P (2011) [23]	101	57 (56.4)	59 (35-79)	53/47	≥1st	OXA-/5-FU-/CPT-11-based	CTC AE v 3.0	grade ≥1	ORR,PFS, OS
Horinouchi Y (2011) [21]	36	10 (27.8)	66 (36-81)	20/16	1st and 2nd	FOLFOX, FOLFIRI	CTC AE v 3.0	grade ≥1	ORR,PFS
Yamamura K (2011) [20]	13	9 (69.0)	64.4 (51-79)	7/6	1st	FOLFOX	CTC AE v 3.0	grade ≥1	ORR
Dewdney A (2012) [13]	45	7 (15.5)	NR	NR	1st	XELOX	CTC AE v 3.0	grade ≥1	ORR,PFS, OS
Tahover E (2013) [26]	181	81 (44.8)	61 (25-89)	95/86	1st and 2nd	OXA+5-FU/CPT-11+5-FU/OX-A+CPT-11+5-FU	CTC AE v 4.0	grade ≥2	OS,PFS
Hurwitz HI (2013) [24] AVF2107g	402	88 (22.5)	59.5 (NR)	237/165	1st	IFL	CTC AE v 2.0	a change in SBP >20mmHg or DBP>10 mmHg	OS,PFS
Hurwitz HI (2013) [24] NO16966	699	131 (18.8)	60 (18-86)	418/281	1st	FOLFOX/XELOX	CTC AE v 3.0	a change in SBP >20mmHg or DBP>10 mmHg	OS,PFS

HTN: hypertension, M: male, F: female, NR: not reported, SBP: systolic blood pressure, DBP: diastolic blood pressure, ORR: objective response rate, OS: overall survival, PFS: progression free survival, CTC: common terminology criteria, AE: adverse events

Hypertension is a common adverse event during antiangiogenic treatment which can be used to further select anti-VEGF MABs recipients among patients with mCRC. Cai et al. [27] have performed a recent meta-analysis, which included 7 studies and a total of 528 cases of mCRC, to investigate the relationship between hypertension and the efficacy of bevacizumab. However, the included studies were not all-inclusive, which might lead to inappropriate results. Therefore, we reconducted a systematic review of the current evidence. We identified 9 nonoverlapping studies that explored the association of hypertension with the clinical outcomes of anti-VEGF MAB treatment. The overall rate of hypertension (26.3%) was similar to previously reported series [28]. It was found that bevacizumab-related hypertension was significantly associated with more benefit from the treatment whether in terms of PFS, OS or objective response.

Previous studies to determine whether some molecular or pathologic factors can be used to predict bevacizumab efficacy in order to identify subgroups of patients who are more likely to respond to the drug have not been successful [29,30]. Expression of VEGF, VEGFR, B-raf, K-ras and p53 failed to help select patients for bevacizumab treatment. Recently, CA 19-9 level [31], proangiogenic tumor proteins [32], and gene expression marker [33] have also been studied. Although some positive results have been shown, it might not make much sense due to the limited samples.

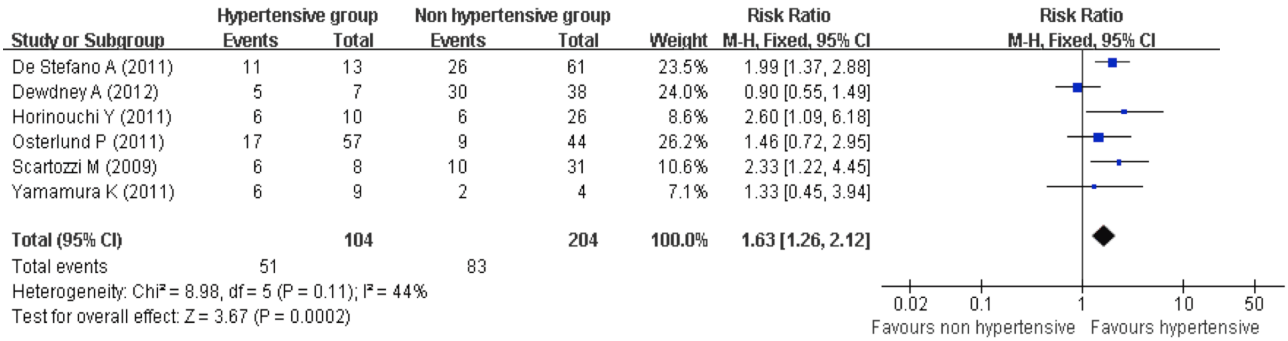

Figure 2. Association of hypertension with objective response of metastatic colorectal cancer patients receiving bevacizumab.

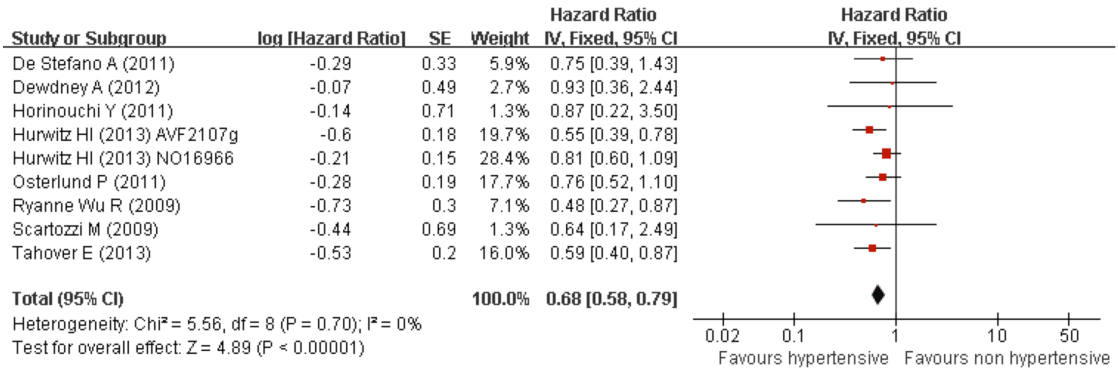

Figure 3. Association of hypertension with progression-free survival of metastatic colorectal cancer patients treated with bevacizumab.

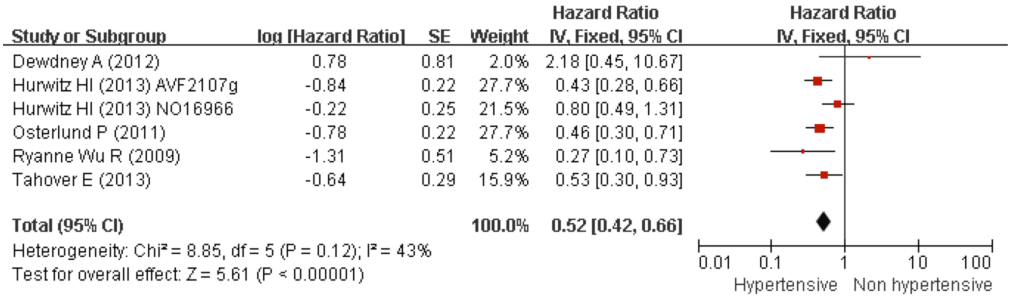

Figure 4. Association of hypertension with overall survival of metastatic colorectal cancer patients treated with bevacizumab.

The key point here is that the target of bevacizumab is host endothelial cells rather than the tumor tissue itself. Bevacizumab inhibits VEGF signalling to endothelial cells, which lessens tumor growth and leads to rapid rise in blood pressure [34,35]. Inhibition of VEGF signalling pathway leads to endothelial cell apoptosis and capillary rarefaction. On the other hand, it can elevate blood pressure by reducing the amount of endothelial cell-derived nitric oxide. Since development of treatment-related hypertension and tumor control have similar mechanisms, hypertension might be a valuable predictor of VEGF activity, thereby possibly predicting the efficacy of bevacizumab. This is similar to previous results indicating that the rash serves as a predictive marker of anti-EGFR effect in mCRC. It was found that the occurrence of rash, induced by inhibiting EGFR in hair follicles, is closely related to increased survival in patients treated with anti-EGFR agents [36,37]. Our results seem also to go along with those regarding other cancer patients treated with bevacizumab. Extensive retrospective analyses of the data from several randomised, phase 3 trials in breast

[38], non-small cell lung [39], and renal cancer [40] have shown that hypertension induced by bevacizumab was associated with prolonged PFS or OS.

Patients receiving bevacizumab should have their blood pressure monitored throughout the treatment. Discontinuation of bevacizumab due to the appearance of hypertension should be avoided, and appropriate anti-hypertensive therapy should be administered in order to obtain the best benefit from anti-angiogenic treatment. Cessation in the absence of hypertension may be wise if the patient has poor tolerability, if economical restraints for the use of the drug exist, or if alternative therapies are available, for example, EGFR inhibitors.

Although our results support bevacizumab-related hypertension represents a predictive factor of clinical outcomes in patients with mCRC, there still exist some obstacles for a future clinical application of it. There is considerable variation in the methods of recording and defining hypertension. The clinically important cut-off values for percentage rise in blood pressure has yet to be established. Also unclear is whether a history of hypertension or medical management of hypertension affects the predictive value of this factor. In addition, the use of an adverse event as a biomarker has limitations. However, studying the mechanisms of bevacizumab-related hypertension may help find some other potentially useful predictive biomarkers. For instance, certain VEGF genotypes may protect against VEGF signalling pathway inhibitor-induced hypertension. And polymorphisms in VEGF and VEGF receptor 2 have been implicated as potential candidate biomarkers to predict for the benefit of bevacizumab in a breast cancer study [38]. Factors that predict bevacizumab-induced hypertension could assist in the prospective selection of patients for treatment.

However, the results of this meta-analysis should be interpreted by taking into account the following issues: First, all of the included studies were retrospective cohort studies, of which the quality varied. Owing to lack of individual patient data, we were unable to conduct sub-group analyses to explore potential confounding factors. Fortunately, almost all studies included in each meta-analysis showed similar trends. Therefore, we argue that our overall conclusion is unlikely to be jeopardized by the adverse factors. Secondly, based on the current evidence, we cannot clarify whether arterial hypertension has similar predictive power in patients untreated with bevacizumab. Elevation of blood pressure may be only a marker of better prognosis due to the inherent characteristics of tumor and not a marker of drug efficacy. Further research in this topic is warranted in the future.

Despite these limitations, current evidence shows that bevacizumab-related hypertension was significantly associated with better PFS, OS and ORR among patients with mCRC receiving bevacizumab. Thus, it is a promising biomarker to identify those patients who are more likely to benefit from this treatment. In the future, well-designed large randomized controlled trials conducted in patients with mCRC receiving treatment with bevacizumab according to hypertension status are essential to fully assess its clinical relevance and to develop an algorithm with optimal combination of existing biomarkers to get a better prediction ability.

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