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ORIGINAL RESEARCH

A systematic review and meta-analysis on the effect of angiogenesis blockade for the treatment of gastric cancer

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Introduction: To date, anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb, bevacizumab), anti-VEGF receptor mAb (ramucirumab) and selective vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (sunitinib, sorafenib and apatinib) have been tested in the clinical trials.

Materials and methods: In the current study, results of 32 clinical trials (24 Phase I or II, 8 Phase III) were systematically reviewed and meta-analysis was performed in 8 Phase III trial results.

Results: It was found that median overall survival (OS) time and progression-free survival (PFS) time were significantly longer in the patients treated with antiangiogenic reagents compared to that in the patients with placebo when all of 8 Phase III clinical trials were analyzed together (OS: odds ratio = 0.805, 95% CI: 0.719–0.901, $P < 0.001$; PFS: odds ratio = 0.719, 95% CI: 0.533–969, $P = 0.030$).

Conclusion: Meta-analysis on bevacizumab (4 out 8 Phase III trials) indicated that neither OS nor PFS was significantly different between the groups treated with bevacizumab or placebo with or without combination of other chemotherapeutic reagents (OS: odds ratio = 0.909, 95% CI: 0.780–1.059, $P = 0.221$; PFS: odds ratio = 0.985, 95% CI: 0.865–1.122, $P = 0.826$). By contrast, meta-analysis on ramucirumab (3 out of 8 Phase III trials) revealed that ramucirumab was significantly favored in the treatment of gastric cancer with significant different OS between the two groups (odds ratio = 0.720, 95% CI: 0.604–0.858, $P < 0.001$). In addition, patients treated with VEGF or VEGFR blockers had higher morbidity of hypertension and neutropenia, but lower risk of side effects of vomiting and anemia. These findings suggest that addition of antiangiogenesis reagents, especially anti-VEGFR-mAb, to the first- or second-line chemotherapy could prolong patient's OS and PFS time in the advanced or metastatic gastric cancer.

Keywords: anti-VEGF monoclonal antibody, anti-VEGF receptor mAb, VEGFR tyrosine kinase inhibitors, Phase III trial, overall survival, progression-free survival, chemotherapy

Introduction

Despite improvements in systemic chemotherapy, the prognosis of advanced or metastatic gastric cancer remains poor. Recent progress in understanding the molecular biology of gastric cancer and the related signaling pathways provides promising strategies for the targeted therapies for the treatment of gastric cancer. In this context, angiogenesis is widely considered as one of the main processes for tumor progression. Vascular endothelial growth factor (VEGF), also known as VEGF-A, is the primary driver of this angiogenesis process in the solid tumors. The family of VEGF molecules also includes VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor. Each component of this family can bind to several VEGF receptors (VEGFR), known as

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VEGFR1, VEGFR2 and VEGFR3, and 2 co-receptors, neuropilin 1 and 2. In particular VEGF-A binds to VEGFR-1 and -2, and the most important receptor is VEGFR-2,[1–3] which regulates the proliferation of endothelial cells through a number of different mechanisms.[1,4]

Although there are no validated biomarkers to select patients for antiangiogenic therapy, strategies of targeting angiogenic process in solid tumors include 1) targeting pro-angiogenic factors (VEGF) with monoclonal antibody (mAb); 2) targeting angiogenic receptors (VEGFR) with mAb and 3) selectively targeting VEGFR associated tyrosine kinase with inhibitors (TKI). To date, two humanized mAbs, bevacizumab (anti-VEGF-mAb) and ramucirumab (anti-VEGFR-mAb), have been approved and tested in the varying phases of clinical trials. In addition, VEGFR-selective TKIs, such as sorafenib, sunitinib and apatinib, have also been tested in clinical trials for the treatment of common solid tumors including gastric cancer.

Results of clinical trials with the aforementioned VEGF blockers including anti-VEGF-mAb, anti-VEGFR-mAb and VEGFR-TKIs, however, were inconsistent. The current study was, therefore, designed to systematically review results of the clinical trials for the treatment of gastric cancer with anti-VEGF-mAb, anti-VEGFR-mAb or VEGFR-TKIs, and furthermore to perform meta-analysis on the Phase III clinical trials.

Materials and methods

Data sources

Relevant literature up to October 10th, 2017, was searched in the sites of PubMed, Embase and Web of Science with the following phrases: "gastric cancer" and "VEGF, VEGFR antagonist" or "VEGF, VEGFR blockade" or "VEGF, VEGFR inhibitor" or "VEGFR tyrosine kinase inhibitor" and "Clinical trial". The search was limited to English and Chinese. In addition, relevant literatures were also identified by hand-searching the references.

Inclusion and exclusion criteria

Following studies were included into the current systematic review and meta-analysis: 1) clinical studies on the treatment of primary or metastatic gastric cancer with anti-VEGF-mAb (bevacizumab), anti-VEGFR-mAb (ramucirumab) inhibitors or VEGFR-TKIs (sorafenib, sunitinib, apatinib) with or without combination of other chemotherapeutic reagents and 2) studies with full text articles. Studies were excluded if they were preclinical studies or published in a language other than English.

Data extraction

Data extraction was conducted by two investigators (ZB and ZZ). Data extraction included study name (the first author' last name), year of publication, treatment regimen, total number of cases for each treatment group, median overall survival (OS) months, median progression-free survival (PFS) month and morbidity of adverse effects (Table 1). The senior author (ZB) was involved in consulting for the eligibility of a study if a divergence between the two data-extracting investigators existed.

Statistical analysis

The following format of data entry was used: 1) median survival month of OS, number of cases and *P*-value; 2) median survival month of disease or progression-free interval, number of cases and *P*-value and 3) computerized odds ratio and *P*-value. The strength of therapeutic effect by VEGFR blockers on gastric cancer was measured by odds ratio, and the morbidity of side effect was measured by risk ratio. A fixed effect model was applied when no heterogeneity was observed among the studies. Alternatively, a random effect model was applied if the heterogeneity between studies was $P < 0.10$ and $I^2 > 50\%$, which was considered as heterogeneous between the studies.[5,6] All meta-analysis was performed using the Comprehensive Meta-analysis software (Version 3, NJ, USA).

Table 1 Summary of data extraction of Phase III clinical trials for meta-analysis

Year	Author	Country	Treatment	Cancer type
2011	Ohtsu et al[8]	Multi-countries	Bev + Cis + Cap	Advanced gastric cancer
2014	Fuchs et al[16]	Multi-countries	Ram after first-line	Advanced gastric/gastroesophageal
2014	Wilke et al[17]	Multi-countries	Ram + Pac	Advanced gastric/gastroesophageal
2015	Ma et al[18]	China	Bev + Doc/Oxa/5-FU	Locally advanced gastric cancer
2015	Shen et al[19]	China	Bev + Cisp/Cap	Advanced or metastatic gastric/gastroesophageal
2016	Al-Batran et al[20]	Multi-countries	Ram + Pac	Advanced gastric/gastroesophageal
2013	Li et al[36]	China	Apatinib	Advanced or metastatic gastric/gastroesophageal
2017	Cunningham et al[23]	UK	Bem + chemotherapy	Esophagogastric adenocarcinoma

Abbreviations: Bev, bevacizumab; Cis, cisplatin; Cap, capecitabine; Doc, docetaxel; Oxa, oxaliplatin; Ram, ramucirumab; Pac, paclitaxel.

Results

General information of the enrolled studies

As shown in Figure 1, after careful reading of the abstracts, 43 full-text articles were retrieved. The articles were then independently assessed, and data were extracted by two investigators. After excluding reviews and case report articles, 32 articles were included in the systematic review[7–36] and 8 articles of Phase III clinical trials were further included in the meta-analysis.[8,16–20,22,23,37] Of the 32 articles for systematic review and meta-analysis, 6 articles were from the USA;[7,10,13,28,29,38] 5 articles were from Korea;[24,26,30,35] 4 articles were from multiple centers in different countries;[8,16,17,20] 5 articles were from People's Republic of China;[18,19,21,22,36] 4 were from Japan,[9,11,25,34] 2 were from Germany;[27,32] one each was from Israel,[12] Netherlands,[14] Spain[31] and UK.[23]

Commonly used agents for targeting VEGF/VEGFR signaling pathways were bevacizumab, ramucirumab, apatinib, sunitinib and sorafenib. Of them, bevacizumab is a mAb that targets VEGF-A, which was studied in 4 out of 8 Phase III clinical trials;[8,18,19,23] ramucirumab is a mAb that targets VEGF receptor, which was studied in 3 out of 8 Phase III clinical trials.[16,17,20] One out 8 Phase III clinical trials was on the effect of apatinib, a selective VEGFR TKIs.[22]

Effect of targeting VEGF or VEGFR on OS and PFS

Of the 32 articles selected for systematic review, 8 studies were randomized Phase III trials on the effect of anti-VEGF-mAb (bevacizumab), anti-VEGFR-mAb (ramucirumab) or selective VEGFR-TKI inhibitors (apatinib) in comparison with placebo in combination with or without chemotherapy for the treatment of gastric cancers,[8,16–20,22,23,37] and 24 studies were Phase I or II trials on effect and safety of anti-VEGF-mAb, anti-VEGFR-mAb or VEGFR-TKI inhibitors.[7–15,21,24–36]

By quantitative meta-analysis of the selected 8 Phase III trials, it was found that median OS time was significantly

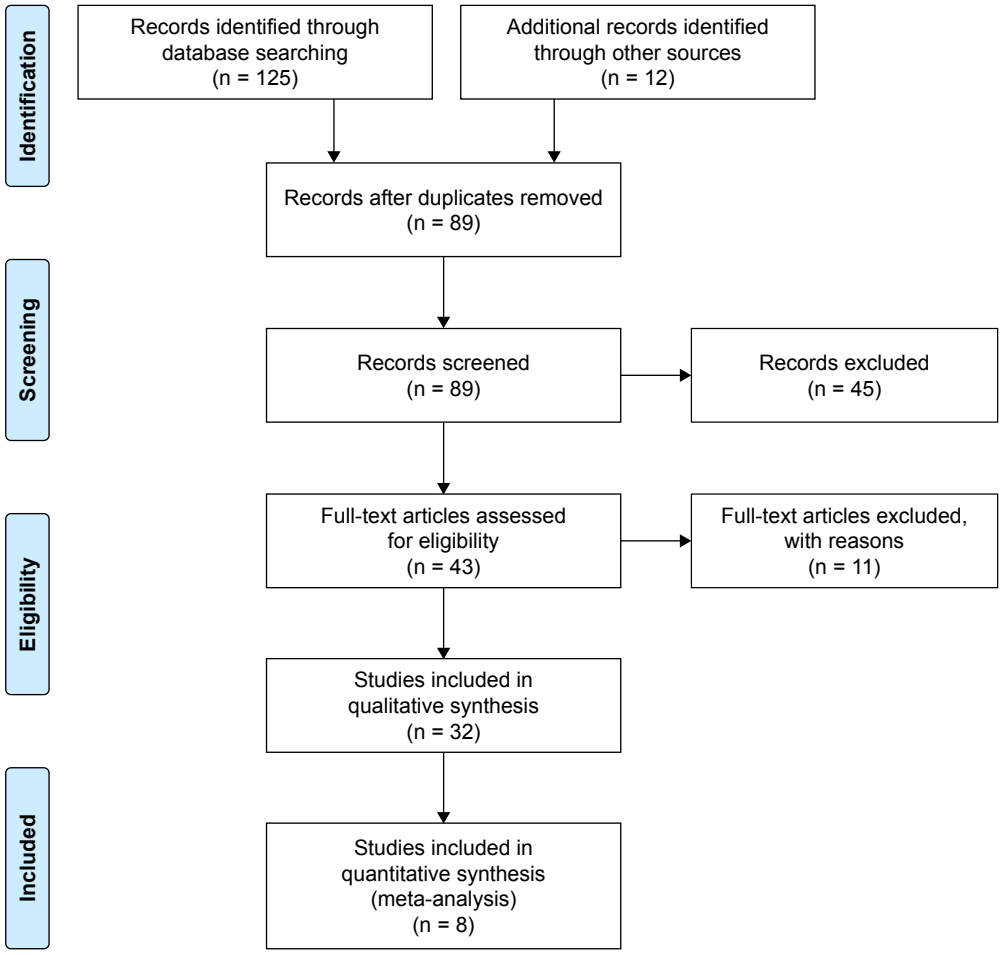

Figure 1 Flow chart of database search and literature selection.

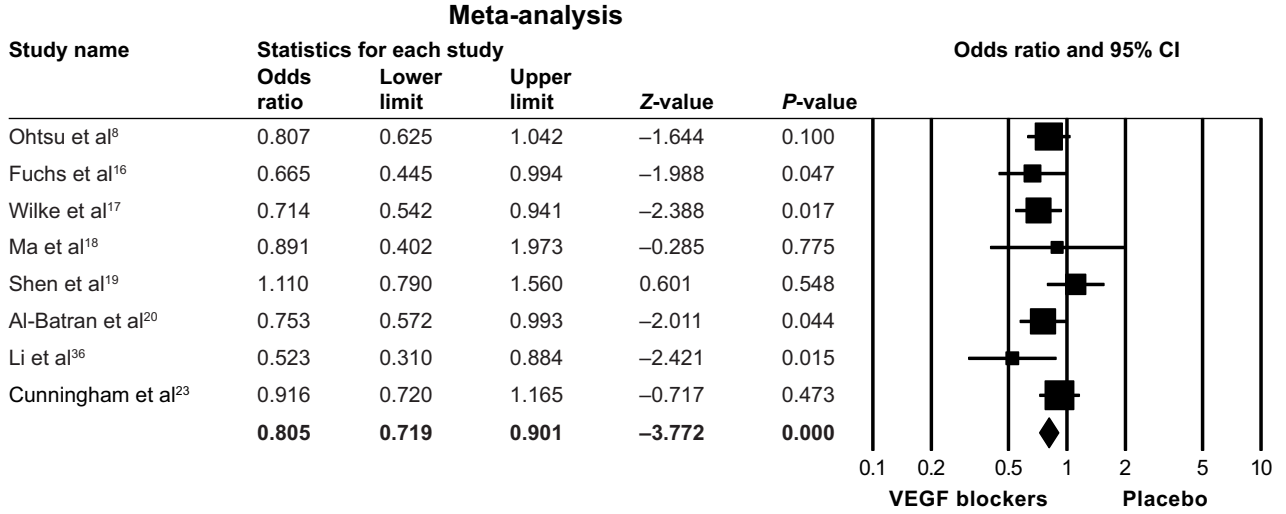

Figure 2 Forest plot for median survival time of gastric cancer patients with or without vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) blocker in addition to chemotherapy.

Notes: A fixed effect model was used due to non-significant heterogeneity of publications ($I^2 = 22.17$, $P = 0.253$). Effect size was assessed by odds ratio and 95% CI, and the median overall survival (OS) time was in favor VEGF or VEGFR blocker therapy (odds ratio = 0.805; 95% CI: 0.719–0.901, $P < 0.001$). Bold values represent the median.

longer in the patients treated with VEGF/VEGFR blockers compared to that in the patients without the blockers (odds ratio = 0.805, 95% CI: 0.719–0.901, $P < 0.001$, Figure 2), although Ohtsu et al,[8] Shen et al[19] and Cunningham et al[23] reported that there was no significant difference in overall median survival time between the patients treated with bevacizumab or placebo. Furthermore, as shown in Figure 3A and B, when meta-analysis was performed on the results of

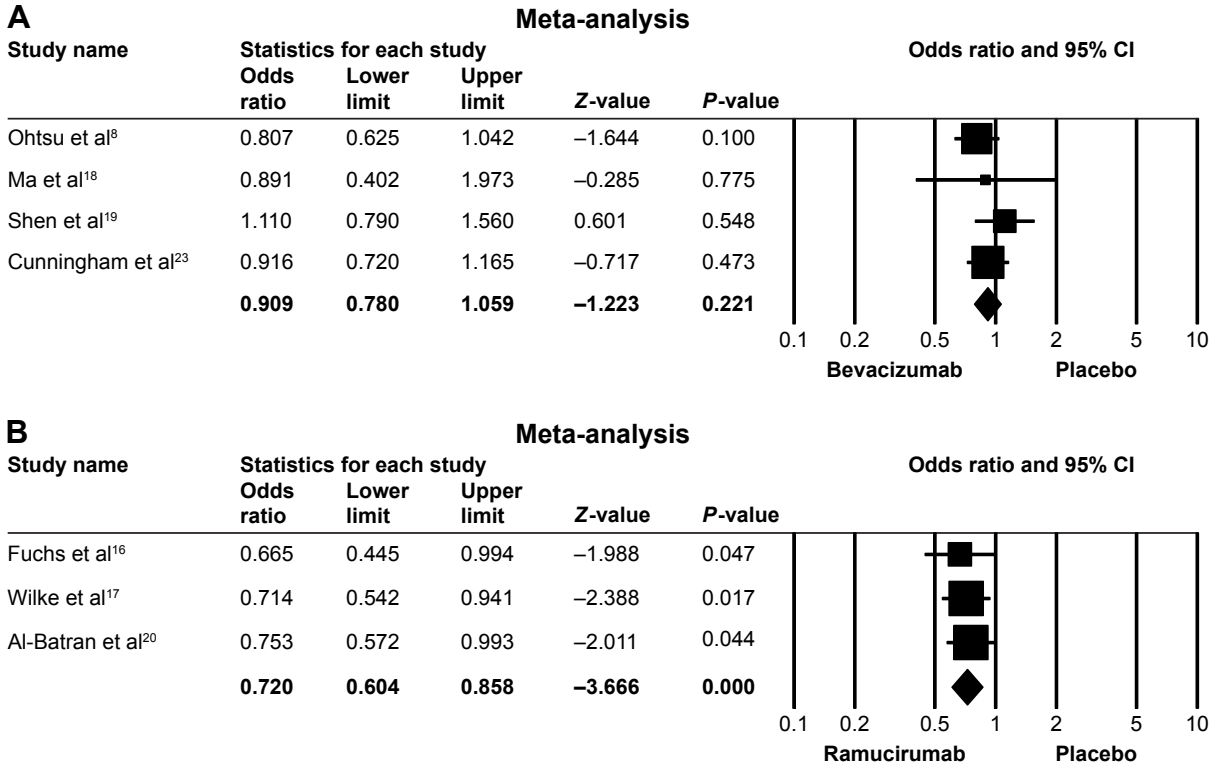

Figure 3 Forest plot for overall survival (OS) for patients with anti-vascular endothelial growth factor (VEGF)-mAb (bevacizumab) or anti-vascular endothelial growth factor receptor (VEGFR)-mAb (ramucirumab) in addition to chemotherapy.

Notes: (**A**) OS with bevacizumab. A fixed effect model was used due to significant heterogeneity of publications ($I^2 = 0$, $P = 0.539$). Effect size was assessed by odds ratio and 95% CI, and the OS time was not favored with bevacizumab in addition to chemotherapy (odds ratio = 0.909, 95% CI: 0.780–1.053, $P = 0.221$). (**B**) OS with ramucirumab. A fixed effect model was used due to significant heterogeneity of publications ($I^2 = 0$, $P = 0.880$). Effect size was assessed by odds ratio and 95% CI, and the OS time was not favored with bevacizumab in addition to chemotherapy (odds ratio = 0.720, 95% CI: 0.604–0.858, $P < 0.001$). Bold values represent the median.

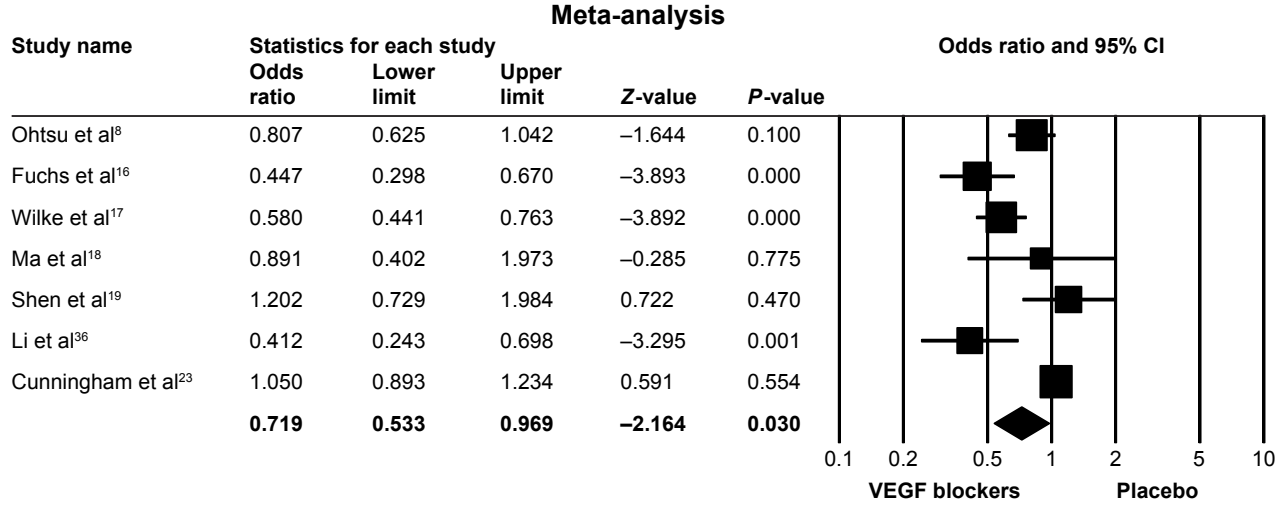

Figure 4 Forest plot for progression-free survival (PFS) for patients with or without vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) blocker in addition to chemotherapy.
Notes: A random effect model was used due to significant heterogeneity of publications ($I^2 = 81.56$, $P < 0.01$). Effect size was assessed by odds ratio and 95% CI, and the PFS time was in favor of VEGF or VEGFR blocker in addition to chemotherapy (odds ratio = 0.821, 95% CI: 0.735–0.917, $P < 0.001$). Bold values represent the median.

ramucirumab (3 out of 8 Phase III trials) or bevacizumab (4 out of 8 Phase III trials), ramucirumab treatment was favored in terms of OS (odds ratio = 0.720, 95% CI: 0.604–0.858, $P < 0.001$, Figure 3B), while bevacizumab was not favored in comparison to the placebo treatment (OS: odds ratio = 0.909, 95% CI: 0.780–1.059, $P = 0.221$, Figure 3A).

VEGF/VEGFR blockers were favored in terms of PFS time. The PFS was significantly longer in patients treated with VEGF/VEGFR blockers than that in patients treated with placebo (odds ratio = 0.719, 95% CI: 0.533–0.969, $P = 0.030$, Figure 4). Furthermore, Phase I or II studies indicated that average PFS of gastric cancer patients treated with VEGF/VEGFR blockers in combination with commonly used chemotherapeutic drugs such as oxaliplatin or cisplatin and docetaxel was 10.5 months (6.6–15.1).[7–15] All of the 24 Phase I/II clinical studies without proper controls demonstrated that humanized mAbs of targeting angiogenesis were safe to use although various side effects were inevitable.

Side effects of VEGF/VEGFR blockers

Most of the 32 articles enrolled into the current systematic review and meta-analysis reported that various adverse effects were associated with VEGF/VEGFR blockers. Most common side effects of using VEGF/VEGFR blockers were hypertension, vomiting, neutropenia and anemia. As shown in Figure 5 of the meta-analysis result, patients treated with

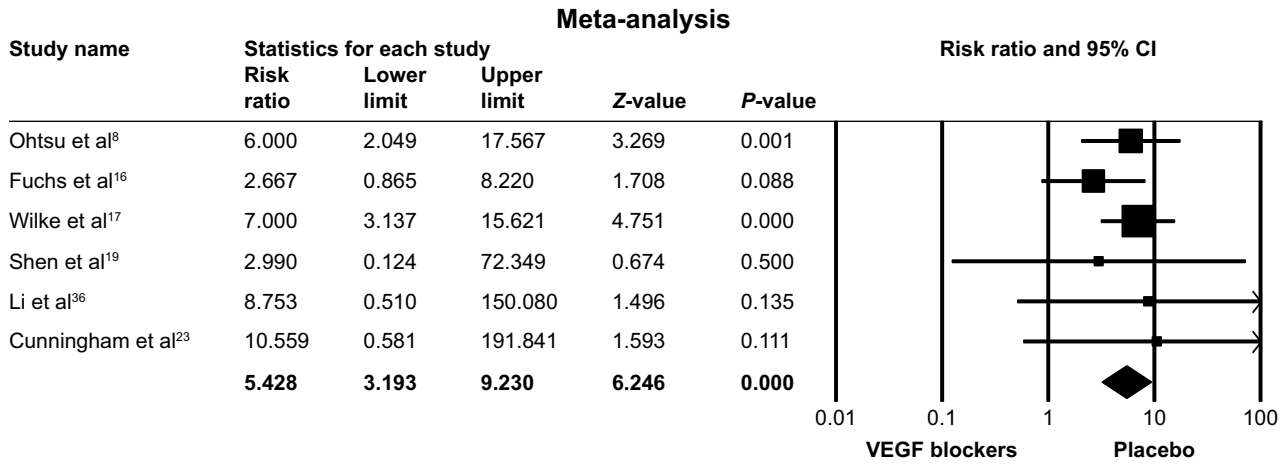

Figure 5 Forest plot for hypertension morbidity in patients with or without vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) blocker in addition to chemotherapy.
Notes: A fixed effect model was used due to non-significant heterogeneity of publications ($I^2 < 0.01$, $P = 0.780$). Effect size was assessed by risk ratio and 95% CI, and the hypertension was in favor of placebo treatment in addition to chemotherapy (risk ratio: 5.428; 95% CI: 3.193–9.230; $P < 0.001$). Bold values represent the median.

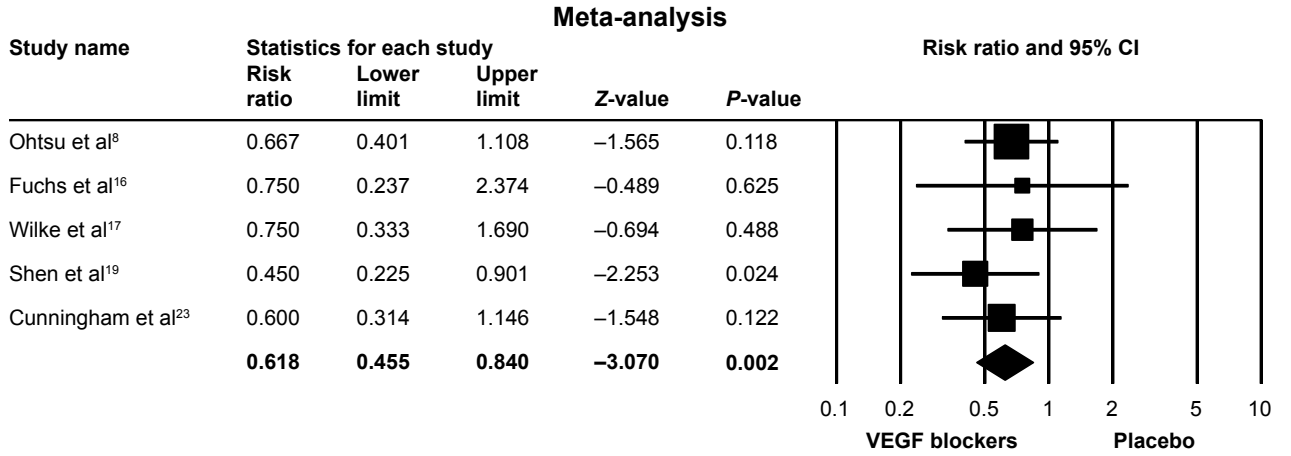

Figure 6 Forest plot for vomiting morbidity in patients with or without vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) blocker in addition to chemotherapy.
Notes: A fixed effect model was used due to non-significant heterogeneity of publications ($I^2 < 0.01$, $P = 0.819$). Effect size was assessed by risk ratio and 95% CI, and the hypertension was in favor of VEGF or VEGFR blocker in addition to chemotherapy (risk ratio: 0.599; 95% CI: 0.431–0.833; $P = 0.002$). Bold values represent the median.

VEGF/VEGFR blockers had higher risk in terms of hypertension morbidity, which was significantly different between the two groups (risk ratio: 5.428; 95% CI: 3.193–9.230; $P < 0.001$). Interestingly, however, morbidity of vomiting was favorably less in patients with VEGF/VEGFR blockers in combination with chemotherapy than that in patients treated with placebo (risk ratio: 0.618; 95% CI: 0.455–0.840; $P < 0.001$, Figure 6). Similarly, risk of neutropenia morbidity was slightly but not significantly higher in the patients with VEGF/VEGFR blockers (risk ratio: 1.102; 95% CI: 0.961–0.1.265; $P = 0.164$, Figure 7), while risk of anemia was favorably less (risk ratio: 0.842; 95% CI: 0.644–1.102; $P = 0.210$, Figure 8) in the patients treated with VEGF or VEGFR blockers although neither was significantly different between the two groups ($P > 0.05$).

Risk of bias in individual studies

As shown in Figure S1, Begg's funnel plot of standard error by log odds ratio indicated that there was no significant evidence for publication bias.

Discussion

Gastric cancer is the second leading cause of cancer-related death. Despite recent progress in understanding the molecular biology of gastric cancer and the related signaling pathways offer promising treatment for selected groups of

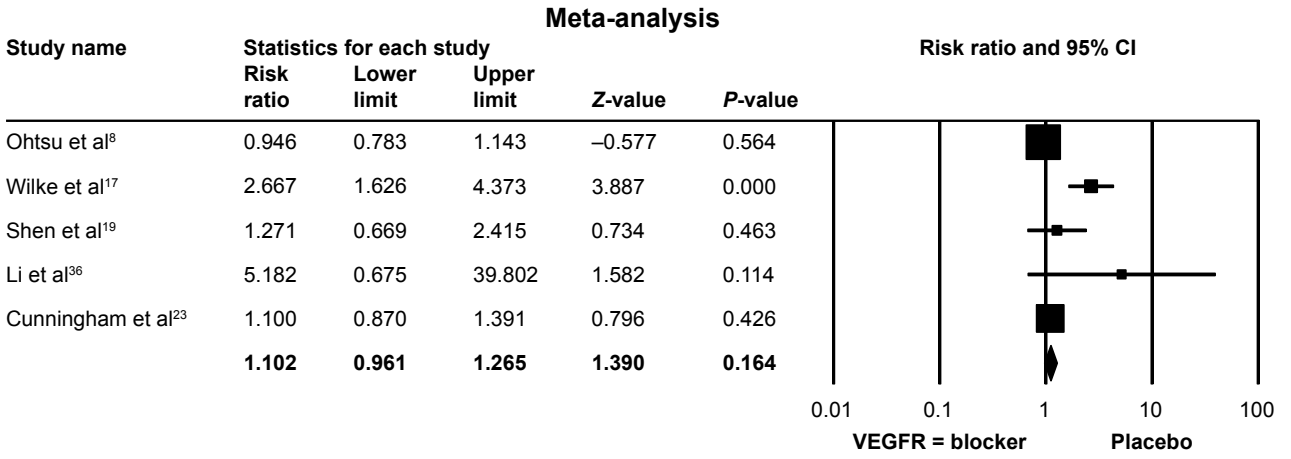

Figure 7 Forest plot for neutropenia morbidity in patients with or without vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) blocker in addition to chemotherapy.
Notes: A random effect model was used due to significant heterogeneity of publications ($I^2 = 75.46$, $P = 0.003$). Effect size was assessed by risk ratio and 95% CI, and the hypertension was in favor of placebo treatment in addition to chemotherapy, which was without significant difference (risk ratio: 1.102; 95% CI: 0.961–0.1.265; $P = 0.164$). Bold values represent the median.

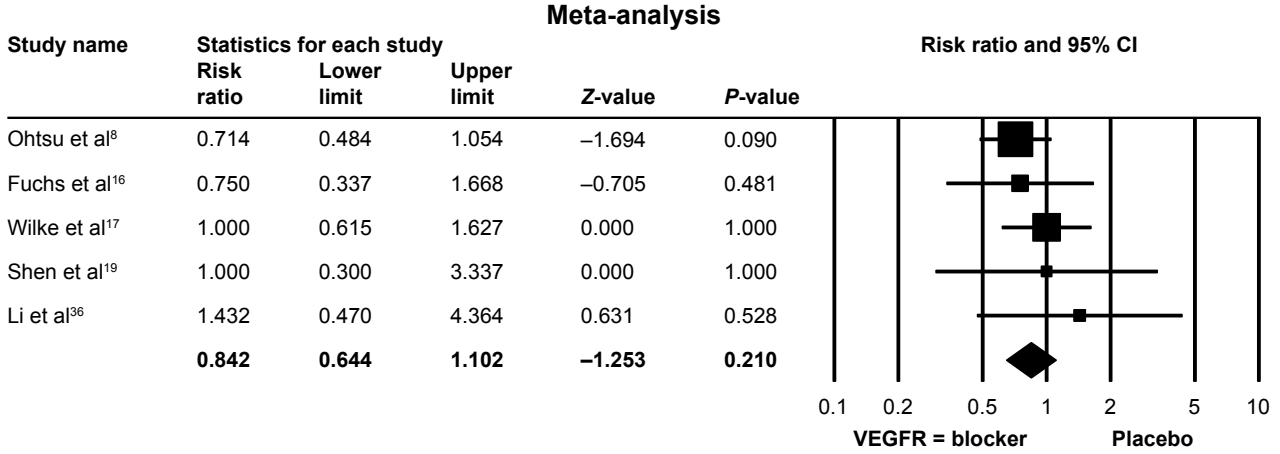

Figure 8 Forest plot for anemia morbidity in patients with or without vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) blocker in addition to chemotherapy.

Notes: A fixed effect model was used due to non-significant heterogeneity of publications ($I^2 < 0.01$, $P = 0.685$). Effect size was assessed by risk ratio and 95% CI, and the hypertension was in favor of VEGF or VEGFR blocker in addition to chemotherapy, which was without significant difference (risk ratio: 0.842; 95% CI: 0.644–1.102; $P = 0.210$). Bold values represent the median.

patients, OS and PFS rate are still poor. Recently, however, targeted therapies have significantly impacted the treatment strategy of several common solid tumor gastric cancer. In this regard, several antiangiogenesis reagents have been approved for the treatment of advanced or metastatic gastric cancer. Here, we systematically reviewed and performed meta-analysis on clinical trials for the treatment of advanced or metastatic gastric cancers with antiangiogenesis reagents including anti-VEGF mAb (bevacizumab), anti-VEGFR mAb (ramucirumab) and selective VEGFR TKI (apatinib). It was found that median OS time was significantly longer in the patients treated with VEGF/VEGFR blockers compared to that in the patients without the blockers when all of 8 selected Phase III clinical trials were analyzed together, although not all of the trials achieved positive results.[8,19,23] In addition, PFS time was also significantly longer in patients treated with VEGF/VEGFR blockers than that in patients treated with placebo. Interestingly, 4 out of the selected 8 Phase III trials tested bevacizumab and meta-analysis on these 4 studies indicated that there was no significant difference between bevacizumab and placebo with or without combination of other chemotherapeutic reagents. By contrast, 3 out of the selected 8 Phase III trials tested ramucirumab and meta-analysis on these 3 studies revealed that ramucirumab was significantly favored in the treatment of gastric cancer. In addition, patients treated with VEGF/VEGFR blockers had higher morbidity of hypertension and neutropenia but had less risk side effects of vomiting and anemia. These findings suggest that addition of antiangiogenesis reagents to the first- or second-line chemotherapy, especially the anti-VEGFR-mAb, prolongs patients' OS and PFS time in advanced or metastatic gastric cancer.

The pathogenesis of gastric cancer involves multiple alteration of signaling pathways including epithermal growth factor (EGF) and its receptor (HER2), VEGF and its receptor (VEGFR). Novel mAbs selectively targeting these growth factors and their receptors have been developed for the treatment of gastric cancer. In this context, the addition of trastuzumab has significantly improved survival in patients with HER2-positive gastric cancer.[39] However, this therapeutic option is available only for a few patients, as the overexpression or amplification of HER2 has been identified in <20% of patients.[39,40]

In contrast to EGF/EGFR signaling, studies have indicated that activation of VEGF/VEGFR signaling promotes aberrant tumor angiogenesis, which could be a potential target in variety of solid cancers including gastric cancer. To date, following strategies have been developed to target angiogenic signaling in solid tumors including gastric cancer: 1) targeting pro-angiogenic factor (VEGF) with mAb (bevacizumab); 2) targeting VEGF receptors (VEGFR) with mAb (ramucirumab) and 3) selectively targeting intracellular signaling with TKI (sunitinib, sorafenib, apatinib). In the current review, therefore, Phase I–III clinical trials on gastric cancer with anti-VEGF-mAb, anti-VEGFR-mAb and selective VEGFR downstream TKI were selected and systematically reviewed, and furthermore, meta-analysis on OS and PFS was performed.

While several tumors including gastric cancer are sensitive to VEGF inhibitors, no biomarkers of response to

antiangiogenic agents were identified in clinical practice. However, since angiogenesis plays a key role in the development and progression of gastric cancer and increased expression of VEGF pathway proteins in most of human cancers, agents that specifically target angiogenesis in gastric cancer including anti-VEGF-mAb, anti-VEGFR-mAb and selective VEGFR downstream TKI are desirable.

Bevacizumab is a humanized mAb targeting VEGF-A, a protein playing a significant role in angiogenesis. This mAb had been tested in the AVAGAST Phase III trial.[8] In this Phase III trial, 774 patients were enrolled and the combination of cisplatin and fluoropyrimidine with and without bevacizumab in the first-line treatment was compared. Unfortunately, this trial failed to meet the primary endpoint (OS). Consistent with result of this Phase III trial, meta-analysis of the current study in this clinical trial together with other 3 Phase III clinical trials[18,23] indicated that addition of bevacizumab on top of the first- or second-line chemotherapy failed to prolong patients' life. In addition, a Phase Ib/II study, which tested weekly docetaxel and cisplatin together with capecitabine and bevacizumab for the treatment of advanced gastric cancer, was closed early because of the accumulation of toxicity-related deaths.[12] These findings suggested that strategy of directly targeting pro-angiogenic factor (VEGF-A) with mAb is not a promising strategy.

Ramucirumab is a fully humanized mAb targeting VEGFR-2 and it has been approved by FDA as a single agent or in combination with fluoropyrimidine- or platinum-containing chemotherapeutic agent for the treatment of patients with advanced or metastatic gastric cancer. VEGFR-2 is the main mediator of angiogenic signaling in endothelial cells and a primary responder to VEGF. VEGFR-2 activation plays a crucial role in tumor angiogenesis, and inhibition of the VEGFR-2 signaling pathway has become an attractive approach for cancer therapy. Most recently, a systematic review and meta-analysis indicated that VEGFR-2 overexpression is a promising negative prognosis predictor for patients with gastric cancer.[41] The REGARD[16] and RAINBOW[17] randomized Phase III clinical trials tested the efficacy of ramucirumab in advanced/metastatic pretreated gastric cancers; the primary end point (OS rate) was met in both studies. In the REGARD trial,[16] median OS was 5.2 vs 3.8 months and median PFS was 2.1 vs 1.3 months with advantage in the ramucirumab arm. In the RAINBOW study,[17] median OS was 9.6 vs 7.4 months and median PFS was 4.4 vs 2.9 months with advantage in the ramucirumab group. Consistently, meta-analysis of the current study on the total of 3 out of the selected 8 Phase III clinical trials demonstrated that patients who received ramucirumab had significantly longer OS and PFS compared to the patients who received placebo, suggesting that targeting VEGF receptor is a promising strategy for the treatment of gastric cancer.

Similar to sunitinib and sorafenib, apatinib is a TKI that selectively blocks downstream signaling of VEGFR. Although 13 Phase I or II clinical trials on the VEGFR-TKI (sunitinib, sorafenib or apatinib) have been reported,[24–36] only one Phase III trial on apatinib consisting of 267 patients was reported,[22] and it was found that median OS and PF were significantly improved in the apatinib group (6.5 m and 2.6 m) compared with the placebo group (4.7 m and 1.8 m, respectively). However, adverse events such as hand-foot syndrome, proteinuria and hypertension were also higher in the patients who received apatinib.[22] In addition to aforementioned TKIs, several Phase I and II studies have also tested antitumor effect of several types of TKIs including axitinib,[11] pazopanib[20,42] and regorafenib.[43,44] Of them, pazopanib and regorafenib are orally bioavailable and multitargeted TKI, mainly targeting VEGFR2, PDGFR and FGFR tyrosine kinase.[42,45] It has been reported that pazopanib alone or the combination of pazopanib and capecitabine and oxaliplatin showed moderate antitumor activity and an acceptable toxicity when they were used as a first-line treatment in metastatic/recurrent advanced gastric cancer patients;[46,47] and that regorafenib was effective in prolonging PFS in refractory advanced gastric adenocarcinoma.[43] However, antitumor effect of these TKIs remains to be further determined through randomized and controlled clinical trials.

Preliminary pharmacokinetic data from patients enrolled into the selected 8 Phase III clinical trials found increased toxicity with higher exposures of bevacizumab and ramucirumab. In this regard, adverse effects including hypertension, neutropenia, vomiting, anemia and embolism have been reported. Interestingly, patients treated with VEGF or VEGFR mAbs had higher morbidity of hypertension and neutropenia, but less risk in the morbidity of vomiting and anemia. The mechanisms of these side effects, however, remain to be further investigated.

There are several limitations in the current study. First, limited number of Phase III clinical trials were enrolled into this study, which remains to be further updated with findings of accumulated clinical trials. Second, due to limited number of the randomized clinical trials, sub-group analysis on the gastric cancers in terms of tumor stages, metastasis status, location of the cancer in the gastroenterological tract and ethnic difference was not performed. In this regard, it has been reported that *VEGF-634* G>CC allele and GG genotype

were associated with gastric cancer risk in Caucasians, while *VEGF*+1612G/A gen polymorphism was associated with gastric cancer risk for the Asian population,[41] and that ethnic difference was associated with outcomes of TKI treatment between Caucasian and Asian patients with malignant tumor.[48] Third, only one Phase III trial on the VEGF receptor TKI (apatinib) was enrolled and analyzed together with other studies with anti-VEGF-A mAb or anti-VEGFR mAb, and thus more randomized clinical trials data on VEGFR-TKI are necessary to confirm the benefit of selective VEGFR-TKI on gastric cancer treatment.

Taken together, in the current study, general therapeutic and side effects of anti-VEGF mAb, anti-VEGFR mAb and anti-VEGFR-TKI with or without other chemotherapeutic drugs for the treatment of gastric cancer were systematically reviewed followed by meta-analysis performance. Compared with the placebo, antiangiogenic reagents with or without combination of chemotherapeutic drugs could significantly prolong gastric cancer patients' median OS and PFS. Furthermore, treatment with the anti-VEGFR mAb ramucirumab, but not the anti-VEGF mAb bevacizumab, resulted in significant improvement of median OS and PFS. In addition, patients who received anti-VEGF-mAb or anti-VEGFR-mAb had higher morbidity of hypertension and neutropenia, but less risk in the morbidity of vomiting and anemia. These findings suggested that a fully humanized anti-VEGFR mAb could be an effective therapeutic agent for the treatment of gastric cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

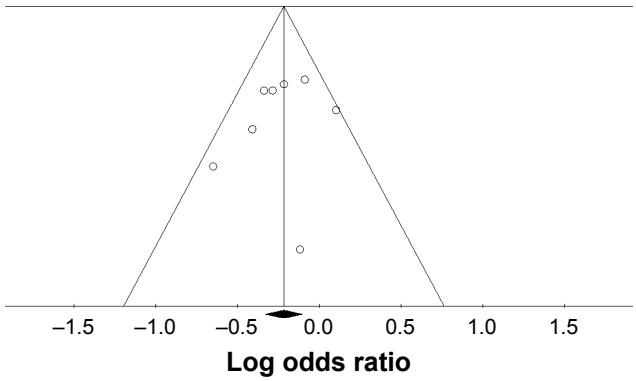

Figure S1 Funnel plot of standard error by log odds ratio assessing publication bias.