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Mini-review

Controlling angiogenesis in gastric cancer: A systematic review of anti-angiogenic trials

Fei Shan, Rulin Miao, Kan Xue, Zhemin Li, Ziyu Li, Zhaode Bu, Aiwen Wu, Lianhai Zhang, Xiaojiang Wu, Xianglong Zong, Xiaohong Wang, Shuangxi Li, Xin Ji, Ziyu Jia, Ziran Li, Jiafu Ji *

Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery, Peking University Cancer Hospital & Institute, Beijing 100142, China

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ABSTRACT

Purpose: Angiogenesis is a promising therapeutic target to inhibit tumor growth. This review summarizes data from clinical trials of anti-angiogenic agents in gastric cancer.
Design: A systematic search of PubMed, Embase and conference databases is performed to identify clinical trials with specific anti-angiogenic agents in gastric cancer treatment
Results: The risk of disease progression (37–52%) and death (19–22%) with ramucirumab as second-line treatment decreases in phase III trials in advanced gastric cancer. No significant improvement in overall survival (OS) with the addition of bevacizumab to chemotherapy is shown. Bevacizumab or ramucirumab combined with traditional chemotherapy is associated with higher adverse event rate compared to chemotherapy alone. Except for apatinib, phase II trials of other tyrosine kinase inhibitors (TKIs) may improve overall response rate, but there are no significant improvements in OS and progression-free survival (PFS) when combined with chemotherapy.
Conclusion: Phase III trials in advanced gastric cancer have demonstrated improved outcome with ramucirumab as second-line treatment. Most of the other studies on anti-angiogenic agents in gastric cancer have reported improvement in response rate but not in OS compared to chemotherapy alone. Future research is expected in optimizing the anti-angiogenic therapy combined with traditional treatment.

Introduction

Anti-angiogenesis treatment is based on the hypotheses that tumor growth depends on nutrients and oxygen supplied by a continuously expanding network of capillaries; the downstream effects of angiogenesis can be blocked therapeutically to inhibit the capillary growth without severe adverse events to the host, and by which to cause a state of tumor dormancy. The discovery of the vascular endothelial growth factor (VEGF) family of angiogenesis stimulators (VEGF-A, B, C, D and placental growth factor) and the development of several VEGF pathway-targeting agents have confirmed the theories of the anti-angiogenesis therapy [1]. These agents include antibodies to VEGF-A and its receptors, and a host of small molecule tyrosine kinase inhibitors (TKIs) [1–3]. Pre-clinical and clinical trials demonstrate that overexpression of VEGF could induce angiogenesis, leading to proliferation and metastasis of gastric cancer cells. Moreover, the expression of VEGF in tissues and plasma is proven to have a positive correlation with vascular invasion and lymphatic metastasis, but negative with prognosis [4,5].

This systematic review analyzes data from randomized clinical trials of anti-angiogenic agents and other relative research in gastric cancer, discusses the possible factors affecting the effects of anti-angiogenic agents in metastatic gastric cancer and explores strategies for improving risk-to-benefit ratios.

Methods

Search strategy

Our search includes PubMed (no limit to May 2014), Embase (no limit to May 2014), and American Society of Clinical Oncology (2009–2014) databases, investigating the potential effects of anti-angiogenic monoclonal antibodies on safety and efficacy. The databases are searched using the following searching string in titles and abstracts (also in combination with MESH terms): gastric cancer AND (angiogenesis OR VEGF) AND ((inhibitors AND (agents OR treatment OR therapy)) OR (aflibercept, apatinib OR bevacizumab, cediranib OR erlotinib OR flavopiridol OR lapatinib OR pazopanib OR ramucirumab OR sorafenib OR sunitinib OR telatinib OR TSU-68 OR vandetanib OR monoclonal antibodies OR protein kinase inhibitors)). Additional relevant studies are identified via bibliographic review of the reports identified during the systematic search. Data from full text articles and presentations are used when available. Detailed CONSORT diagram is shown in Fig. 1.

The ClinicalTrials.gov database is searched on May 22, 2014 for ongoing phase III clinical trials of specific anti-angiogenic agents using the search terms 'gastric cancer'

Fei Shan, Rulin Miao, Kan Xue and Zhemin Li contribute equally to this work.
* Corresponding author. Tel.: +86 010 8819 6048; fax: +86 010 8819 6698.
E-mail address: jiafuj@hotmail.com (J. Ji).

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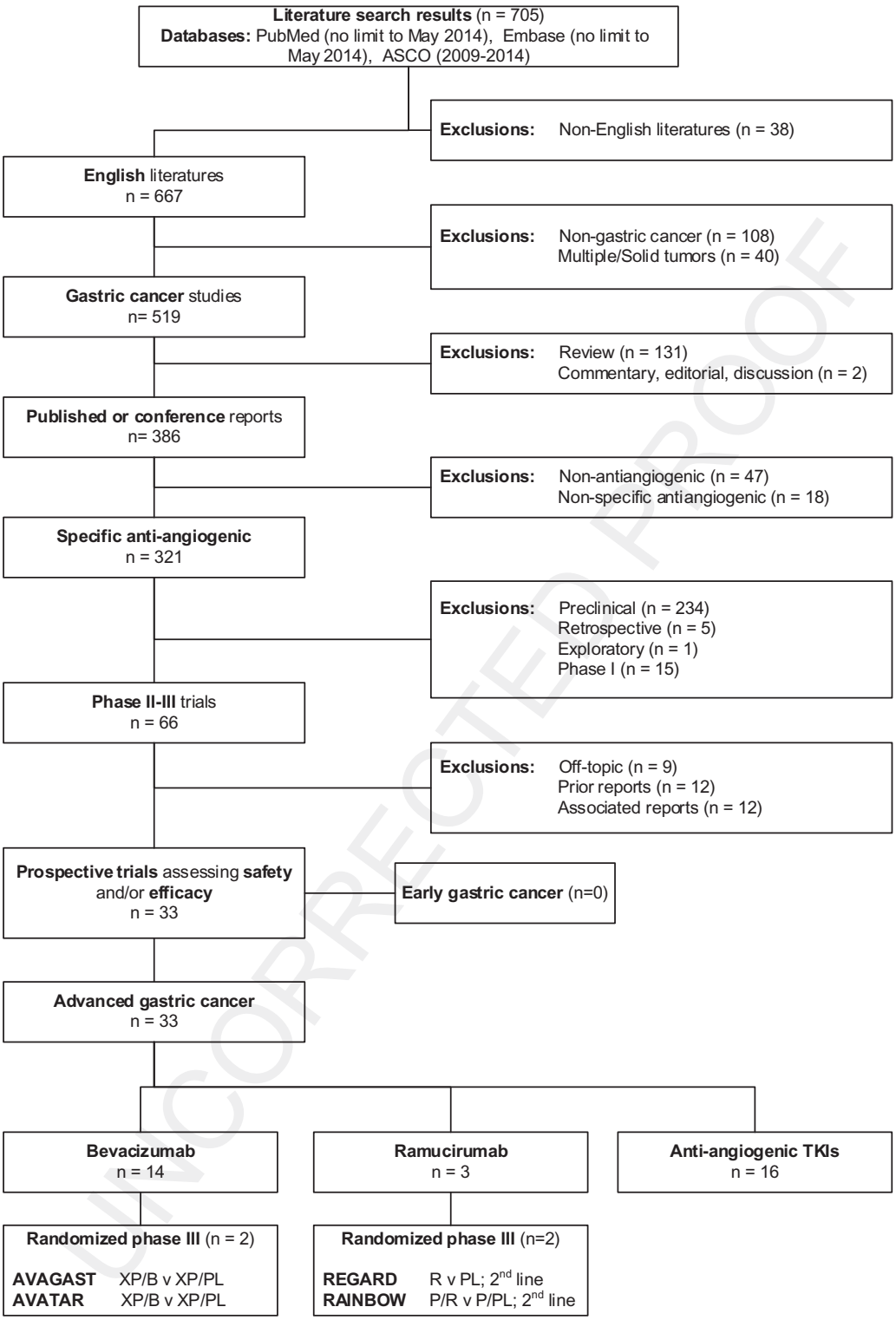

Fig. 1. CONSORT diagram detailing literature search and study inclusion/exclusion methods. ASCO, American Society of Clinical Oncology Meeting Library; B, bevacizumab; R, ramucirumab; TKI, tyrosine kinase inhibitor; X, capecitabine; P, cisplatin; PL, placebo.

or names of specific anti-angiogenic agents as indicated above, limiting interventions to 'Anti-angiogenic' and study type to 'Interventional' (Fig. 2).

Study selection

Original studies are included if they met the following criteria: (i) gastric cancer focused researches; (ii) specific anti-angiogenic; (iii) prospective phase II–III trials; (iv) assessing safety and/or efficacy.

Exclusion criteria included: (i) non-clinical studies, (ii) non-English literatures; (iii) inability to obtain adequate details of study methodology or results from the article or the investigators.

Data extraction

Eligible studies are reviewed and the following data are abstracted: (1) first author's name; (2) year of publication; (3) study location; (4) patients enrolled; (5)

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