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Anti-Tumour Treatment

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

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ABSTRACT

Purpose: Angiogenesis is critical for tumor growth and a promising therapeutic target. This review will summarize and analyze data from clinical trials of anti-angiogenic agents in the treatment of breast cancer (BC).

Design: A systematic search of PubMed and conference databases was performed to identify reports of randomized clinical trials investigating specific anti-angiogenic agents in the treatment of BC.

Results and discussion: Phase III trials in advanced BC have demonstrated a reduction in the risk of disease progression (22–52%), improved response rates and net improvements in progression-free survival of 1.2 to 5.5 months, but no significant improvements in overall survival with the addition of bevacizumab to chemotherapy. Results of phase III trials in early breast cancer have been inconsistent. Bevacizumab-containing regimens have also been associated with higher overall adverse event rates compared to chemotherapy alone. Phase III trials of the tyrosine kinase inhibitor sunitinib were negative, while randomized phase II trials of sorafenib and pazopanib have improved some outcomes when combined with chemotherapy or targeted therapy compared to controls. In addition to expected vascular class safety signals, tyrosine kinase inhibitors show "off-target" side effects. Ongoing clinical trials evaluating combinatorial strategies based on biological synergies and translational studies identifying biological predictors of response will be crucial to establish meaningful clinical benefits in selected BC populations.

Conclusion: Most trials of anti-angiogenic agents in BC have reported improved response rate and progression-free survival but no increase in overall survival compared to chemotherapy alone. Optimizing the therapeutic indices of these agents is a focus of ongoing research and will be critical to their future development.

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Introduction

Treatment of cancer using anti-angiogenic agents is based on several hypotheses: (i) there is a continuously expanding network of capillaries supplying nutrients and oxygen to support tumor growth; (ii) the process of angiogenesis can be blocked therapeutically without causing excessive host toxicity; and (iii) such therapeutic interventions will induce a state of tumor dormancy.[1] It was initially thought that there would be a small number of tumor angiogenesis factors (TAFs) produced and secreted by tumor cells acting in a paracrine manner on the vascular endothelium of mature vessels to initiate angiogenesis. Thus a specific neutralizing anti-TAF antibody was hypothesized to have potential anti-angiogenic and therefore anti-tumor activity.[1] 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 validated many of the principles of the anti-angiogenic treatment concept.[2] These agents include antibodies to VEGF-A (''VEGF'') and its receptors, as well as a host of small molecule tyrosine kinase inhibitors (TKIs) that act intracellularly to target the catalytic function of vascular endothelial growth factor receptors (VEGFRs) expressed by endothelial cells.[2–4]

Clinical benefits of anti-angiogenic agents have been reported in colorectal cancer, non-small cell lung carcinoma[5,6] and renal cell carcinoma[7] and have led to the adoption of anti-angiogenic therapies for these diseases in many jurisdictions. Preclinical studies have confirmed that angiogenesis also plays a central role in breast cancer carcinogenesis and metastatic potential.[8–11] The tumor microvessel density of breast cancers is known to be predictive of bone marrow micrometastases, recurrence and overall survival (OS),[12–15] establishing angiogenesis as a potential therapeutic target for breast cancer.[16] Our systematic review will analyze data from randomized clinical trials of anti-angiogenic agents in breast cancer, discuss possible factors limiting the impact of anti-angiogenic agents in metastatic breast cancer (MBC) and explore strategies for improving risk-to-benefit ratios.

Methods

English language reports of clinical trials investigating anti-angiogenic agents in the treatment of breast cancer were systematically identified through a search of PubMed (no limit to February 2010), American Society of Clinical Oncology (2007–2009) and American Society of Clinical Oncology Breast Cancer (2007–2009) databases (Fig. 1) using the search string: breast cancer AND angiogenesis (vascular, VEGF) AND inhibitors ([agents, treatment, therapy] OR [bevacizumab, pazopanib, axitinib, sunitinib, sorafenib, vandetanib, motesanib, AMG-106, vatalanib, aflibercept, ramucirumab, cediranib and alternate names of agents, or

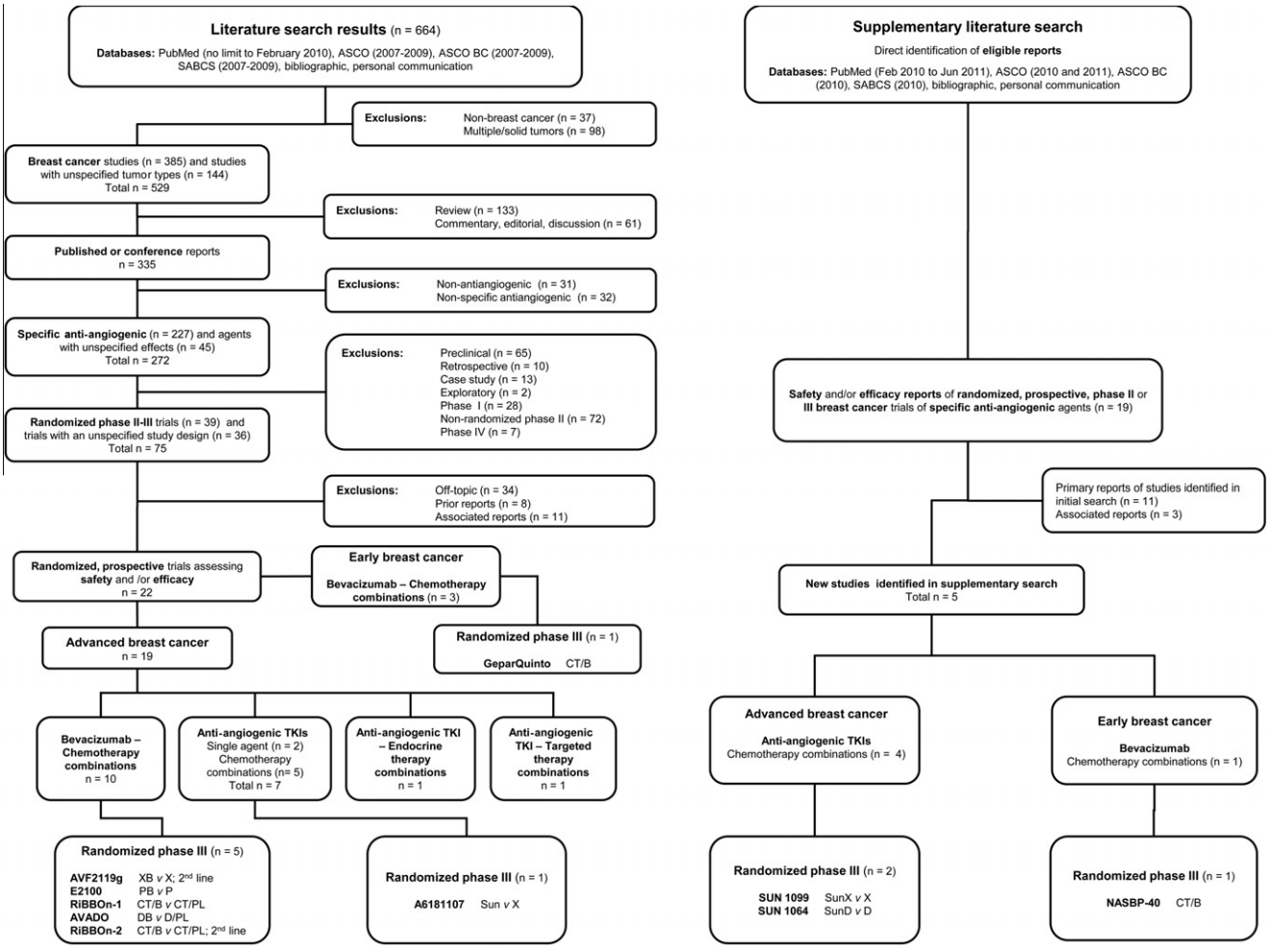

Fig. 1. CONSORT diagram detailing literature search and study inclusion/exclusion methods ASCO, American Society of Clinical Oncology Annual Meeting; ASCO BC, American Society of Clinical Oncology Breast Cancer Symposium; B, bevacizumab; CT, chemotherapy; D, docetaxel; P, paclitaxel; PL, placebo; SABCS, San Antonio Breast Cancer Symposium; Sun, sunitinib; TKI, tyrosine kinase inhibitor; X, capecitabine.