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Perspective

Revision of the concept of anti-angiogenesis and its applications in tumor treatment

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Abstract

Anti-angiogenesis therapy, by blocking formation of new blood vessels in tumors, is the standard-of-care therapy for various cancer types. The classic concept of anti-angiogenesis is expected to turn a tumor into a "dormant" disease. However, the combination of anti-angiogenesis agents with conventional therapeutics has generally produced only modest survival benefits for cancer patients in clinical trials. Therefore, the concept and applications of anti-angiogenesis have evolved dramatically along with lessons learned from recent clinical experience. In this article, we will discuss the revised concept of anti-angiogenesis therapy and the applications of anti-angiogenesis drugs, and focus particularly on how to utilize current anti-angiogenesis agents and develop new approaches to provide more benefits to patients with cancer.

Keywords: Anti-angiogenesis; Angiogenesis; Vascular endothelial growth factor; Cancer

Introduction

Oncogenic progression in solid tumors relies on sprouting new vessels from existing vessels, namely tumor angiogenesis, to supply oxygen and nutrients as well as remove metabolic wastes. Several decades' efforts have been dedicated to the development of anti-angiogenesis agents that were expected to turn cancer into a chronic or dormant disease with tangible clinical benefits.

Anti-angiogenesis is one of the standard-of-care therapies for multiple types of solid tumors. Vascular endothelial growth factor (VEGF) and its receptors are the most studied targets in blocking tumor angiogenesis, with more than 10 approved drugs for various tumors being used in clinical practice. The concept of the mechanism of these therapeutics and applications in clinical practice evolves along with lessons learned from clinical trials. To better utilize the existing anti-

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angiogenesis agents and provide more clinical benefits to patients with cancer, we must reevaluate the concept of anti-angiogenesis and its principles inspired by preclinical and clinical studies.

Here, we review the concept revisions of anti-angiogenesis to emphasize the importance of self-renewal of knowledge when managing cancer patients and the perspective of anti-angiogenesis treatment in the view of "precision medicine".

Development of "angiogenesis" and anti-angiogenesis agents

The term "angiogenesis" was invented by the Scottish surgeon Dr. John Hunter who discovered that new blood vessel formation was a crucial step in tissue expansion more than 2 centuries ago.[1] However, there were few reports of angiogenesis in tumors in the following 100 years until extensive formation of blood vessels during tumor progression was visualized by Professor E. Goldmann in 1907.[2] Experimental studies of angiogenesis, instead of simply observing anatomical specimens, began in the late 1930s and early 1940s.[3] It was generally thought that tumor angiogenesis was a side effect of dying tumor cells before the 1970s.[3] In 1971, Folkman et al[4] proposed the hypothesis that no tumors could grow beyond 2 mm^3 unless they are vascularized and tumors could be restricted to tiny sizes and placed in a dormant state by blocking new vessel formation. This "anti-angiogenesis" hypothesis became the main theory motivating studies on developing agents for solid tumors ever since and moved one step further when basic fibroblast growth factor (bFGF) and VEGF were identified by different research groups in the 1980s.[5–8] VEGF was soon chosen as the preferred potential target for anti-angiogenesis agent development since VEGF showed a key role in angiogenesis in loss-of-function studies.[9] The VEGF antibody first demonstrated by Ferrara's group in 1993 became the foundation for targeted anti-angiogenesis therapeutics development ever since.[10,11]

The monoclonal antibody bevacizumab, which targets VEGFA, was proven to benefit patients with metastatic colon cancer by prolonging overall survival when combined with conventional therapy in 2003.[12] Soon, bevacizumab was approved by the US Food and Drug Administration (FDA) as the first monoclonal antibody anti-angiogenesis drug. Subsequently, bevacizumab combined with chemotherapy was shown to significantly improve progression-free survival, overall survival, and response rates in advanced non-small cell lung cancer (NSCLC)[13] and advanced cervical cancer.[14] Many pharmaceutical companies, motivated by the clinical success of bevacizumab, joined in the development of other VEGFA pathway inhibitors and a number of other monoclonal antibodies targeting VEGF or small molecules that block its receptors have been approved by the FDA and/or European Medicines Agency (EMA).

Sorafenib, a multi-tyrosine kinase inhibitor targeting all vascular endothelial growth factor receptors (VEGFRs), demonstrated significantly longer progression-free survival *vs.* placebo in patients with advanced renal cancer in a randomized phase III trial and was approved as second-line therapy for advanced renal cancer by the FDA in 2005.[15] Other anti-angiogenesis drugs that target all VEGFRs, such as sunitinib,[16] pazopanib,[17] vandetanib,[18] axitinib,[19] regorafenib,[20] cabozantinib,[21] and lenvatinib[22] were successively approved by the FDA for application in patients with various cancers. Notably, a monoclonal antibody against VEGFR2, ramucirumab,[23] which blocks ligand binding and a recombinant fusion protein aflibercept,[24] which targets VEGFA, VEGFB, and placental growth factor (PLGF) were also approved by the FDA.

The development timeline of "angiogenesis" and targeted anti-angiogenesis therapeutics are shown in Fig. 1. The noted time for anti-angiogenesis drugs is the year when they were first approved by the FDA. The targets and implications of these anti-angiogenesis drugs are listed in Table 1.

Concept evolves with clinical practice

Targeted therapeutics, including agents targeting oncogenic or angiogenic pathways, benefit millions of patients with advanced tumors worldwide. However, the theoretical potential of anti-angiogenesis therapies has not been achieved in medical reality. The overall survival benefits are limited to months for some tumors that are intrinsically resistant to these agents, whereas others develop drug resistance after an initial response. The concept of "starving tumors to death" by targeting the tumor vasculature has led to the development of a number of anti-angiogenesis drugs. However, the concept of anti-angiogenesis evolves along with the lessons we learn from large randomized clinical trials and preclinical results.

First, the original concept of anti-angiogenesis therapy supports the idea that a stand-alone treatment would work, whereas in most approved indications in the clinic VEGF inhibitors are used in combination with chemotherapy.[25] Bevacizumab is generally claimed to be