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.

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
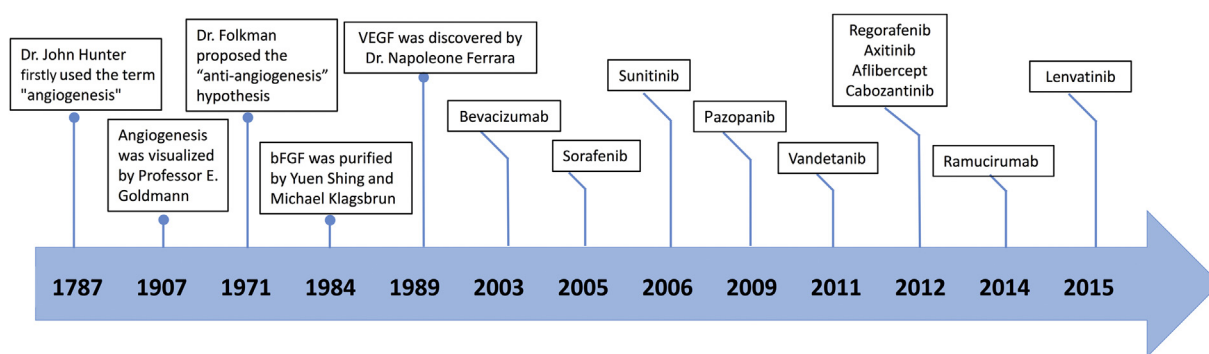
Fig. 1. Timeline of highlights in the development of "angiogenesis" and anti-angiogenesis drugs. Lines ending with dots indicate historical findings in angiogenesis research while broken lines indicate targeted therapeutics approved by FDA. The note time for each drug is the year when it was first approved by the FDA. bFGF: basic fibroblast growth factor; VEGF: vascular endothelial growth factor.

inactive unless combined with chemotherapy. How do we explain the combination effect of chemotherapy plus VEGF inhibitors? The most predominant hypothesis is the vascular normalization effect.[26,27] This hypothesis changes the way we treat blood vessels in tumors by suggesting that inhibition of VEGF and its receptors act by selectively blocking the formation of immature blood vessels but leaving behind the mature and functional vasculature. The resulting vascular network is more efficient, leading to enhanced circulation and decreased tumor interstitial pressure. This seems to be paradoxical since enhanced oxygenation and perfusion throughout the tumor would promote the growth of the tumor. In fact, however, the more we try to exterminate tumor vessels, the more aggressively tumors respond to these efforts. The mechanism behind this paradox is that a reduced blood supply causes hypoxia and acidosis and this abnormal microenvironment helps cancer cells

Table 1
Targets and indications of anti-angiogenesis drugs.

Drug name	Targets	Tumor indications	Brand
Bevacizumab	VEGFA	Metastatic colorectal cancer	Avastin
		Non-squamous non-small cell lung cancer	
		Recurrent glioblastoma	
		Metastatic renal cell carcinoma	
		Platinum-resistant recurrent ovarian cancer	
		Persistent, recurrent, or metastatic cervical cancer	
Ramucirumab	VEGFR2	Metastatic colorectal cancer	Cyramza
		Platinum-resistant metastatic non-small cell lung cancer	
		Advanced gastric or gastroesophageal junction adenocarcinoma	
		Gastric or gastroesophageal junction adenocarcinoma	
Aflibercept	VEGFA, VEGFB, PLGF	Second-line metastatic colorectal cancer	Zaltrap
Axitinib	All VEGFRs	Second-line advanced renal cell carcinoma	lnlyta
Pazopanib	All VEGFRs	Second-line advanced soft tissue sarcoma	Votrient
		Advanced renal cell carcinoma	
Regorafenib	All VEGFRs	Advanced gastrointestinal stromal tumors	Stivarga
		Second-line metastatic colorectal cancer	
Sorafenib	All VEGFRs	Second-line metastatic or recurrent thyroid carcinoma	Nexavar
		Advanced renal cell carcinoma	
		Unresectable hepatocellular carcinoma	
Sunitinib	All VEGFRs	Unresectable, locally advanced, or metastatic pancreatic neuroendocrine carcinoma	Sutent
		Advanced renal cell carcinoma	
		Gastrointestinal stromal tumors	
Vandetanib	All VEGFRs	Unresectable, locally advanced, or metastatic medullary thyroid cancer	Caprelsa
Cabozantinib	All VEGFRs	Progressive metastatic medullary thyroid cancer	Cometriq
Lenvatinib	All VEGFRs	Radioactive iodine-refractory thyroid cancer	Lenvima

VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; PLGF: placental growth factor.

evade the immune system, increasing their invasive and metastatic potential and selecting for "cancer stem cells."[28–30] Moreover, within the abnormal tumor microenvironment, the killing potential of the immune effector cells is attenuated by the hypoxia and acidosis. Hypoxia can upregulate the expression of programmed death-ligand 1 (PD-L1), an immune checkpoint protein, and increase tumor cells' resistance to cytotoxic T lymphocytes-mediated lysis.[31,32] As a result, tumor vessel normalization by VEGF and its receptors can subsequently activate antitumor immunity, thus creating conditions for better drug delivery and efficacy.[26]

The effect of chemotherapy and radiation therapy would be expected to increase within a short time window when combined with anti-angiogenesis. For example, chloroquine, an antimalarial drug, can promote Notch signaling in endothelial cells and induce vascular normalization, leading to improved blood perfusion in tumors and reduced metastasis.[33] Furthermore, motivated by this theory, recent research demonstrated that promoting tumor angiogenesis can increase chemotherapy sensitivity in cancer cells.[34] Moreover, co-administration of low-dose cilengitide and verapamil reduces tumor growth and metastasis and minimizes side effects while extending survival by increasing tumor angiogenesis, leakiness, blood flow, and gemcitabine delivery.[34]

Second, the tumor blood vessel normalization theory confirmed that a short window can be used to gain more clinical benefit when anti-angiogenesis agents are combined with chemotherapy or radiation therapy. However, this achievement is still far from reaching the ultimate goal to turn tumors into a dormant disease. More importantly, how to manage tumor patients after the initial response during the window? Does the classic anti-angiogenesis concept work? It is conceivable that after maximal pruning of existing tumor vessels by the initial treatment, continuation of VEGF inhibition would prevent new vessel formation.[25] Preclinical experiments proved that continuous anti-angiogenesis inhibition preserves low tumor vessel densities and reduces tumor growth rate but these effects rapidly dissipate upon treatment cessation.[35] Evidence from available clinical trials also supports the idea that continuous treatment with VEGF inhibitors after disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines can be associated with clinical benefit.[36,37] These results support the efficacy of VEGF inhibitors, especially in the later phases of treatment. This also raises the question about the underlying mechanisms of the different concepts with the same drug applied at different timings. One hypothesis is that adjuvant treatment with anti-angiogenesis would not induce hypoxia or acidosis in tiny tumors after initial treatment and thus would prevent the invisible residual lesions from progressing to clinical apparent disease. However, this approach is troubled by drug toxicity and is limited in clinical trials. In two large clinical trials, adjuvant therapy with bevacizumab has a significant effect when tumors are exposed to chemotherapy drugs but the effect disappears upon treatment cessation.[38,39] Further confirmation in clinical practice is required for anti-angiogenesis drugs even when used in combination with chemotherapy drugs. Continuous treatment with anti-angiogenesis therapy could only be realized with drugs that have a long half-time, extraordinary safety and tolerability, and the capability to fully inhibit all of the potential factors involved in angiogenesis in tumors.

Third, an important feature that distinguishes anti-angiogenesis drugs from other targeted therapies in tumors is that anti-angiogenesis drugs are given to unselected patients within approved indications. Biomarkers are usually applied in selecting proper patients when giving cancer cell-targeted therapeutics and this approach improves their benefits. Therefore, predictive biomarkers to identify patients who are more likely to respond to anti-angiogenesis therapies should be developed. For example, recurrent and newly diagnosed glioblastoma patients whose tumor blood perfusion or oxygenation increases after the initiation of anti-angiogenesis therapy survive 6–9 months longer than those whose tumor perfusion does not change or, instead, decreases.[40–42] Efforts are being made to identify predictive biomarkers for VEGF inhibitors such as expression of VEGF in tumors and blood including different isoforms of VEGF, tumor perfusion status, and other angiogenic factors.[43–47] Unfortunately, currently there are no validated diagnostics for therapies targeting the VEGF pathway. These emerging data suggest that we might be able to improve overall survival with a more personalized use of existing anti-angiogenesis agents.

Targets beyond tumor blood vessels

Anti-angiogenesis drugs normalize tumor blood vessels, but blood vessels are not the only target of these drugs. The targets of anti-angiogenesis drugs also include cancer and stromal cells. Moreover, VEGF also plays an important role in promoting epithelial-mesenchymal transitions (EMT) and proliferation of

stem and progenitor cells in tumors.[48] Thus, manipulating VEGF bioavailability leads to profound effects not only on the vasculature but also on epithelial stem and progenitor cells.[48] VEGF can also block the maturation of dendritic cells.[49] Anti-angiogenesis intervention inhibits tumor growth, and displays systemic effects, including reversal of the tumor-induced shrinkage of sinusoidal vessels and an altered population balance of hematopoietic stem cells in the bone marrow, manifested by the restoration of sinusoidal vessel morphology and hematopoietic homeostasis.[50] Other angiogenic factors such as platelet-derived growth factor (PDGF), angiopoietins (ANGPT), stromal cell-derived factor 1α (SDF-1α), and tumor growth factor-β (TGF-β), are also the targets of anti-angiogenesis drugs, and these factors also promote the survival, proliferation, and migration of various cancer and stromal cells.[51]

In addition, oncogenic pathways also participate in angiogenesis and can serve as potential targets. Although blocking VEGF and its receptors in endothelial or perivascular cells can directly promote vascular normalization, finding new potential targets that have the same effect might facilitate our understanding of angiogenesis mechanisms and provide alternative approaches to overcome drug resistance when conventional drugs fail. Oncogenic pathways including phosphatidylinositol bisphosphate 3-kinase (PI3K), Akt, epidermal growth factor receptor (EGFR), and *BRAF* are proven to be involved in angiogenesis in tumors and inhibition of these targets can lower the expression of VEGF and other proangiogenic factors.[52] Therefore, inhibitors targeting these oncogenic pathways have dual effects of killing cancer cells and improving tumor perfusion through blood vessel normalization.

Summary and perspective

In conclusion, anti-angiogenesis therapy, even when given to unselected patients, has become part of the standard of care for various cancers and has benefited numerous patients worldwide with advanced tumors and no other options. This approach provides measurable benefits to cancer patients when handled with caution. However, the concept that seemed to be straightforward at the beginning has turned out to be far more complex with the concept evolving along with lessons learned from clinical trials. It is worthy and meaningful to maximize the efficacy of old drugs and develop new agents or new ways so that we can realize the ultimate goal of turning tumors into a dormant disease or even curing cases of cancer.

One widely adopted strategy to maximize the efficacy of anti-angiogenesis is to combine drugs targeting multiple pathways in angiogenesis. Dll4/Notch signaling inhibition enhances non-functional vessel proliferation and limits tumor growth by reducing blood perfusion in malignancies.[53] ANGPT-tyrosine kinase with immunoglobulin and epidermal growth factor homology domain-2 (Tie2) also has crucial roles in the tumor angiogenic switch.[54] Several inhibitors targeting the ANGPT-Tie2 and Notch-Dll4 pathways have been tested in the clinic, with or without concurrent VEGF inhibitors.[53,55] However, there are several considerations when combining multiple anti-angiogenesis therapeutic drugs. The safety and toxicity of such combinations are not easily predictable since the benefits of anti-angiogenesis are dose and tumor size dependent.[27] For example, a recent study showed that low doses of an inhibitor targeting Dll4 may promote productive angiogenesis and tumor growth.[53] Moreover, the timeline of targeting multiple angiogenesis pathways is tricky. The roles of these pathways depend on the cellular context. It is difficult to determine when to inhibit each pathway, and this decision becomes even more complex when combined with chemotherapy or radiation therapy.

The more in-depth studies we conduct on anti-angiogenesis, the more questions are brought up. In fact, there are no unified opinions on these clinical issues. For example, contrary evidence has been reported against the most prominent hypothesis of the vascular normalization effect in anti-angiogenesis therapy.[56] Direct evidence of increased chemotherapy delivery in cancer patients has yet to be obtained. The sobering realization is that it is a long journey between the idea of anti-angiogenesis and the reality of clinical practice. The major gap between them is the discordance between preclinical and clinical results. To address these issues, clinically relevant cancer models in animals should be developed. This is an extremely challenging task given the complexity of cancer biology.

The era of "precision medicine" is becoming a large focus underpinning research.[57] Clinical trials involving anti-angiogenesis drugs are in progress with promising results. The two trends in these trials are combinations with targeted tyrosine kinase inhibitors (TKIs) or immunotherapy and long-term anti-angiogenesis management. For example, in the JO25567 study, a randomized phase II study to investigate the efficacy of combination therapy consisting of erlotinib and bevacizumab for NSCLC patients with *EGFR* mutations, showed that the progression-free survival of the

combination therapy group (median survival time = 16.0 months, 95% *CI*: 13.9−18.1) was longer than that of the erlotinib monotherapy group (median survival time = 9.7 months, 95% *CI*: 5.7−11.1).[58,59]

These encouraging results may change the standard therapies in clinical practice in the future along with the results of other ongoing trials such as RC1126, a randomized phase II trial of how well erlotinib with or without bevacizumab works in treating patients with stage IV NSCLC with *EGFR* mutations. Notably, with several immunotherapy drugs targeting PD-1 or PD-L1 approved, clinical trials to investigate combinations of immunotherapy and anti-angiogenesis treatment are also underway.[60] Clinical trials such as NCT02366143 (a phase III study of anti PD-L1 antibody MPDL3280A in combination with carboplatin and paclitaxel with or without bevacizumab in patients with stage IV NSCLC) and NCT02039674 (a phase I and II study of pembrolizumab in combination with chemotherapy that includes bevacizumab for lung cancer) are currently recruiting patients. Meanwhile, the clinical trials WJOG 5910L,[61] AvaALL,[62] and ARIES,[63] are showing early promising benefits from long-term bevacizumab treatment in cancer patients.

Beyond these clinical trials, the technologies of the multi-omics have revolutionized our capacity to unravel these complex phenotypes, with emerging evidence showing that the patient genetic background could possibly contribute to the efficacy of anti-angiogenesis therapy. Through Big Data emerging from multi-omics research streams of genomics, transcriptomics, proteomics, and epigenomics, we can advance the depth and breadth of research in anti-angiogenesis.

Addressing these challenges by applying the refined knowledge to the development of new drugs or strategies may take us one step further to realize the full potential of the original hypothesis, and is certain to increase the survival benefits in selected patients.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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