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Review

Mechanisms of and strategies for overcoming resistance to anti-vascular endothelial growth factor therapy in non-small cell lung cancer

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A B S T R A C T

Sustained angiogenesis is a hallmark of cancer. Because of the primary role of vascular endothelial growth factors (VEGFs) and their receptors in angiogenesis, VEGF-targeted agents have been developed to inhibit these signaling processes in non-small cell lung cancer (NSCLC). However, the clinical benefits are transient and resistance often rapidly develops. Insights into the molecular mechanisms of resistance would help to develop novel strategies to improve the efficacy of antiangiogenic therapies. This review discusses the mechanisms of resistance to anti-VEGF therapy and the postulated strategies to optimize antiangiogenic therapy. A number of multitargeted tyrosine kinase inhibitors currently in phase III clinical development for NSCLC are summarized. The emerging combination of antiangiogenic therapy with tumor immunotherapy is also discussed.

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1. Introduction

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 84% of all lung cancers in the United States [1]. The 5-year survival rate for NSCLC is currently below 20% [1], highlighting the need for new treatment strategies.

Angiogenesis is an essential component of primary tumor growth and metastasis (Table 1) [2]. The key proteins involved in angiogenesis include members of the vascular endothelial growth factor (VEGF) family, which consists of 5 members in mammals: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PlGF) [3]. Of these, VEGF-A is the primary growth factor associated with vessel formation [2,3]. VEGF binds to a family of receptor tyrosine kinases called VEGF receptors (VEGFRs), including VEGFR-1, VEGFR-2, and VEGFR-3, and causes dimerization of the tyrosine kinase domain. The dominant VEGFR in angiogenic signaling with VEGF-A is VEGFR-2 [3]. Neuropilin-1 (NRP-1) and -2 (NRP-2) are co-receptors for VEGF family members and play a role in VEGF-mediated angiogenesis [4,5].

Antiangiogenic therapies (Fig. 1) have been investigated (and some approved) in several solid tumors [2]. The first antiangiogenic agent approved for NSCLC is bevacizumab (approved in 2006; Avastin®, Genentech; South San Francisco, CA, US), a monoclonal antibody to VEGF-A [6]. Bevacizumab in combination with carboplatin/paclitaxel improved both progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone in patients with advanced NSCLC [7]. However, similar to cancer cell targeted therapies, the clinical benefits from VEGF inhibitors are often on the orders of months and usually followed by the rapid emergence of resistance [8–10]. It is important to recognize that, unlike cancer cell targeted therapies which are only given to a subset of patients according to biomarkers, antiangiogenic agents are usually given to all patients for the approved indications. Therefore, informed selection of patients would likely significantly improve their clinical benefits. For example, recurrent glioblastoma patients with an increase in tumor blood perfusion after cediranib treatment survive about 6 months longer than those with stable perfusion [11]. Thus, the insights into the resistant mechanisms would improve the application of antiangiogenic therapy and achieve better clinical outcomes.

Both primary and acquired resistance can limit the efficacy of antiangiogenic therapy. Primary resistance occurs when the agent fails to have any effect on the tumor upon initial treatment, while acquired resistance to therapy describes tumor progression when treatment is ongoing following a previous response [12]. This article will provide an overview of proposed mechanisms of primary and acquired resistance to VEGF-targeted therapy, followed by a discussion of completed and ongoing clinical trials of multitargeted tyrosine kinase inhibitors (TKIs) in advanced NSCLC.

Table 1
Angiogenic factors involved in NSCLC.

Factor	Role in non-tumor cells
ALK1 [28]	Type I transforming growth factor β subclass involved in vasculogenesis
Angiogenin [110]	Ribonuclease active in angiogenesis
Ang-1 [109]	Binds to Tie2 to control vessel stabilization
DLL4 [29]	Signaling in vascular development and angiogenesis
Ephrins [20]	VEGF-independent regulation of angiogenesis
FGFs (acidic and basic) [20]	VEGF-independent regulation of angiogenesis
HIF-1α [111]	Regulation of oxygen homeostasis
HGF [112]	Involved in embryonic angiogenesis
IL-8 [113]	Promotes angiogenesis in endothelial cells
NRP-1 and -2 [25]	Modulators of VEGF pathway
PD-ECGF [114]	Non-heparin binding angiogenic factor, originally isolated from platelets
PDGFβ [109]	Involved in vessel wall development
PlGF [3]	Placental member of VEGF family
VEGF [3]	Primary signaling factors involved in angiogenesis

NSCLC, non-small cell lung cancer; ALK1, activin A receptor type II-like 1; Ang, angiopoietin; DLL4, delta-like ligand 4; FGF, fibroblast growth factor; HIF, hypoxia-inducible factor; HGF, hepatocyte growth factor; IL, interleukin; NRP, neuropilin; PD-ECGF, platelet-derived endothelial cell growth factor; PDGF, platelet-derived growth factor; PlGF, placental growth factor; VEGF, vascular endothelial growth factor.

2. Resistance to VEGF-targeted therapy

Primary resistance is likely attributed to a number of different mechanisms. These may include hypovascularity (eg, pancreatic cancer) [8], other modes of tumor vascularization (eg, vessel co-option and vasculogenic mimicry) [13], and pre-existing redundant proangiogenic pathways [8]. Even without primary resistance, eventual acquired resistance to antiangiogenic therapy usually occurs, also via multiple distinct mechanisms [12,14]. These may include mutations resulting from the chromosomal instability of endothelial cells [15], selection of hypoxia-resistant clones [16], recruitment of angio-promoting bone marrow-derived cells [8], and upregulated compensatory proangiogenic factors due to the plasticity and adaptability of cancer cells and stromal cells [8,17].

2.1. Redundant or compensatory proangiogenic factors

Compensatory proangiogenic factors (treatment-induced or intrinsic) may trigger VEGF-independent tumor neovascularization and lead to resistance to VEGF-targeted therapy. For example, in mouse xenograft models of human lung adenocarcinoma, pericytes have been shown to adapt to anti-VEGF treatment and induce expression of epidermal growth factor (EGF), leading to vascular remodeling and resistance to antiangiogenic therapy [17,18]. Some tumors treated with anti-VEGF therapy can overcome inhibition through upregulation of platelet-derived growth factor C (PDGF-C) in tumor-associated fibroblasts [19]. Similarly, fibroblast growth factor 1 (FGF-1) and FGF-2 have been shown to be upregulated in pancreatic islet cell tumors unsuccessfully treated with an anti-VEGFR-2 antibody, with preclinical evidence that such increases may occur as part of a hypoxia-mediated phenomenon that ultimately leads to resistance to VEGFR blockade [20]. In a murine model, an anti-placental growth factor (anti-PlGF) antibody effectively inhibited growth of tumors resistant to treatment with an anti-VEGFR-2 antibody; these effects were attributed to its ability to prevent macrophage infiltration without causing severe hypoxia or triggering compensatory angiogenic activity [21]. However, a subsequent study showed that PlGF blockade did not inhibit tumor growth nor improve the effect of anti-VEGF antibody treatment in several murine tumor models [22]. In addition, aflibercept (VEGF Trap [ziv-aflibercept in the US]; Zaltrap®, Sanofi; Paris, France and Regeneron Pharmaceuticals; Tarrytown, NY, US), which was designed to neutralize VEGF family ligands and PlGF simultaneously, did not improve OS when added to standard docetaxel therapy for advanced NSCLC [23]. The reasons for such discrepancy remain unclear, but may be related to tumor type and stage. Clinical observations also support that tumor progression on antiangiogenic therapy is preceded by an increase in angiogenic cytokines other than VEGF, such as basic FGF, hepatocyte growth factor, and interleukin-6 in advanced renal cell carcinoma [24]. Collectively, these results suggest that VEGF-independent signaling, such as FGF, PDGF, EGF, or PlGF, may be involved in escape from anti-VEGF therapy in some cancers [16].

In addition, some intrinsic angiogenic factors can modulate vessel formation and have been implicated in resistance to VEGF-targeted therapy. Neuropilins (NRPs) modulate the VEGF pathway and may compensate during VEGF blockade [25]. Using H1299 xenografts, a NSCLC model with high expression (vascular and stromal) of NRP1, Pan and colleagues observed additive antitumor activity with the combination of anti-VEGF and anti-NRP1 antibodies [25]. In addition, angiopoietins and their endothelial receptor Tie2 are involved in regulation of vessel stability [26] and have been implicated in resistance to VEGFR-targeted therapy in preclinical models [20,27]. The activin A

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