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Multitargeted anti-angiogenic agents and NSCLC: Clinical update and future directions

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Abstract

Increasing understanding of the molecular abnormalities driving cell growth and proliferation has resulted in extensive research into molecularly targeted therapies. Angiogenesis is an appealing target for the treatment of non small cell lung cancer (NSCLC). Bevacizumab, a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), is already approved for the treatment of NSCLC. Many other anti-angiogenic agents under development form the focus of this review. A variety of agents, including sorafenib, sunitinib, cediranib, axitinib, motesanib, linifinib and brivanib inhibit VEGF in addition to either platelet derived growth factor (PDGF), or fibroblast derived

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growth factor (FGF). To date, none of these agents in combination with chemotherapy have resulted in improvements in overall survival for patients with advanced NSCLC. Triple angiokinase inhibitors, which inhibit VEGF, PDGF and FGF, have potential to improve the therapeutic outcomes for patients with NSCLC. However, there is a need for identification of appropriate biomarkers to improve patient selection and identify those patients benefiting from anti-angiogenesis therapy.

Keywords: Non-small cell lung cancer (NSCLC); Vascular endothelial growth factor (VEGF); Platelet-derived growth factor (PDGF); Fibroblast growth factor (FGF); Multitargeted kinase inhibitors; Anti-angiogenic agents

1. Introduction

Chemotherapy for non small cell lung cancer (NSCLC) has shown modest improvements in both overall survival (OS) and quality of life, although recent data would suggest we have reached a therapeutic plateau [1–3]. At the same time, our knowledge of the molecular abnormalities driving cell growth and proliferation of lung cancers has grown. Protein overexpression, increased gene copy number, and gene mutations have all been identified as important oncogenic drivers [4]. Pathways linked to the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) have become therapeutic targets resulting in new treatment options for NSCLC, including agents such as gefitinib (Iressa®, AstraZeneca; Wilmington, DE, USA) [5], erlotinib (Tarceva®, Genentech; South San Francisco, CA, USA) [6], cetuximab (Erbitux®, Bristol-Myers Squibb; New York, NY, USA) [7], and bevacizumab (Avastin®, Genentech; South San Francisco, CA, USA) [8,9].

This review provides an overview of the rationale for targeting angiogenic pathways for NSCLC treatment. While bevacizumab is the only approved anti-angiogenic agent for NSCLC, several other agents are in various phases of testing, including drugs targeting multiple receptors, as well as other angiogenic pathways. The review will focus on emerging anti-angiogenic agents, particularly multi-angiokinase inhibitors that are currently being evaluated for NSCLC.

2. Rationale for targeting angiogenic pathways in NSCLC

Tumor growth is dependent upon the development of new blood vessels. In vitro data support the importance of both serum VEGF-A and VEGFR-2 in tumor induced angiogenesis [10]. VEGF-A and VEGFR-2 are both commonly expressed in NSCLC and are an important component of tumor growth and proliferation, progression, and metastasis [11,12]. The prognostic importance of such expression is less clear though [10,13].

However, angiogenesis is a complex process regulated by several pro- and anti-angiogenic factors. Pro-angiogenic factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and the angiopoietins. Serum VEGF (also known as VEGF-A) is the best studied pro-angiogenic signaling factor [14,15] and stimulates angiogenesis primarily through activation of VEGFR-2 [16]. In response to ligand binding, VEGFR-2 undergoes dimerization, autophosphorylation, and activation. Downstream targets include phosphoinositide 3 kinase (PI3K), v-src sarcoma viral oncogene homolog (Src), and phospholipase-Cγ + (PLCγ). Activation of these targets stimulates prosurvival, mitogenic, and migratory processes [17]. Given the importance of the VEGF/VEGFR-2 pathway in angiogenesis, it has become a primary target for anti-angiogenic treatment.

A second pro-angiogenic pathway is mediated through the PDGF family of receptors. PDGF has an important role in wound healing. In addition, in vitro data also support a role for PDGF in autocrine stimulation of tumor cells [18]. Activation of these pathways can occur through 2 receptor tyrosine kinases, PDGF receptor α (PDGFR-α) and PDGF receptor β (PDGFR-β) [18,19]. Ligand binding results in receptor dimerization, activation, and stimulation of downstream signaling pathways, including PI3K and extracellular signal-regulated kinase (Erk) [20]. Preclinical models suggest that resistance to anti-VEGF therapy is associated with increased PDGFR tumoral expression [21,22]. Mouse models have shown increased efficacy with combined inhibition of VEGFR and PDGFR than with VEGFR inhibition alone [21–23]. This provides a biological rationale that combined inhibition of VEGFR and PDGFR may result in more effective inhibition of angiogenesis-mediated cell growth and proliferation.

FGF is a third important pro-angiogenic factor. Of the 22 ligands in the FGF family, FGF-1, FGF-2, FGF-4, FGF-5, and FGF-8 stimulate angiogenesis [24]. Similar to VEGF and PDGF, ligand binding causes receptor dimerization, activation of the tyrosine kinase domain, and stimulation of downstream targets, including PI3K and the mitogen-activated protein kinase (Mek)-Erk pathways [24]. In addition to its angiogenic activity, FGF regulates vascular integrity [25]. The emergence of resistance to VEGF inhibition is also reported to be associated with activation of FGF pathways [26,27].

In vitro data suggest synergism between FGF, VEGF, and PDGF pathways in stimulating angiogenesis and cellular growth [28,29]. Because resistance to anti-VEGF therapy may be due in part to upregulation of compensatory angiogenic signaling pathways (cross-talk), such as PDGF and FGF, inhibition of multiple pro-angiogenic pathways represents a rationale treatment strategy for patients with NSCLC.

Anti-angiogenic approaches in lung cancer have generally been used in combination with standard cytotoxic agents. The