Antiangiogenic Agents and Vascular Disrupting Agents for the Treatment of Lung Cancer

A Review

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Abstract: Although lung cancer therapy has slowly improved with standard cytotoxic chemotherapy drugs, we have reached an efficacy plateau. The addition of targeted agents, such as those with antiangiogenesis activity, to chemotherapy can improve response and survival outcomes. The first of these agents to gain approval in lung cancer in October 2006 was the antivascular endothelial growth factor antibody, bevacizumab. Small molecule tyrosine kinase inhibitors targeting the vascular endothelial growth factor receptor also have proven activity and are under active investigation. Vascular disrupting agents target existing tumor vasculature leading to tumor necrosis, and are being studied in solid tumors, including lung cancer, both as single agents and in combination with chemotherapy. This article will review these new targeted antiangiogenic and antivascular agents with a focus on their use as lung cancer therapeutics.

Key Words: Lung cancer, Antiangiogenic agents, Vascular disrupting Agents.

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Lung cancer is the leading cause of cancer-related death in the United States, with an estimated 215,020 new cases and 161,840-related deaths in 2008.[1] Despite advances in treatment, nearly 80% of lung cancer cases are diagnosed at advanced stages (IIIB or IV), and the 5-year survival rate has not exceeded 15%.[1,2] Current chemotherapeutic options are not curative in advanced stage disease but provide some benefit in survival and quality of life.[3] For the past few years, novel vascular-targeted agents with activity in different cancer pathways have been emerging. The most developed, with survival benefit demonstrated in a randomized trial, are the angiogenesis inhibitors.[4]

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In October 2006, the antiangiogenic agent bevacizumab was granted a labeling extension by the US Food and Drug Administration for the first-line treatment of advanced, nonsquamous, non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy.[4] Nevertheless, the prognosis for patients with lung cancer remains poor, and agents with greater activity are needed. Other vascular-targeted agents are being investigated in trials for the treatment of NSCLC and small cell lung cancer (SCLC). This article focuses on these new targeted drugs, including antiangiogenic agents and tumor-vascular disrupting agents.

ANTIANGIOGENIC AGENTS

Solid tumor growth and metastases depend on development of new vasculature (neovascularization). Blocking angiogenesis inhibits tumor growth and metastasis and is thus a valid treatment strategy,[5–8] as first hypothesized by Folkman[7] over 30 years ago.

The most active angiogenic cytokines are vascular endothelial growth factor (VEGF), fibroblast growth factor, hepatocyte growth factor, transforming growth factors-α and -β, platelet-derived growth factor (PDGF), tumor necrosis factor-α (TNF-α), and interleukin-8.[9–11] The VEGF family plays a key proangiogenic role in vascular development[12] by inducing endothelial cell proliferation, protease expression, cell migration, vascular permeability, and vascular immaturity.[13,14] VEGF ligand is secreted by tumor cells and macrophages. Studies have found that VEGF is expressed in 42 to 75% of NSCLC, and increased VEGF expression is associated with poor prognosis.[15] Three cell surface receptors have been identified [VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3].[16,17] VEGFR-2 is the key receptor in angiogenesis because its activation leads to endothelial cell proliferation, survival, and migration. VEGFR-1 plays a regulatory role through VEGF sequestration or stimulation of hematopoietic stem-cell migration. VEGFR-3 mediates lymphangiogenesis and has been associated with lymph node metastasis. Both VEGFR-1 and VEGFR-2 activation in tumors are involved in the recruitment of endothelial cell precursors to the developing tumor vasculature.[18]

The first antiangiogenic agents developed target either VEGF directly or VEGFR. They inhibit neovascularization, thereby limiting tumor growth. Modification of tumor vascu-

TABLE 1. Antibodies and Other Constructs Targeting the VEGF Pathway

Molecule	VEGF	VEGFR-1	VEGFR-2
Bevacizumab	+	−	−
Rh-Endostatin	−	−	+
VEGF Trap	+	−	−
Ramucirumab (IMC 1121B)	−	−	+
IMC18F1	−	+	−

VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

lature, allowing for improved chemotherapy delivery, has also been hypothesized.[19]

ANTI-VEGF AGENTS

The original classes of antiangiogenic agents are molecules, mostly antibodies, which target the VEGF pathway (Table 1). The largest class is the tyrosine kinase inhibitors (TKIs) that block VEGFR-2, among other targets (Table 2).[20–24]

Molecules Targeting the VEGF Ligand

Bevacizumab, a recombinant humanized monoclonal antibody directed against VEGF, is the first antiangiogenic agent to demonstrate efficacy in solid tumors.[25] It has been approved for treatment of nonsquamous NSCLC in combination with carboplatin and paclitaxel in the United States and in combination with any chemotherapy doublet in the European Union.

A phase II trial of patients with newly diagnosed NSCLC compared carboplatin plus paclitaxel with or without bevacizumab (7.5 or 15 mg/kg). In this trial, the primary end point was time to progression (TTP), and the 15 mg/kg bevacizumab arm showed not only an improvement in TTP but also increased response rate (RR) and a trend in overall survival (OS) benefit and was taken forward into phase III testing. However, patients with central tumors or squamous cell histology had a higher risk of fatal bleeding.[26] In addition, it is worth noting that the 7.5 mg/kg bevacizumab arm had higher numbers of squamous cell patients and increased fatal hemoptysis, which adversely affected survival.

The subsequent phase III trial, Eastern Cooperative Oncology Group 4599, evaluated a combination of carboplatin (AUC = 6 every 3 weeks) and paclitaxel (200 mg/m^2 every 3 weeks) for 6 cycles with or without bevacizumab (15 mg/kg every 3 weeks) in patients with untreated advanced NSCLC.[4] Because of the risk of bleeding, this trial excluded patients with squamous cell histology, brain metastases, anticoagulation therapy, and history of gross hemoptysis. The study enrolled 878 patients and found an increase in median survival (10.3 versus 12.3 months; $p = 0.003$, hazard ratio (HR = 0.79, $p = 0.003$)), progression-free survival (PFS: 4.5 versus 6.2 months; $p < 0.001$, HR = 0.66, <0.001), and RR (15% versus 35%; $p < 0.001$) in favor of the bevacizumab arm. In this trial, the most common adverse event (AE) was bleeding in the bevacizumab arm (0.7% versus 4.4%; $p < 0.001$). Fifteen treatment-related deaths occurred in the bevacizumab arm, including five incidents of pulmonary hemorrhage, five episodes of febrile neutropenia, two gastrointestinal bleeding events, two cerebrovascular events, and one pulmonary embolus. Other AEs were grade three hypertension (<1% versus 7%), and grade 3 neutropenia (17% versus 26%) in the placebo arm and bevacizumab arm, respectively ($p < 0.05$).[4] In a subgroup analysis, men in the bevacizumab arm had a greater survival benefit than women,[27] though in a recent reanalysis of the data, women aged <60 years had substantial survival benefit with bevacizumab.[28] Following this trial, bevacizumab was approved for treatment of first-line NSCLC in combination with carboplatin and paclitaxel. However, because of the safety concerns raised in the phase II trials, it was not indicated for patients with squamous histology, those with brain metastases, or on anticoagulation,[29] though the restrictions on brain metastases and anticoagulation are being lifted with more recent data.[30]

A second phase III trial, AVAIL, used a different chemotherapy regimen and included patients with untreated or recurrent nonsquamous NSCLC without brain metastasis or tumor invasion into major vessels (though central tumors were allowed).[31] This trial, in contrast to E4599, was placebo

TABLE 2. Small Molecule Inhibitors of VEGF Receptors

Inhibitors	VEGFR-1	VEGFR-2	VEGFR-3	PDGFR	c-kit	EGFR	Other
AZD2171 (Cediranib)	+	++	+	+	−	−	
BAY43-9006 (Sorafenib)	+	+	+	+	+	−	raf, ret, FGFR
Sunitinib	+	+	+	+	+	−	ret, FGFR
AMG-706 (Motesanib)	+	+		+	+		ret
ZD6474 (Vandetanib)	−	+	+	+/−	−	+	ret
Axitinib	+	+	+	+	+	−	
PTK787 (Valatanib)	+	+	+	+	+	−	cFms
BIBF1120	+	+	+	+			FGFR
XL-647	+	+	+			+	Her-2
GW786034 (Pazopanib)	+	+	+			−	
ABT-869	+	+	+	+		−	

VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epithelial growth factor receptor; FGFR, fibroblast growth factor receptor.