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.

controlled. In this trial, 1043 patients were enrolled in 3 arms. All patients received cisplatin + gemcitabine with placebo or bevacizumab at 7.5 or 15 mg/kg. Each of the bevacizumab arms were compared separately to placebo, but the trial was not designed to directly compare the two doses of bevacizumab. An improvement in the primary end point of PFS was observed in both bevacizumab arms (6.5 versus 6.7 versus 6.1 months in the 15 mg/kg, 7.5 mg/kg, and placebo arms, respectively, $p = 0.003$). The RR was also significantly improved in the bevacizumab arms (30% versus 34% versus 20% in 15 mg/kg, 7.5 mg/kg, and placebo arms, respectively). The incidence of hemoptysis, neutropenia, hypertension, vomiting and epistaxis were higher in the bevacizumab arms. This trial did not, however, show a significant OS benefit with median OS of 13.4, 13.6, and 13.1 months, respectively, in the 15 mg/kg, 7.5 mg/kg, and placebo arms.[31,32] Despite the conflicting results in OS benefit in the two studies, the response and PFS benefit persist in both studies. Based on these trials, bevacizumab is approved in the United States with a dose of 15 mg/kg in combination with carboplatin/paclitaxel and in Europe at either 7.5 or 15 mg/kg with cisplatin-based combination chemotherapy. Special patient populations including the elderly and those with brain metastases will be discussed later.

Bevacizumab has also been studied in combination with other agents including erlotinib. BeTA, a phase III trial, randomized patients with advanced NSCLC after failure of a standard first-line chemotherapy (excluding prior bevacizumab therapy) to receive erlotinib (150 mg daily) + bevacizumab (15 mg/kg every 3 weeks) or placebo. In this trial, the primary end point was to analyze OS. A total of 636 patients were enrolled. Activity of the combination was demonstrated, with a median PFS of 3.4 months versus 1.7 months (HR = 0.62, $p < 0.001$), and an objective response rate (ORR) of 12.6% versus 6.2%, $p = 0.006$, in the erlotinib + bevacizumab and erlotinib + placebo arms, respectively. However, the trial failed to meet its primary end point, with similar median OS between the two arms (9.3 and 9.2 months for erlotinib + bevacizumab and erlotinib + placebo, respectively).[33]

The ATLAS trial ($n = 1160$) also looked at the combination of bevacizumab and erlotinib but from the perspective of adding erlotinib to bevacizumab for patients receiving maintenance bevacizumab after completion of 4 cycles of chemotherapy + bevacizumab. No new safety signals were seen, and the primary end point of PFS improvement was met (HR = 0.72 [$p = 0.0012$]).[34] Combinations of bevacizumab with other agents have been investigated in phase II studies, including docetaxel and carboplatin, oxaliplatin and pemetrexed, pemetrexed and carboplatin, docetaxel and gemcitabine, cisplatin and docetaxel, cisplatin and irinotecan, and nanoparticle albumin-bound paclitaxel and carboplatin.[35–40]

A four-drug regimen of bevacizumab, carboplatin, paclitaxel, and cetuximab is under active investigation in the Southwest Oncology Group. In phase II trial, 110 patients with advanced NSCLC received carboplatin AUC 6, paclitaxel 200 mg/m^2, bevacizumab 15 mg/kg IV day 1 every 3 weeks, and cetuximab 400 mg/m^2 day 1 then 250 mg/m^2 weekly for up to 6 cycles with continuation of the bevacizumab and cetuximab until progression.[41] In this trial, PFS was 7 months, OS was 14 months, and the grade 4 hemorrhage was <2%.

Given the potential for toxicity with bevacizumab, subset analyses of the elderly have been evaluated separately. In the E4599 study, in a subset analysis that was not statistically significant, addition of bevacizumab in patients >70 years of age did not result in the same survival advantage as their younger counterparts, though RR and PFS improved.[42] Elderly patients experienced more neutropenia (34% versus 22%), bleeding (7.9% versus 3.2%), proteinuria (7.9% versus 1.3%), muscle weakness (7.9% versus 2.2%), and motor neuropathy (3.5% versus 0.6%) with carboplatin + paclitaxel + bevacizumab than younger. In contrast, in the AVAIL trial, the PFS benefit from bevacizumab is similar in patients younger and older than 65 years, and no differential toxicity was seen in the older patients.[43]

In trials including patients with brain metastases (ATLAS and PASSPORT), no significant bleeding risk has been identified in patients treated with bevacizumab after local therapy for brain metastases.[30,44] Therefore, current guidelines suggest that bevacizumab can be considered in patients with treated, stable brain metastases. Results in squamous cell patients have continued to be concerning with bleeding signals seen after radiation or stabilizing chemotherapy.[45]

Studies investigating use of bevacizumab in earlier stages of disease are ongoing. They include trials of patients with stage III disease treated in combination with radiation therapy. Toxicity concerns, such as bleeding and fistula formation, have been raised in these trials. The Eastern Cooperative Oncology Group is leading a multinational effort with the E1505 study, which evaluates the addition of bevacizumab to adjuvant chemotherapy in resected stage IB–IIIA NSCLC.[46] Preclinical studies have raised the concern that antiangiogenic agents used in the adjuvant setting could lead to resistance mechanisms that may increase the propensity of a tumor to metastases.[47,48] However, this data are preliminary and will need to be supported with additional research before altering clinical trials currently underway.

Encouraging phase II, nonrandomized trials of bevacizumab in SCLC have led to the ongoing phase II trial, SALUTE,[49] which randomizes patients with untreated SCLC to chemotherapy with or without bevacizumab.

Other anti-VEGF antibody strategies are in development, including the humanized monoclonal antibodies IMC-1121B (Ramucirumab, Imclone Systems) and IMC-18F1, which target the extracellular domain of VEGFR-2 and VEGFR-1, respectively.[50,51] Both of these agents are in early stages of development.

Another anti-VEGF pathway approach is Rh-Endostatin (Endostar, YH-16), an endogenous collagen XVIII fragment with antiangiogenic properties, which reduces the expression of VEGF.[52] A phase II trial randomized patients to two groups to receive 7.5 mg/m^2 or 15 mg/m^2 of Rh-Endostatin. Sixty-eight patients were included, the RR was 3.0% in both groups ($p > 0.05$), the median TTP was 60 days versus 71 days ($p > 0.05$), and the AEs were 48.6% versus 38.7% ($p > 0.05$).[53] A phase III trial using cisplatin and

vinorelbine as the chemotherapy backbone demonstrated an improved RR (35.4% versus 19.5%, $p = 0.003$) and TTP (6.3 months versus 3.6 months, $p < 0.001$) with the drug,[54] and an ongoing trial is now exploring combination therapy with carboplatin + paclitaxel.[55]

VEGF Trap (Aflibercept) is a human, soluble VEGF receptor decoy that combines components of VEGFR-1 and VEGFR-2 fused to the Fc portion of immunoglobulin G1 in a chimeric molecule. Some single-agent activity of the drug was demonstrated in a phase II trial,[56] and multiple phase II combination trials using the agent are ongoing in nonsquamous NSCLC. A phase III study (VITAL) comparing docetaxel with or without Aflibercept in second line is also recruiting patients.[57]

Multikinase Inhibitors

The largest class of anti-VEGF pathway agents is the TKIs that inhibit VEGFR. TKIs are small molecules, most of which bind to the ATP-binding site of the receptor, thus inhibiting activation and downstream signaling. In addition to inhibiting VEGFR-2, antiangiogenic TKIs have multiple other targets, leading to the variable toxicity and efficacy results seen to date. Although some have single-agent activity, the results of chemotherapy combination trials with them have so far been disappointing.

Vandetanib (ZD6474, Zactima) is an oral anilinoquinazoline that inhibits VEGFR-1, VEGFR-2, VEGFR-3, RET, and EGFR (Table 2).[58] A phase I study of 77 patients identified a maximum tolerated dose of 300 mg daily. Hypertension and QTc prolongation were the most common AEs.[59] No unexpected toxicities were seen in phase I/II combination trials with pemetrexed or docetaxel.[60] In a randomized phase II study versus gefitinib in 168 patients, PFS was 11 weeks and 8.1 weeks for vandetanib and gefitinib, respectively. Grade 3/4 AEs were diarrhea (8.4%) and rash (4.8%).[61] Another phase II study tested 3 arms (arm A: vandetanib 100 mg + docetaxel, arm B: vandetanib 300 mg + docetaxel, and arm C: docetaxel alone) in 127 patients with NSCLC previously treated with platinum-based chemotherapy. The median PFS was 18.7, 17, and 12 weeks for arms A, B, and C, respectively ($p = 0.037$), in favor of the two arms with vandetanib.[62] These results led to four recently completed phase III trials, ZEST, ZEAL, ZEPHYR, and ZODIAC. ZODIAC and ZEAL were second-line trials of docetaxel or pemetrexed, respectively, with or without vandetinib. ZODIAC enrolled 1391 patients, who received vandetanib + docetaxel or placebo + docetaxel. Addition of vandetanib to docetaxel showed a statistically significant improvement in PFS versus docetaxel (HR = 0.79, 98% confidence interval 0.70–0.90; $p < 0.001$), in RR (17% versus 10%, $p < 0.001$), and time to deterioration of symptoms (HR = 0.78, $p = 0.002$). OS was better in the vandetanib arm but was not statistically significant (HR = 0.91, $p = 0.196$). The AEs increased in the vandetanib arm were diarrhea (42% versus 33%), rash (42% versus 24%) and neutropenia (32% versus 27%), and hypertension (6% versus 2%). AEs that were less frequent in the vandetanib arm were nausea (23% versus 32%), vomiting (16% versus 21%), and anemia (10% versus 15%).[63] It is unclear why a reduction in toxicity was seen, though preclinical data showing increased hematopoeisis in the setting of VEGF inhibition has been described.[64] ZEAL enrolled 534 patients, who were randomized to receive vandetanib + pemetrexed or placebo + pemetrexed. There were positive trends seen for vandetanib + pemetrexed for both PFS ($p = 0.108$) and OS ($p = 0.219$), but the study failed to find a statistically significant improvement in either outcome with the addition of vandetanib to pemetrexed. Why the ZODIAC trial found a statistically significant PFS benefit, but the ZEAL trail did not is a matter of debate and may be due to the smaller size of the ZEAL trial. There was no increase in bleeding or thrombotic events in the vandetanib arm of ZEAL.[65] A direct comparison of vandetinib to erlotinib (ZEST) found equivalent PFS and OS.[66] Results are not yet known for the ZEPHYR study that randomized patients to vandetinib or placebo. In SCLC, this molecule failed to show a benefit in survival[67] or was a PFS benefit found in a randomized phase II study when added to first line carboplatin + paclitaxel.

Cediranib (AZD2171) inhibits VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-β, and c-kit (Table 2).[68] As a single agent, the drug is well tolerated at doses up to 45 mg daily. Toxicities in a phase I monotherapy trial were hypertension, headache, diarrhea, and voice hoarseness.[69] In phase II chemotherapy combination trials in patients with previously untreated advanced stage NSCLC, RR was high (45%) and toxicities included fatigue, diarrhea, febrile neutropenia, mucositis, anorexia, and hypertension, with increased toxicity associated with daily doses greater than 45 mg.[70] A National Cancer Institute-Canada phase II/III trial of carboplatin + paclitaxel with or without cediranib, BR.24, found the combination active (with a significantly increased RR of 38% versus 16% a trend for an improved survival HR = 0.78, $p = 0.11$)[71] but too toxic even at 30 mg, causing suspension of the phase III portion of the trial. The BR.29 study was recently opened using the same phase II/III design but with a 20 mg dose of cediranib. Combinations with cediranib and gefitinib in SCLC are also ongoing.

Sorafenib (Nexavar) inhibits RAF, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, Flt-3, c-kit, and p38-α (Table 2)[72,73] and has proven activity in renal cell carcinoma[74] and hepatocellular carcinoma.[75] The commonly used dose of 400 mg twice daily is associated with diarrhea and skin toxicities (hand-foot syndrome). Single-agent activity in NSCLC is limited, though prolongation of disease stability has been observed. In a monotherapy trial in untreated stage IIIB/IV NSCLC ($n = 20$), ORR was 12%, disease control rate was 40%, and median survival was 8.8 months. Grade 3 AEs included fatigue (20%), diarrhea (8%), and dyspnea (8%), and there was one episode of grade 4 pulmonary hemorrhage.[76] Trials of the drug in patients with NSCLC who had received prior therapy reported similar toxicity profiles with RR 0 to 13%, disease stability >50%, and PFS around 5 months.[77–80] Most recently, a large phase II trial, using a randomized discontinuation design provided more definitive evidence for single-agent activity of sorafenib. E2501 enrolled more than 300 patients and compared sorafenib with placebo in patients with NSCLC after failure with two prior

regimens of chemotherapy. After a 2-month lead-in period during which all patients received active drug, those with stable disease ($n = 83$) were randomized to sorafenib or placebo. Twenty-four patients had stable disease or a partial response after 2 additional months of sorafenib compared with only six in the placebo arm. The median PFS was 3.6 and 2 months in the sorafenib and placebo arms, respectively ($p = 0.01$). Grade 5 AEs were renal failure ($n = 1$) and pulmonary hemorrhage ($n = 1$). Grade 4 cerebrovascular ischemia events ($n = 4$) were noted. The other AEs were fatigue, hand-foot reaction, and rash.[81] A randomized phase III trial of sorafenib versus placebo in patients with prior chemotherapy is currently underway. Another trial tested sorafenib in NSCLC with k-ras mutation with encouraging results in a small number of patients.[82]

Combination trials with sorafenib have been less encouraging. In combination with gefitinib, sorafenib (400 mg) did not increase RR over that seen with gefitinib alone and 9% of patients discontinued the trial due to toxicity, particularly hypertension.[83] When sorafenib was combined with erlotinib though in a randomized phase II study for previously treated advanced stage NSCLC trial, the PFS was 3.1 months versus 1.87 months ($p = 0.06$) in the erlotinib + sorafenib arm, and erlotinib + placebo arm, respectively. There were more AEs in the sorafenib arm, and no increase in RR was observed.[84] In a phase III trial of 926 chemotherapy-naive patients with stage IIIB/IV NSCLC randomized to receive carboplatin + paclitaxel with or without sorafenib, sorafenib failed to show an improvement in survival. Furthermore, greater toxicities were observed in the sorafenib arm, particularly in patients with squamous histology. Thirteen patients had a fatal pulmonary hemorrhage.[85] A similar phase III trial (NEXUS), but with a restriction to patients with nonsquamous histology, used cisplatin + gemcitabine with or without sorafenib and completed accrual in February 2009[86] with results pending. Trials in SCLC are ongoing with cisplatin or topotecan.

Sunitinib (SU11248, Sutent) is an oral multitarget TKI against VEGFR-1, VEGFR-2, PDGFR, c-kit, and FLT-3 (Table 2) approved by the US Food and Drug Administration for the treatment of renal cell carcinoma and refractory gastrointestinal stromal tumors. Dose-limiting toxicities observed in phase I trials were asthenia, hypertension, and bullous skin toxicity.[87] In phase II, single-agent trials in NSCLC, toxicities were as expected but with the addition of pulmonary hemorrhage, which was fatal in at least 1 patient.[88,89] Single-agent activity (ORR = 9.5%) was seen with an intermittent dosing schedule (4 weeks on/2 weeks off).[88–91] In a randomized phase II study of patients with nonsquamous NSCLC treated with carboplatin + paclitaxel + bevacizumab with or without sunitinib, there were 5 deaths of 56 patients.[92] Although the toxicity in combination with first-line chemotherapy is concerning, the single-agent activity of the compound is very encouraging, and the Cancer and Leukemia Group B is planning a large phase III maintenance trial after completion of first-line chemotherapy. In the planned trial of 240 patients, patients will be randomized to receive sunitinib at 37.5 mg orally daily or placebo after completion of first-line chemotherapy. Three other phase II studies with sunitinib are in development within the Cancer and Leukemia Group B including a second line trial of pemetrexed (500 mg/m^2 every 3 weeks), sunitinib (37.5 mg orally daily continuously), or both agents. In SCLC, a phase II trial is ongoing for extensive disease in first or second line.

Motesanib (AMG 706) is an oral multikinase inhibitor against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, RET, and c-kit (Table 2). This molecule was analyzed in a phase I study in patients with advanced solid tumor with a maximum tolerated dose of 125 mg daily.[93] Combination trials of the drug with panitumumab and carboplatin + paclitaxel or panitumumab with cisplatin + gemcitabine have been conducted with grade 3/4 AEs of fatigue (45%), hypertension (27%), dyspnea (9%), sinusitis (9%), and pulmonary embolism (9%).[94,95] Currently, a phase III trial in combination with carboplatin + paclitaxel is ongoing.[96] This trial was closed for higher early mortality and a higher rate of hemoptysis in patients with squamous histology, then reopened with exclusion of this patient population.[96]

Axitinib (AG-013736) is a small molecule that inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and c-kit (Table 2). In a phase I study, the maximum tolerated dose was 5 mg twice daily, with AEs including hypertension, seizure, elevation of liver tests, and mesenteric vein thrombosis with pancreatitis.[97] A phase II trial testing the efficacy and safety of axitinib in NSCLC as a single agent showed in 32 patients, a RR of 41%, PFS of 4.9 months, and a median OS of 14.8 months. The most common grade 3 AEs were fatigue (22%), hypertension (9%), and hyponatremia (9%).[98] Currently, a phase III trial of single-agent axitinib in advanced NSCLC is ongoing.

Vatalanib (PTK787, ZK-222584) inhibits VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-kit, and c-Fms with AEs including fatigue, dizziness, vomiting, hypertension, ataxia, and dyspnea (Table 2).[99] In a phase II monotherapy trial in previously treated NSCLC, the agent had a moderate efficacy with a RR of 10%, and an OS of 7 months, but three fatalities occurred (two pulmonary hemorrhages and one pulmonary embolism).[100] Another phase II trial in pretreated NSCLC using dynamic contrast-enhanced magnetic resonance imaging showed a statistically significant reduction in tumor vascular parameters.[101]

Pazopanib (GW786034) was tested in patients with stage I/II NSCLC treated for 2 to 6 weeks before surgery. Twenty of 23 patients (87%) had reduction of the tumor volume, and three had partial response. Further, treatment was associated with decreases in soluble VEGFR-2 (sVEGFR-2), and a strong correlation existed between sVEGFR-2 changes and tumor shrinkage (Table 2).[102]

Another small molecule with potential antiangiogenic effects is enzastaurin (LY317615), a competitive selective inhibitor of protein kinase C-β and PI3K/AKT. Extensive phases I and II testing of the compound in combination with chemotherapeutics and biologics such as erlotinib has been conducted with fatigue reported as the predominant toxicity.[103] Results from two of the phase II trials that tested enzastaurin in combination with chemotherapy were presented at the

American Society of Clinical Oncology Annual Meeting 2009. The first trial compared carboplatin + pemetrexed + bevacizumab with or without enzastaurin in nonsquamous stage IIIB/IV NSCLC and the second compared carboplatin + pemetrexed with or without enzastaurin versus carboplatin + docetaxel in stage IIIB/IV NSCLC as first-line therapy. Neither of these trials showed a significantly prolonged PFS in the enzastaurin arm.[104,105] A phase II study included 48 patients with advanced NSCLC previously treated by one or two prior regimens. All patients received erlotinib 150 mg and enzastaurin 500 mg daily and orally. The addition of enzastaurin to erlotinib did not improve the RR and the disease control rate. PFS and OS are pending. The main AEs were rash (≥70%), diarrhea (≥55%), fatigue (≥25%), and nausea (≥25%).[106]

Other VEGFR-TKIs in early stages of development include BIBF 1120, XL647 (which has more EGFR-TKI activity), CP-547,632, E7080, AEE788, KRN951, ABT-869, OSI-930, and BMS-690514, among others (Table 2).

TUMOR-VASCULAR DISRUPTING AGENTS

Another approach to anticancer therapy is direct disruption of the existing tumor vasculature, as opposed to targeting neovascularization as previously discussed. Compared with normal vasculature, the structure of tumor blood vessels is abnormal, with irregular blood flow, increased permeability related to immaturity, and disorganization of the vessels.[107] These differences provide the opportunity for selective activity against the vessels supplying the tumor with oxygen and nutrients.

The first beneficial effects of vascular disrupting agents, vessel occlusion, inhibition of blood flow and necrosis, were identified in 1932 with the use of colchicine by Dominici.[108] Because of toxicity, development of colchicine as an antineoplastic was halted until the 1980s when two classes of vascular disrupting agents were studied that target established tumor blood vessels and the related vascular endothelial cells.[109]

Vascular disrupting agents are composed of flavonoids [flavone-8-acetic acid (FAA), LM985, ASA404 (DMXAA AS1404 or ASA404, Novartis International AG, Basel, Switzerland)], tubulin-binding drugs [Combretastatin A4 (CA4P), ZD6126 (AstraZeneca, San Francisco, CA), ABT-751 (Abbott, Il), and other agents, including Thalidomide, analogues of Thalidomide (Celgene, Summit, NJ), AVE8062 (Ajinomoto Company, Japan), Exherin TM (ADH-1, Adherex, Ottawa, Ontario), OXi4503 (Oxygene Inc., Baltimore, MD), Dolastatin 10 (Pierre Fabre Medicament, Boulogne Billancourt, France), and Auristatin (Seattle Genetics, Seattle, WA)] (Table 3).[24,109–112]

TABLE 3. Tumor-Vascular Disrupting Agents

Molecules	TNF α	NO	Tubulin	Other Target
Flavonoids				
FAA	+	−	−	−
ASA404	+	+	−	−
Tubulin-binding agents				
CA4P	−	−	+	−
ZD6126	−	−	+	−
ABT-751	−	−	+	−
AVE8062A	−	−	+	−
OXi4503	−	−	+	−
Dolostatin	−	−	+	−
Auristatin	−	−	+	−
Others				
Thalidomide	+	−	−	−
Exherin	−	−	−	*N*-cadherin
Cilengitide	−	−	−	Integrin
TNP-470	−	−	−	MAP
NPI-2358	−	−	−	Tubulin dimerization

NO, nitric oxide; FAA, flavone-8-acetic acid; MAP, methionine aminopeptidase.

Flavonoids

FAA and its ester (LM095) were the first drugs reported to have activity as vascular disrupting agents. FAA, the precursor of ASA404 (DMXAA), caused a selective shutdown of tumor blood flow with this action apparently related to the production of TNF-α.[113–115]

Another compound, LM985, demonstrated a dose-limiting toxicity of reversible hypotension at 1500 mg/m^2 administered intravenously every 3 weeks with other toxicities including urticarial rash, muscle aches, flushing, hypotension, diarrhea, nausea, vomiting, and cholestatic jaundice but no clear activity.[116,117]

ASA404 [DMXAA (5,6-dimethylxanthenone-4 acetic acid)] works by disrupting the actin cytoskeleton of tumor vascular endothelial cells, making tumor vasculature more permeable. ASA404 has a dual mechanism of action (direct and indirect). The direct action induces apoptosis in tumor vascular endothelial cells within 30 minutes, which must be kept in mind when considering combination therapy. The indirect action is associated with an increase of TNF-α, nitric oxide, and other cytokines, which can be enhanced with the combination with chemotherapy.[118,119] Precursors to the compound were initially discovered due to their induction of hemorrhagic necrosis in murine tumors. ASA404 induces apoptosis of tumor endothelial cells. Additional mechanisms of action are an increase of TNF-α and production of nitric oxide. This, in turn, induces a relaxation of the vascular smooth muscle, causing an increase in vascular permeability.[120–122] In phase I testing, the dose-limiting toxicities were visual disturbances, dizziness, headaches, anxiety, urinary incontinence, tumor pain, and, at higher doses, QTc prolongation. These events were dose dependent and reversible.[123] Dynamic contrast enhanced magnetic resonance imaging in patients, given ASA404 (500–4900 mg/m^2) has demonstrated a selective reduction in tumor blood flow.[124] Based on these results, further testing has been done with 1200 and 1800 mg/m^2 of ASA404.

In a randomized phase Ib/II study, 78 patients with previously untreated advanced stage NSCLC were treated with carboplatin + paclitaxel alone, carboplatin + paclitaxel + ASA404 1200 mg/m^2 or carboplatin + paclitaxel + ASA404 1800 mg/m^2; median survival was 8.8, 14.0, and 14.9 months, respectively.[125,126] In addition to expected toxicities, grade

3/4 cardiac AEs occurred in 4 patients with ASA404 but only in the 1200 mg/m^2 arm (1 event each of angina pectoris, cardiomyopathy, cardiovascular disorder and tachyarrhythmia). There were no apparent differences in safety between squamous and nonsquamous patients receiving ASA404 1800 mg/m^2. These encouraging results have led to two ongoing phase III trials: ATTRACT-1 randomizes previously untreated patients to carboplatin + paclitaxel with ASA404 or placebo and ATTRACT-2 treats NSCLC with second-line docetaxel with or without ASA404.[127,128] Cardiac toxicity will be closely monitored.

Tubulin-Binding Agents

CA4P, a water-soluble drug with similarity to colchicine, is derived from the Cape Bushwillow tree *Combretum caffrum*.[129,130] It affects tubulin and actin filaments, leading to increased permeability of the tumor vasculature among other effects. In phase I and early phase II testing with the agent given every once 3 weeks or daily for 5 days every 3 weeks, the main AEs were tumor pain, pulmonary toxicity, nausea, neuropathy, fatigue, hypotension, visual disturbances, and acute coronary syndrome. Objective responses were reported in a variety of tumor types.[131–133] CA4P is currently in phase II trials in combination with chemotherapy and radiotherapy.

Another colchicine analog, ZD6126, is a phosphate prodrug that disrupts the tubulin cytoskeleton.[134] In phase I testing of the agent administered once every 3 weeks, AEs were pain, anorexia, constipation, dyspnea, fatigue, headache, nausea, vomiting, and cardiac ischemic events in addition to increased intracranial pressure in two patients with active brain metastases unsuspected at trial entry.[135,136]

ABT-751 also binds tubulin and is the furthest along in lung cancer development of the colchicine analogs. Toxicities in a phase I trial included neuropathy, constipation, fatigue, myalgia, anemia, nausea, and vomiting.[137] In the phase I dose-escalation trial of ABT-751 and carboplatin in previously treated NSCLC, dose-limiting toxicities were thrombocytopenia and neutropenia. Of the seven evaluable patients, two had partial response, four had stable disease, and the median TTP was 18.7 weeks. Some responses have been seen in phase II monotherapy studies of previously treated NSCLC, with toxicities similar to those seen in phase I.[138]

Other colchicine-disrupting agents in development include AVE8062A, a CA4P analog, and OXi4503, a prodrug of combretastatin.[139] The tubulin-binding agent dolastatin 10 and a derivative known as auristatin PE (TZT1027)[140] are also in early development.

Other Vascular Disrupting Agents

Based on activity of thalidomide (Celgene, Summit, NJ) on the vasculature through TNF-α, multiple phase I/II trials of the compound in combination with chemotherapy have been explored in NSCLC. A phase III trial of gemcitabine + carboplatin with or without thalidomide in 722 patients with stage IIIB/IV NSCLC observed a median survival for placebo and thalidomide arms of 8.9 and 8.4 months, respectively. More thrombotic events were observed in the thalidomide arm, and it is unlikely this agent will be explored further in NSCLC,[141] though trials with analogs of thalidomide (lenalidomide and pomalidomide, Celgene, Summit, NJ) are ongoing or being considered in SCLC. Two phase III trials were done in patients with SCLC with thalidomide, but none of them found a benefit in survival for the thalidomide arm.[142,143]

Different approaches to vascular targeting are represented by the following agents in early development: exherin, an inhibitor of *N*-cadherin-mediated endothelial cell function[144]; cilengitide (Merck, Darmstadt, Germany), an integrin inhibitor[24,145]; TNP-470 (Intergren Company, Purchase, NY), an inhibitor of the endothelial cell proliferation enzyme methionine aminopeptidase[24,146]; and NPI-2358 (Nereus Pharmaceuticals Inc., San Diego, CA), an inhibitor of tubulin dimerization (Table 3).

Given that TNF-α plays a critical role in tumor vasculature, it was studied in combination with chemotherapy for mesothelioma without success.[147] However, NGR-hTNF is underdevelopment in Italy, primarily for the treatment of SCLC with encouraging data to date. This prodrug compound uses the effects of TNF-α by combining it with the tumor homing peptide, NGR.

One of the biggest challenges in developing compounds that target vasculature is the lack of good correlative markers. Although attempts have been made to find markers that predict response to bevacizumab and the VEGFR-TKIs, they have met with limited success. Soluble intercellular adhesion molecule ICAM and VEGF levels have been found to be prognostic but not predictive in the E4599 study with bevacizumab,[148] and recent work with VEGF polymorphisms have been intriguing, but not definitive.[149] Circulating endothelial cells may be predictive,[150,151] and data with neuropilin are encouraging.[152]

CONCLUSIONS

The potential therapeutic benefit of antiangiogenic agents in lung cancer and other malignancies has now been realized with the anti-VEGF antibody bevacizumab, and other agents that target VEGF directly, along with multiple agents targeting the VEGFR such as sorafenib, sunitinib, vandetanib, and cediranib. The main toxicities are bleeding, hypertension, skin rash, and diarrhea, and most agents have shown increased toxicity in squamous cell histology. How best to use these agents in which patients and in which combination with other drugs remain areas of active investigation. The hope is that tumor markers predictive of response will soon be discovered to help improve the therapeutic window with these drugs. The promise of cure initially envisioned from mouse models with the antiangiogenic drugs has yet to be realized, but they offer clear response and progression benefits for numerous patients with NSCLC. Another very exciting class of drugs targets the existing tumor vasculature. These vascular disrupting agents, including ASA404 and others earlier in development, work directly on tumor vasculature leading to tumor necrosis. They have a distinct toxicity profile with increased risk for cardiac toxicity compared with the VEGF-targeted agents but very promising randomized phase II efficacy data, and no differential toxicity by histology has been noted to date. The results of ongoing

phase III studies with these agents are eagerly awaited as hope for better targeted drugs in lung cancer therapy persists. Once the efficacy of these agents is established, combination regimens of anti-VEGF and VDAs will be considered, which may hold even further promise.

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