Bevacizumab in Non–Small Cell Lung Cancer
Alan Sandler

Abstract
Angiogenesis, the growth of new vessels from preexisting vessels, is a fundamental step in tumor growth and progression. Vascular endothelial growth factor (VEGF) is a key angiogenic factor implicated in tumor blood vessel formation and permeability. Overexpression of VEGF has been observed in a variety of cancers and has been associated with a worse relapse-free and overall survival. The antiangiogenic agent bevacizumab, a monoclonal antibody directed against VEGF, has shown clinical benefit in multiple cancers, including non–small cell lung cancer (NSCLC). Based on the favorable results of a prior randomized, phase II trial, the Eastern Cooperative Oncology Group conducted a trial (E4599) to evaluate the efficacy of bevacizumab in combination with paclitaxel and carboplatin in patients with recurrent or advanced stage IIIb or IV non–squamous cell NSCLC. Exclusion criteria included squamous cell histology, brain metastases, significant hemoptysis, or inadequate organ function or performance status ≥1. The primary study end point was overall survival. The median duration of survival in the chemotherapy plus bevacizumab group was 12.3 months compared with 10.3 months in the chemotherapy alone group (P = 0.003). Significant bleeding was more frequent in the chemotherapy plus bevacizumab group, 4.4% compared with 0.9% (P = 0.001). There were 15 treatment-related deaths in the chemotherapy plus bevacizumab group, including 5 due to pulmonary hemorrhage. Future and current directions include evaluation of bevacizumab in earlier stages of NSCLC, in SCLC, and in combination with other targeted agents, such as erlotinib.

Angiogenesis and Vascular Endothelial Growth Factor
Markers of angiogenesis have been shown to have prognostic significance in solid tumors (1). Vascular endothelial growth factor (VEGF) is a potent angiogenic factor acting on VEGF receptor-1 (Flt-1) and VEGF receptor-2 (KDR, Flk-1). Inhibition of VEGF has been shown to prevent tumor growth (2). Tumor VEGF overexpression in patients with early-stage lung cancer has been associated clinically with worse relapse-free and overall survival (3–6). Elevated VEGF expression has also been linked with development of brain metastases and pleural effusions in murine models of non–small cell lung cancer (NSCLC; refs. 7, 8). VEGF expression is elevated by diverse stimuli, which include proto-oncogene activation and hypoxia (9), the latter frequently arising in solid tumors because of inadequate perfusion.

Bevacizumab and Chemotherapy
Bevacizumab is a humanized monoclonal antibody against VEGF. Bevacizumab has been studied in a variety of solid tumors both as a single agent and in combination with cytotoxic therapy. In the only randomized trial of single-agent bevacizumab, treatment of patients with metastatic renal cell carcinoma seemed to result in a significant increase in time to progression, but no improvement was seen in overall survival (10). However, several studies in patients with metastatic colorectal, lung, and breast cancer have shown improvements in progression-free and overall survival when bevacizumab has been used in combination with chemotherapy (11–15).

A phase II randomized trial of 99 patients with advanced or recurrent NSCLC compared bevacizumab (7.5 or 15 mg/kg) plus up to six cycles of chemotherapy with carboplatin (area under the curve of 6) and paclitaxel (200 mg/m) every 3 weeks with carboplatin and paclitaxel alone (16). Patients who did not progress during chemotherapy were continued on bevacizumab alone for up to 18 cycles. The addition of 15 mg/m bevacizumab to chemotherapy resulted in an increase in time to progression, 7.4 versus 4.2 months, compared with chemotherapy alone (P = 0.023). There was also a nonsignificant improvement in overall survival, 17.7 versus 14.9 months (P = 0.63). This was not seen at the lower dose of bevacizumab, 7.5 mg/m, where the time to progression of 4.3 months was similar to treatment with carboplatin alone. A higher incidence in hemorrhage was noted in patients treated with bevacizumab. Squamous histology, tumor location close to major blood vessels, and tumor necrosis or cavitation were all associated with increased risk of bleeding (17).

The results of this study led to the Eastern Cooperative Oncology Group 4599 trial, the only phase III randomized trial of an antiangiogenic agent in combination with chemotherapy completed to date in patients with lung cancer (18). In this study, 878 chemotherapy-naive patients with predominantly
nonsquamous cell histology and advanced NSCLC (wet stage IIIB or IV) were randomized to carboplatin (area under the curve of 6) and paclitaxel (200 mg/m²) with or without bevacizumab (15 mg/kg). Chemotherapy was administered with bevacizumab every 3 weeks for six cycles, and then single-agent bevacizumab was continued until disease progression. Exclusion criteria were histologic evidence of predominantly squamous cell cancer; hemoptysis (1/2 teaspoon or more per event, a criterion added after a grade 5 pulmonary hemorrhage occurred in a patient with pretreatment hemoptysis); central nervous system metastases; pregnancy or lactation; documented hemorrhagic diathesis or coagulopathy; anticoagulation therapy; regular use of aspirin (>325 mg/d), nonsteroidal anti-inflammatory agents, or other agents known to inhibit platelet function; radiation therapy within 21 days before enrollment or major surgery within 28 days before enrollment; clinically significant cardiovascular disease; and medically uncontrolled hypertension.

Patient characteristics were well balanced by treatment group except for a slight difference in gender distribution (males: 58% of chemotherapy only arm, 50% of investigational arm, \( P = 0.03 \), Fisher's exact test). The median number of cycles of therapy was five on the chemotherapy only arm and seven on the bevacizumab arm. The addition of bevacizumab to paclitaxel and carboplatin chemotherapy resulted in an increase in overall survival from 10.3 to 12.3 months and 2-year survival from 15% to 23% (Fig. 1). Progression-free survival was also significantly improved with the addition of bevacizumab to paclitaxel/carboplatin (6.2 versus 4.5 months), corresponding to a hazard ratio for progression of 0.66 (\( P < 0.001 \)). Response rate was also improved, from 15% for chemotherapy alone to 35%.

There was a significantly higher incidence of hematologic toxicities, febrile neutropenia, hemorrhage, hypertension, and proteinuria in patients receiving bevacizumab. There were 17 treatment-related deaths: 2 deaths (gastrointestinal hemorrhage and febrile neutropenia) occurred with chemotherapy alone (0.5%) and 15 deaths occurred on the bevacizumab arm (3.5%; \( P = 0.001 \)). Of the 15 bevacizumab-related deaths, 5 were attributed to pulmonary hemorrhage, 5 to complications of neutropenic fever, 2 each to a cerebrovascular event or gastrointestinal hemorrhage, and 1 due to a probable pulmonary embolus. Of the 5 deaths from pulmonary hemorrhage, 1 patient had experienced hemoptysis before study entry and should not have been enrolled and 1 patient developed hemoptysis during the first cycle. The latter patient was continued on study and suffered a fatal event during the second cycle of treatment. In retrospect, this patient should not have continued on bevacizumab. A combined analysis of the phase II and III trials identified patient history of hemoptysis and presence of cavitation on imaging as risk factors for early-onset severe pulmonary hemorrhage following treatment with bevacizumab (17).

**Bevacizumab in Combination with Erlotinib**

Several lines of evidence lent support to the notion that combining erlotinib and bevacizumab for the treatment of recurrent NSCLC might confer additional clinical benefit. HER1/epidermal growth factor receptor (EGFR) and VEGF share common downstream signaling pathways (Fig. 2). They exert effects both directly and indirectly on tumor cells, and combining drugs that target these molecules may confer additional clinical benefit. HER1/EGFR is involved in angiogenesis; it has been detected in the endothelial cells of tumor vasculature preclinically (19). Coexpression of HER1/EGFR and transforming growth factor-\( \alpha \) has been correlated with increased microvessel density in invasive breast cancer (20). VEGF is also down-regulated by HER1/EGFR inhibition (21, 22), and a recent study suggested that blockade of VEGF may also inhibit HER1/EGFR autocrine signaling (23). Therefore, it is rational to suggest that dual blockade of these molecular targets may produce additive and even synergistic cytostatic effects. Against this background, several preclinical studies have investigated the antitumor activity of combined anti-HER1/EGFR and anti-VEGF agents. A combination of the HER1/EGFR small-molecule tyrosine kinase inhibitor erlotinib and the anti-VEGF monoclonal antibody bevacizumab delayed tumor progression in three of four human colon tumor xenograft models: the level of inhibition was much greater than with either agent alone (24). In two separate preclinical studies, both cetuximab (an anti-HER1/EGFR antibody) in combination with DC101 (an anti-VEGF receptor-2 antibody) and VEGF-AS (a human VEGF antisense 21-mer phosphorothioate oligonucleotide that inhibits VEGF production in human GEO colon cancer cells) decreased tumor growth compared with controls (25, 26). In the latter study, overall survival was superior in mice treated with both agents compared with either agent alone (\( P < 0.001 \)).

In a phase I/II study conducted at M. D. Anderson and Vanderbilt, treatment with erlotinib (150 mg daily) and bevacizumab (15 mg/kg every 3 weeks) was administered to 40 patients with previously treated, nonsquamous NSCLC (27). Patient characteristics included 80% of patients (32 of 40) with stage IV disease; >90% (37 of 40) of patients had a Karnofsky performance score \( \geq 80 \) at screening: 75% (30 of 40) of patients had adenocarcinoma; over half (22 of 40) had received two or more prior systemic chemotherapy regimens for NSCLC; finally, 9 (22.5%) patients had never smoked. No treatment-related grade 3 or 4 toxicities were reported in the phase I portion of the study. In the phase II portion, which enrolled 34 patients, the most common adverse events were rash (85%), diarrhea (65%), infection (29%), hematuria (32%), proteinuria (9%), and epistaxis (6%). Results of this trial included a 20% response rate, progression-free survival of 6.2 months, and an overall survival of 12.6 months.

Fig. 1. Kaplan-Meier curves showing overall survival from the 4599 trial for the bevacizumab with paclitaxel/carboplatin (BPC) arm versus paclitaxel/carboplatin alone (PC). Reprinted with permission from Sandler et al. (18).
This led to a multicenter randomized phase II trial of 120 patients with previously treated nonsquamous NSCLC that compared treatment with chemotherapy alone (75 mg/m² docetaxel and 500 mg/m² pemetrexed) with bevacizumab plus chemotherapy (docetaxel or pemetrexed) or erlotinib. Treatment with bevacizumab plus chemotherapy or erlotinib produced response rates of 52.5% and 51.3% and progression-free survival of 4.8 and 4.4 months, respectively, compared with a response rate of 39% and a progression-free survival of 3.0 months with chemotherapy alone. As in prior studies, fatal hemorrhage and thrombosis were seen in bevacizumab-treated patients. The incidence of neutropenia was similar between patients treated with chemotherapy with and without bevacizumab (28). An ongoing phase III trial is comparing erlotinib alone versus erlotinib plus bevacizumab.

**Future Directions**

The positive results in these studies have led to a multitude of clinical trials combining bevacizumab with a variety of chemotherapy agents in patients with NSCLC in the first- and second-line metastatic settings. Some trials are investigating unique patient populations, such as those with brain metastasis or squamous cell histology. Once an agent establishes activity in the metastatic setting, it is logical to evaluate the benefit of that agent in earlier-stage disease. The Eastern Cooperative Oncology Group is leading an international trial that will compare adjuvant cisplatin-based chemotherapy with or without bevacizumab for 1 year in patients with stage IB to IIIA NSCLC. Additional trials are under way evaluating the feasibility of bevacizumab in combination with radiation therapy and chemotherapy for unresectable stage III disease.

**Open Discussion**

**Dr. Thomas Lynch:** The rationale for the dose was based heavily on the phase II experience. In colorectal and breast cancer, they are using a different dose. What do you think about the dose of bevacizumab?

**Dr. Sandler:** You are right. It was based on the randomized phase II study, where the 15 mg/kg arm looked better than the 7 mg/kg, although there were more of the squamous cell patients in that particular arm. The AVAiL three-arm study does have two different doses of bevacizumab, 7.5 mg/kg and 15 mg/kg every 3 weeks. Going by the available data, we are wedded to the higher dose. Supposedly, doses as low as 1 mg/kg should saturate the VEGF.

**Dr. Roy Herbst:** Despite all the success clinically, the single biggest weakness is the lack of an assay to look at free versus bound VEGF. We are operating blind, and for colon cancer a lower dose is being used. The other tumor types are utilizing the higher dose, just the schedules were adapted. It would be hard now to go lower, given the phase III results.

**Dr. John Heymach:** The concentration of bevacizumab it takes to saturate the ligand is a good minimum. We have data from a few different settings to show that for some drugs there is much less inhibition of the actual target within the tumor microenvironment than one would expect based on plasma levels of the drug. If anything, we are tending to underestimate the amount of drug that might be important within the center of the tumor. If you look at the vein draining the tumor, the VEGF concentrations are dramatically higher than in mixed venous blood. PTK787 is an example of a drug that likely has activity, but which was probably underdosed.

**Dr. Philip Bonomi:** Has anyone seen intestinal perforations with bevacizumab plus chemotherapy in lung cancer patients? Were there any in ECOG 4599?

**Dr. Renato Martins:** Yes, we have had one.

**Dr. Sandler:** The answer to your question was there were no intestinal perforations in the trial; there was one patient with a perforated ulcer, however.

**Dr. Bonomi:** We had three patients, two with perforations needing surgery, one who has what they are calling micro-perforations. This raises the issue for me of whether we can safely put bevacizumab with every chemotherapy agent. I don’t know, but we should find that out.

**Dr. Lynch:** Our institution has a trial in esophageal cancer with docetaxel and bevacizumab. The principal investigator of that trial has been very careful about enrolling patients with gastrointestinal cancers who have active diverticulitis or anything that would possibly predispose to intestinal perforation and bleeding. Maybe this is something to think about in lung cancer as well.
References

Bevacizumab in Non–Small Cell Lung Cancer

Alan Sandler


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/13/15/4613s

Cited articles
This article cites 28 articles, 13 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/13/15/4613s.full.html#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
/content/13/15/4613s.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.