Antiangiogenic Therapy for Advanced Non-Small Cell Lung Cancer

Edited by Alex Adji, M.D., Ph.D., Alan Sandler, M.D., and Mark Socinski, M.D.

U nceasing tumor cell proliferation and the ability of cancer cells to metastasize are driven by a multitude of factors, some of which are related to angiogenesis. About 85% of lung cancers are of non-small-cell type (NSCLC), a form comprised of diverse histological subtypes originating in lung epithelial cells. Most patients are in an advanced stage and mortality rates are high. The beneficial effect of platinum-based chemotherapy regimens has been utilized in routine clinical practice for over a decade, resulting in the development of new therapeutic approaches focused on targeting angiogenesis. Moreover, an increased understanding of the molecular mechanisms that drive cancer cell proliferation has led to the development of targeted therapies with the potential to induce long-term survival benefit. With numerous agents/combinations under investigation for NSCLC, advances in both targeted therapy and the understanding of resistance mechanisms will be required to meet this challenge.

From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this CME activity, Targeting Tumor Angiogenesis, focusing on recent advances in the treatment of advanced non-small-cell lung cancer. I have found an interested and expert group of authors with whom I can share the latest evidence from this exciting area.

To the Authors

Because of the unique and complex nature of this disease, I believe that the reader will find this program informative and helpful. I thank you for your contribution to this endeavor.

- William W. Li, M.D., President, The Angiogenesis Foundation

Antiangiogenic Therapy for Advanced Non-Small Cell Lung Cancer

The FDA approval of bevacizumab (Avastin), a humanized VEGF-targeting monoclonal antibody, for the first-line treatment of advanced or metastatic non-small-cell lung cancer (NSCLC) led to a rapid extension of its use in the treatment of non-squamous NSCLC in the second-line setting. In a phase 2 trial (ECOG 4599) that showed that the addition of 15 mg/kg bevacizumab (BV) to carboplatin/paclitaxel (CP) reduced the risk of death by 43% vs. CP alone (HR, 0.57; 95% CI in the BV arm was 12.3 mo. compared with 10.3 mo. for CP; P=0.005). ECOG 4599 was followed by a second randomized phase 3 trial (AVAdE) of BV 7.5 mg/kg plus cisplatin/gemcitabine (CG) compared with CG plus placebo in 1043 chemo-naive patients with advanced or recurrent NSCLC. While OS was not yet mature at the time of analysis, BV added to CG significantly reduced the risk of disease progression vs. CG/placebo (BV 7.5 mg/kg: HR 0.75, 0.75; P=0.0162; BV 15 mg/kg: HR 0.82; P=0.03).

Kinase Inhibitors in Clinical Trials for NSCLC

The circulating VEGF of NSCLC patients is for oral agents that target VEGF, a key inhibitor, to VEGF-mediated angiogenesis, in addition to other angiogenic targets (see Table). Sunitinib (Sutent) 50 mg, given orally once daily, was evaluated in a single-arm phase 2 study of 63 treatment-refractory NSCLC patients. Median PFS and OS for patients receiving sunitinib were 9.3 mo. and 22.1 mo., respectively, with an objective response rate of 11.1%. In a subsequent phase 2 trial, a median PFS of 8.5 mo. and 9.3 mo. were reported using continuous dosing of sunitinib 57.5 mg/day in 47 NSCLC patients (9). Sunitinib (ZD6474) was also continuous dosing produced a median PFS of 5.7 mo. and 6.7 mo. of OS for patients receiving 50 mg/day sunitinib vs. Sunitinib plus placebo (HR, 0.70; 95% CI in the sunitinib arm was 9.3 mo. compared with 8.1 mo. for placebo; P=0.045).

Safety Issues of Antiangiogenic Therapy in NSCLC

BV is currently under evaluation in two phase 3 trials involving refractory NSCLC patients. BV and erlotinib were reported to be comparable effective and somewhat better tolerated than BV plus chemotherapy (median OS 13.7, 12.6 mo. for BV/erlotinib, BV/chemotherapy vs. 8.6 mo. for chemotherapy alone). Following these results, two phase 3 trials have been initiated: erlotinib ± BV in patients who had no prior anti-EGFR or anti-angiogenic therapy (Bea Lung); and front-line BV/chemotherapy (4 cycles) followed by BV ± erlotinib in NSCLC patients with squamous or nonsquamous histology. These trials have shown that both BV and erlotinib are also in development. Of these, vandetanib (ZD6474), a once-daily oral TKI, is the most clinically mature for NSCLC. Results from several phase 2 trials involving non-squamous NSCLC have shown encouraging results, and four randomized phase 3 trials of vandetanib have been completed. In a recent phase 2 trial of vandetanib, 86% of patients receiving vandetanib had stable disease, and 26% were stabilized. Treated patients receiving sunitinib may require monitoring for development of hypertension, reduced left ventricular ejection fraction (LVEF), and QT interval prolongation. 12

Future Directions

The use of biomarkers for identifying NSCLC patients who are most likely to benefit from antiangiogenic therapies remains an active area of research, but requires validation. From a therapeutic standpoint, vascular disrupting agents (VDAs) with an antivascular approach to NSCLC may select target existing vascular tumor, resulting in rapid tumor necrosis. In a phase 1/2 trial involving 11 of 30 who received the VDA VXDA-365 (SA404) plus CP achieved a PR of 62% and 50% complete response in previously untreated NSCLC patients, with an 8:1 ratio of adenocarcinoma to squamous cell. In addition to these NSCLC-specific safety concerns, VEGF inhibition may be associated with hypertension, impaired wound healing, and increased gastrointestinal perforations, fistula formation, thrombembolic complications, and reversible posterior leukoencephalopathy.

Side effects from sunitinib or sorafenib therapy may include hypertension, nausea, stomatitis, hyperension, and mucosal inflammation. Other agents have also been associated with a number of dermatological side effects, including hand skin reaction and rash (primarily sunitinib), hair depigmentation (sunitinib), and subungal splinter hemmorhages (both agents). Sunitinib has been associated with both pulmonary and cerebral hemorrhage in NSCLC patients. Additionally, patients receiving sunitinib may require monitoring for development of hypertension, reduced left ventricular ejection fraction (LVEF), and QT interval prolongation. 12

For complete references, please see www.angio.org and click on CME Information.