Zeroing in on Non-Small Cell Lung Cancer: Integrating Targeted Therapies into Practice

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Projects In Knowledge®
Education Initiative in Oncology

Penn Medicine
Target Audience
This activity is designed for physicians, including medical oncologists, radiation oncologists, pulmonologists, and other clinicians involved in the care of patients with non-small cell lung cancer.

Activity Goal
The goal of Zeroing in on Non-Small Cell Lung Cancer: Integrating Targeted Therapies into Practice is to provide the latest data and strategies for combining targeted therapies with cytotoxic chemotherapy and radiotherapy to optimize the treatment and outcomes of patients with non-small cell lung cancer.

Learning Objectives
• Assess the genetic profiles of non-small cell lung tumors to determine potentially beneficial therapeutic interventions that improve patient outcomes.
• Formulate treatment regimens for non-small cell lung cancer patients that combine chemotherapy, radiotherapy, and targeted therapies utilizing an understanding of appropriate patient selection and stratification criteria, as well as efficacy and safety data.

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George R. Blumenschein, Jr., MD, is a consultant for Abbott Laboratories, Amgen Inc, and Genentech, Inc.

Dr. Blumenschein will be discussing off-label/investigational use of cetuximab, gefitinib, sorafenib, sunitinib, and vandetanib.

Walter J. Curran, Jr., MD, is a consultant for Amgen Inc, Eli Lilly and Company, Genentech, Inc, and ImClone Systems; and has received salary/honoraria from Bristol-Myers Squibb.

Dr. Curran will be discussing off-label/investigational use of cetuximab and gefitinib.

Fred R. Hirsch, MD, PhD, is a consultant for AstraZeneca, Bristol-Myers Squibb/ImClone Systems, Genentech/OSI, GlaxoSmithKline, Merck & Company, Novartis Pharmaceuticals, and Syndax Pharmaceuticals; and receives research support from Genentech, Inc, Merck & Company, OSI Pharmaceuticals, Syndax Pharmaceuticals, and Ventana-Roche. He is also co-inventor of a University of Colorado-owned patent licensed to Abbott Laboratories.

Dr. Hirsch will be discussing off-label/investigational use of cetuximab and gefitinib.

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There is no fee for this activity.
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George R. Blumenschein, Jr., MD, is associate professor of medicine in the Department of Thoracic/Head & Neck Medical Oncology at the University of Texas M. D. Anderson Cancer Center in Houston, Texas. He received his BA from Vanderbilt University and his MD from the University of Texas Medical School in Houston. He then completed his residency in internal medicine at the University of Texas Health Science Center in Houston and his fellowship training in medical oncology at the University of Texas M. D. Anderson Cancer Center. Dr. Blumenschein has authored or coauthored numerous papers and book chapters on the management of lung and head and neck cancers. His primary area of focus is in new drug development and multimodality therapy for the treatment of lung and head and neck cancers. Specifically, he is interested in the utilization of compounds with novel mechanisms of action in clinical trials for the treatment of these tumors. He serves as the principle investigator on a number of research protocols.

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Genomic Profiling of NSCLC for EGFR Inhibitors

Fred R. Hirsch, MD, PhD

The availability of agents targeting the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) pathways has significantly improved overall and progression-free survival in patients with non-small cell lung cancer (NSCLC). Over the past few years, a variety of clinical and biologic factors has been identified that enables clinicians to match individual patients with the targeted therapy most likely to provide benefit. Clinical factors to be taken into consideration in choosing an EGFR tyrosine kinase inhibitor (TKI) include the patient's gender, tumor histology, smoking status, and race. In addition, the genomic profile of the patient's tumor, including EGFR protein, EGFR gene expression, EGFR mutations, pAKT, and K-ras mutations, has become increasingly important in determining the best therapeutic regimen. The predictive value of EGFR mutation status was illustrated in the recent IPASS trial comparing gefitinib with carboplatin + paclitaxel. Mutation-positive patients experienced significantly greater progression-free survival with gefitinib; in contrast, mutation-negative patients did significantly better with carboplatin + paclitaxel. Efficacy in response to erlotinib also varies with EGFR mutation status. In the OSI 402 study comparing erlotinib alone with carboplatin + paclitaxel + erlotinib, followed by erlotinib again, patients with EGFR-activating mutations had a median progression-free survival of 18.20 months, with a 6-month progression-free survival rate of 89%, compared with a median of 2.10 months and a 6-month rate of 22% in patients with wild-type EGFR.

In studies comparing EGFR TKIs with placebo, EGFR gene copy (FISH) also proved to be predictive of benefit from EGFR TKIs, with better overall survival in response to gefitinib or erlotinib compared with placebo in EGFR (FISH)-positive patients. In EGFR (FISH)-negative patients, overall survival in response to either gefitinib or erlotinib was not significantly different from that seen with placebo. In contrast, when gefitinib was compared with docetaxel, EGFR (FISH) status was not predictive of overall survival. The relationship of EGFR (FISH) score and outcome has also been examined in patients receiving the genomic profile of the patient's tumor, including EGFR protein, EGFR gene expression, EGFR mutations, pAKT, and K-ras mutations. In a trial comparing concurrent cetuximab + chemotherapy, followed by cetuximab (sequential arm) versus chemotherapy alone, followed by cetuximab (sequential arm), FISH-positive patients had significantly better disease control rates than did FISH-negative patients. However, when the concurrent and sequential arms were analyzed separately, a high or low FISH score predicted overall survival only in the concurrent arm.

Perhaps the genomic marker that has attracted the most attention is K-ras gene status, which has been strongly predictive of response to EGFR monoclonal antibodies in patients with colorectal cancer. However, in a study comparing paclitaxel/docetaxel/carboplatin +/- cetuximab, no significant relationship was observed between K-ras status and cetuximab benefit, nor were there any treatment-specific effects noted for EGFR protein (IHC) or EGFR mutation status.

Differences in the prevalence of EGFR mutations as a function of race have been documented, with patients in eastern Japan, Taiwan, China, Korea, and other Asian countries having a higher probability of EGFR mutations (20%–34% of patients) than primarily white populations in the United States, Italy, and Australia (5%–12% of patients). When the prevalence of genetic mutations in African Americans and Italian whites is compared, significantly more Italians had EGFR mutations than did African Americans, but the two populations did not differ in the prevalence of K-ras mutations.

Bevacizumab, a monoclonal antibody targeting VEGF, has also resulted in significantly improved outcomes in NSCLC when combined with chemotherapy, and efforts are under way to identify biomarkers predictive of response to this agent. In studies in patients with NSCLC to date, only baseline intercellular adhesion molecule (ICAM) levels have been shown to predict benefit with bevacizumab in this population.

Without being able to predict patient sensitivity to anticancer agents, clinicians have been forced to provide the same therapy for all. Although responders benefit, nonresponders suffer toxicity without impacting their cancer, while administration of other agents that might benefit them is delayed. In the future, tailored therapy, determined on the basis of biomarkers that predict patient sensitivity, will offer clinicians the tools to match NSCLC patients with the therapy best suited to fight their disease.

Suggested Readings


Current and Emerging Targeted Therapies in NSCLC

George R. Blumenschein, Jr., MD

Over the past few years, numerous molecules involved in the growth and proliferation of tumor cells have been identified that make appropriate targets for therapeutic agents. To date, the agents that have proven most successful in targeting these molecules are the epidermal growth factor (EGFR) inhibitors, cetuximab, gefitinib, and erlotinib, and the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab.

Cetuximab is a monoclonal antibody directed against EGFR, whereas gefitinib and erlotinib are receptor tyrosine kinase inhibitors that block signal transmission intracellularly. In the recently reported FLEX trial comparing cetuximab plus combination chemotherapy with vinorelbine + cisplatin versus combination chemotherapy alone as first-line therapy in patients with advanced non-small cell lung cancer (NSCLC), the addition of cetuximab resulted in significant increases in response rate ($P = .012$), median overall survival ($P = .044$), and time to treatment failure ($P = .015$). When white patients alone were examined, median overall survival increased significantly in the cetuximab-containing arm ($P = .003$), with benefits seen in patients with adenocarcinoma, as well as those with squamous-cell disease. As observed in other studies with cetuximab, patients who developed acne-like rash early in treatment had significantly better overall survival (15.0 months), compared with those who did not develop rash (8.8 months) ($P < .001$). Erlotinib has also demonstrated activity in NSCLC. When compared with placebo in previously treated patients, erlotinib resulted in a significant improvement of 42.5% in median survival ($P < .001$), with a 1-year survival rate of 31% compared with 21% with placebo.

In addition to bevacizumab, which targets the VEGF ligand, a number of small molecule receptor tyrosine kinase inhibitors, including sunitinib, sorafenib, and vandetanib, has also been developed to target the VEGF pathway. As reported in the pivotal bevacizumab trial comparing paclitaxel + carboplatin with paclitaxel + carboplatin + bevacizumab, the addition of bevacizumab increased median survival to 12.3 months, compared with 10.3 months achieved with paclitaxel + carboplatin ($P = .003$).

Anti-VEGF and anti-EGFR agents target different compartments in the pathophysiology of cancer. EGFR inhibitors act on the tumor cell to inhibit cell proliferation, decrease invasion, promote apoptosis, and inhibit metastasis; VEGF inhibitors block the development of new blood vessels necessary for tumor growth. Recently, investigators have begun exploring strategies that permit the targeting of both compartments, either by combining VEGF and EGFR inhibitors or through the use of multikinase inhibitors. Two preliminary trials have combined bevacizumab and erlotinib. In the first, a phase I/II trial in patients with recurrent NSCLC, the combination resulted in stable disease in 65% of patients, with a median progression-free survival of 6.2 months and a median overall survival of 12.6 months. The combination of bevacizumab + erlotinib has also been compared with chemotherapy (docetaxel or pemetrexed) + bevacizumab vs chemotherapy + placebo in patients with recurrent/refractory disease. Overall survival at 6 months was higher in the bevacizumab + erlotinib arm (78.3%) than either the bevacizumab + chemotherapy arm (72.1%) or chemotherapy-alone arm (62.4%).

The small molecule tyrosine kinase inhibitors developed to target the VEGF receptor (VEGFR) also target other molecules involved in tumor pathogenesis. Sunitinib inhibits platelet-derived growth factor receptor (PDGFR), VEGFR, KIT, and FLT3, resulting in antitumor and antiangiogenic activity. Sorafenib inhibits cell proliferation by targeting RAF kinase and blocks angiogenesis by targeting VEGFR-2 and PDGFR-B. Vandetanib also inhibits both VEGF and EGFR signaling. As second- and third-line monotherapies, the three agents have shown encouraging disease control rates of 53%, 59%, and 45%, respectively, with median overall survivals of 24 weeks, 29 weeks, and 26 weeks, respectively. A variety of trials are now exploring these new agents in combination with chemotherapy or other targeted agents, including combinations of erlotinib + sorafenib; erlotinib + sunitinib; vandetanib + docetaxel; and carboplatin + paclitaxel + cetuximab + bevacizumab.

Identification of biomarkers that predict the probability of response to targeted agents, as demonstrated in the recent IPASS trial of gefitinib, makes it possible to further enhance response to these new drugs. Studies are now under way to increase understanding of the effects of various therapies on these serum biomarkers. Results from these and other trials will be critical in guiding patient selection and optimizing outcomes with these exciting agents.

Suggested Readings


Over the past 20 years, numerous studies have demonstrated the value of chemo-radiotherapy (CT-RT) compared with RT alone in improving survival for stage III non-small cell lung cancer (NSCLC) patients with good performance status. Studies have also demonstrated that administering CT concurrently with RT results in greater overall survival benefit than administering the two sequentially. However, several questions remain in determining the most effective multimodality regimens, including the optimal RT dose, the best CT combinations, the place of adjuvant CT , and the role of the newly available targeted agents.

Results of preclinical studies and early trials in other tumors have suggested that an anti-epidermal growth factor receptor (EGFR) monoclonal antibody may enhance results of CT-RT in NSCLC. EGFR is overexpressed in NSCLC, and inhibition of EGFR has resulted in radiosensitization in preclinical studies. The EGFR inhibitor cetuximab enhances the efficacy of RT in patients with head and neck cancer, and there is evidence that the addition of cetuximab increases efficacy of CT in patients with advanced NSCLC. A trial exploring cetuximab (week 1), followed by the combination of paclitaxel, carboplatin, cetuximab, and RT (weeks 2–8), followed by cetuximab (weeks 9–11), followed by paclitaxel, carboplatin, and cetuximab (weeks 12–17), in patients with stage III NSCLC resulted in a median overall survival time of 22.7 months, with a 24-month survival rate of 49.3%. Based on these encouraging results, cetuximab is now being investigated in a randomized trial of standard-dose versus high-dose RT in combination with paclitaxel and carboplatin +/- cetuximab.

The addition of bevacizumab, a vascular endothelial growth factor inhibitor, to paclitaxel and carboplatin has significantly improved progression-free and overall survival compared with paclitaxel and carboplatin alone in patients with advanced NSCLC. Several trials exploring the combination of RT and bevacizumab-containing CT were closed prematurely due to excess toxicities (hemorrhage and/or fistulas). However, a phase I/II trial of bevacizumab + chemotherapy, followed by bevacizumab + CT + RT, followed by bevacizumab + the EGFR inhibitor erlotinib has yielded encouraging preliminary data, with a 1-year survival of 79% and one grade 3 and one grade 5 pulmonary hemorrhage in two squamous cell patients.

Thus, at present, combined CT-RT remains the standard of care for patients with stage III NSCLC. Strategies to further enhance the benefit of multimodality therapy, including the use of targeted agents, await results from current and future clinical trials.

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**Suggested Readings**

