Lung cancer is the leading worldwide cause of cancer deaths. Smoking is the dominant cause of lung cancer and smoking cessation is the established method to reduce lung cancer mortality. While lung cancer risk is reduced in former smokers, they have a lifelong increase in risk, compared to never-smokers. Novel chemoprevention strategies, such as oral or inhaled prostacyclin analogs, hold promise for these subjects. Low-dose spiral computed tomography screening reduced lung cancer mortality by 20% in high-risk heavy smokers older than 50 years. However, the high false-positive rate (96%) means that screened patients required controlled follow-up in experienced centers. An increasing percentage of patients with advanced lung cancer have molecular drivers in genes for which oral tyrosine kinase inhibitors have been developed.

Lung cancer prevention efforts must continue to focus on the 20% of Americans who continue to smoke as these individuals will continue to account for 40% of all new cancer cases. We must also devote research efforts to reduce lung cancers in never-smokers. The most promising way to accomplish reductions in former smokers would be through successful chemoprevention strategies. There are no approved chemoprevention strategies, and research in this area was hampered by a lack of understanding of lung cancer pathogenesis, a lack of intermediate biomarkers, a lack of good risk prediction models, and perhaps a lack of biologically driven agents.

Initial chemoprevention strategies centered on epidemiologic studies that demonstrated that smokers and patients with lung cancer have lower serum levels of several antioxidant vitamins than never-smokers. Large randomized trials of benefit from dietary vitamin supplementation, based on epidemiologic observations including vitamins A and E and their derivatives, failed to reduce lung cancer mortality. A recent large trial also showed a lack of effect of selenium. These failures highlight the need for better preclinical models, for intermediate biomarkers, and for better trial designs.

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Preclinical models demonstrated that prostaglandinds, downstream effectors in COX (cyclooxygenase) pathway, could decrease lung tumor formation in several animal models. The prostacyclin analog iloprost reduced lung cancer development in mice and was evaluated in a randomized phase II trial in high-risk patients defined by a greater than 30-pack-year smoking history and by having atypical cells in their sputum. In this study about 80% of the subjects had endobronchial dysplasia on bronchoscopic biopsy. Daily oral iloprost produced a highly statistical improvement in endobronchial histologic profile, compared to placebo, in former smokers but no reduction in current smokers (Table). This highly promising lead will need further confirmation in follow-up trials but provides an impetus for further studies in high-risk patients.

EARLY DETECTION

Prior studies of yearly chest radiographs and more frequent sputum cytologic analyses failed to show any reduction in lung cancer mortality despite improvement in survival outcomes for those diagnosed with lung cancer. This discrepancy was due to lead-time and length-time biases. Low-dose spiral computed tomography (CT) scans were shown to be more sensitive in the detection of pulmonary nodules in early lung cancers, compared to chest radiographs.

These observations led to several large randomized trials comparing annual low-dose spiral CT scans to annual chest radiographs or to observation. The largest of these trials was the US trial termed National Lung Screening Trial (NLST). This trial randomly assigned more than 50,000 high-risk individuals (defined by a smoking history of ≥20 pack years and age 55–74 years) to annual chest radiography or low-dose spiral CT scanning. The trial demonstrated a 20% reduction in lung cancer mortality and a 7% reduction in overall mortality in the group randomly assigned to an annual spiral CT scanning. This impressive finding is tempered by the fact that one-quarter of the spiral CT scans showed a “positive” result with 1 or more suspicious nodules, but only 4% of these were lung cancer. The evaluation of the 96% of false-positive nodules produced considerable cost, psychologic concern, and thoracotomies that resulted in benign resection in about 30% of cases.

Most major organizations have not yet produced guidelines for general use of low-dose spiral CT screening because of the uncertainties of cost effectiveness and morbidity of evaluation. Still, the striking reduction in lung cancer mortality has led to statements by the International Association for the Study of Lung Cancer (IASLC) and American Cancer Society indicating that physicians should discuss these results with their high-risk patients as defined in the NLST trial.

LUNG CANCER STAGING

The IASLC published recommendations on changes in the TNM classification for lung cancer in 2007, and these recommendations were adopted in the 7th edition of the TNM classification of the Union for International Cancer Control and American Joint Committee on Cancer in 2011. Among the important changes were size changes for T1 to T3, the change of multiple nodules within 1 lobe from T4 to T3, the change of multiple nodules in 1 lung from M1 to T4, and the change of malignant pleural and pericardial effusions from T4 to M1a. This 7th edition of the TNM classification must be applied to all newly diagnosed cases of lung cancer.

LUNG CANCER PATHOLOGY

In 2011 the IASLC Pathology Committee published the IASLC/American Thoracic Society/European Respiratory Society recommendations for changes in the classification of lung adenocarcinomas. Among the most important changes was the elimination of the term bronchoalveolar carcinoma. Tumors previously included in this term were separated into adenocarcinoma in situ versus invasive adenocarcinomas. The invasive adenocarcinomas were subclassified by the predominant pattern of growth. Prognosis was related to the pattern of growth.

LUNG CANCER THERAPY

This section will focus on recent advances in systematic therapy of stage IV non–small cell lung cancer because the greatest changes and advances have been made in this area. Perhaps the most exciting advances have been made in lung cancers driven by molecular changes in driver oncogenes. The first of these molecular drivers linked to specific therapy were mutations in the epidermal growth factor receptor (EGFR) that activated the receptor even in the absence of ligand (epidermal growth factor or transforming growth factor alpha [TGF] α). Erlotinib and gefitinib are small-molecule oral tyrosine kinase inhibitors (TKIs) that bind to the mutated receptor and block its signaling. These EGFR TKIs were shown to produce objective responses in about 10% of unselected patients but in up to 70% of patients with activating EGFR mutations. These observations led to randomized trials comparing erlotinib or gefitinib to combination chemotherapy in the first-line setting for advanced lung cancers. Essentially, all of the patients in these trials had lung adenocarcinomas because these mutations are rare in other histologic profiles. All of these

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**Histologic Findings in Biopsies from Patients on the Randomized Phase II Trial of Iloprost Versus Placebo 6**

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<tr>
<th>Features</th>
<th>Baseline (Current: N = 67)</th>
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<th>Diff</th>
<th>P Value</th>
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Abbreviations: Avg, average; DI, dysplasia index; Diff, difference; Max, maximum; Pre, biopsy result before institution of therapy; Post, biopsy result after 6 months of iloprost therapy; Rx, therapy.

a Former smokers have reduction in bronchial dysplasia (0.4–0.5) by avg/max and 15% by DI.
b Iloprost-treated former smokers have improvement in bronchial dysplasia (1.2–1.5) by avg/max and 24% by DI. Former smokers receiving iloprost exceed the difference between current and former smokers at baseline.

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**EARLY DETECTION**

**LUNG CANCER STAGING**

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studies showed a higher response rate and a longer progression-free survival for patients randomly assigned to receive erlotinib or gefitinib as compared to those randomly assigned to receive chemotherapy.\textsuperscript{15-18} The EGFR TKIs produced significantly less toxicity in each of the trials. In those trials that assessed patient-reported outcomes, including lung cancer symptoms and quality of life, the patient-reported outcomes were superior in the oral TKI–treated groups. Each of the trials allowed crossover to the other treatment at the time of progression. Most likely due to this crossover, there were no significant differences in overall survival in any of the trials, although survival was usually slightly longer in the EGFR TKI–treated group.

A few of these trials included patients lacking EGFR mutations as well as those with activating mutations. The chemotherapy-treated patients in these trials had higher response rates and longer progression-free survival, as well as superior patient-reported outcomes, compared to patients receiving EGFR TKIs. Survival was not significantly different (due to crossover) but favored the chemotherapy arms.

These data suggest that all patients newly diagnosed with advanced non–small cell lung carcinoma (NSCLC) should have their tumor tested for EGFR mutations. Patients having an EGFR mutation should receive erlotinib (or gefitinib) as their initial therapy, whereas those without these mutations should receive chemotherapy.

As these studies were evolving, a Japanese group of investigators\textsuperscript{19} reported in 2007 that some lung adenocarcinomas had activation of the ALK oncogene by a break in chromosome 2 that led to fusion of the \textit{EML4} gene with the \textit{ALK} oncogene, leading to constitutive activation of ALK.\textsuperscript{19} At the time, a small-molecule ALK TKI, crizotinib, was being developed by Pfizer (New York City, New York).\textsuperscript{18} Several patients with lung cancer who had ALK rearrangements were found to have dramatic responses to crizotinib. These dramatic responses led to enrichment of a phase I cohort of lung adenocarcinomas with an \textit{EML4/ALK} fusion. High objective response rates (approximately 70\%) and long progression-free survival (about 10 months) were reported in this group of patients.\textsuperscript{20} A fluorescence in situ hybridization assay using break-apart probes was developed to identify patients with the \textit{EML4/ALK} fusion. With the impressive findings from this study and early results of a randomized trial comparing crizotinib to single-agent chemotherapy in the second- and third-line treatment setting, the FDA gave accelerated approval for crizotinib for lung cancer harboring an \textit{EML4/ALK} fusion in 2011. Randomized phase III trials comparing crizotinib to combination chemotherapy in the first-line setting and to single agent chemotherapy in the second line setting are in progress. Thus, patients with lung adenocarcinoma should all have their tumors tested for \textit{EML4/ALK} fusions at diagnosis. Those patients with \textit{EML4/ALK} fusions should receive crizotinib as their initial therapy or at the time of relapse.

While patients with \textit{EGFR} mutations and \textit{EML4/ALK} fusions have high response rates and long progression-free intervals, relapse and progression are inevitable. Recent studies\textsuperscript{21} have shown several causes for the resistance, which include secondary mutations that prevent TKI binding, activation of other signal pathways such as MET (mouse epididymal transcriptome), or fibroblast growth factor receptor activation of other oncogenes such as \textit{KRAS}, and even transformation to another histologic profile (such as small cell lung cancer). These various causes of resistance indicate that biopsy at progression should be considered to select the next therapy, which could be standard cytotoxic chemotherapy or a novel therapy based on the mechanism of resistance.

There are other molecular changes that can drive lung cancer growth, for which there are novel oral TKIs in development. Among these are \textit{KRAS}, \textit{HER2/neu}, \textit{BRAF}, \textit{NRAS}, \textit{MEK1}, and \textit{AKT1}. There are also other fusions, such as rearrangements activating \textit{ROS} and \textit{RET} oncogenes, and amplification of \textit{MET} and \textit{fibroblast growth factor receptor} genes that may drive lung cancers. The Lung Cancer Mutation Consortium reported that more than 60\% of lung adenocarcinomas harbor 1 of these “actionable” molecular drivers. Thus, it is likely that patients will have panels of oncogenes tested at diagnosis to select the best therapy in the future (ie, individualized therapy).

There have been other major developments in the treatment of advanced NSCLC. Among these was the observation that the combination of pemetrexed plus cisplatin produced superior response rates, progression-free survival, and overall survival as compared to therapy with gemcitabine and cisplatin in advanced NSCLC with a “nonsquamous” histology.\textsuperscript{22} In contrast, patients with a squamous lung cancer histology had a superior outcome with the gemcitabine/cisplatin combination. Randomized trials in the maintenance and second/third-line setting also showed superior outcomes with pemetrexed compared to other therapy (versus placebo in maintenance or versus docetaxel in second/third-line setting) but only for patients with a nonsquamous lung cancer histology. Thus, pemetrexed is indicated only for patients with a nonsquamous lung cancer histology. The reason for the difference based on histology is not entirely clear but likely involves the high expression of the pemetrexed target, thymidylate synthase, in squamous and small cell carcinomas.

Multiple inhibitors of angiogenesis have also been studied in NSCLC therapy. The anti–vascular endothelial growth factor neuroclonal antibody bevacizumab has been studied most extensively. An Eastern Cooperative Oncology Group randomized phase III trial comparing the combination of paclitaxel/ carboplatin to the same combination plus bevacizumab showed superior response rates, progression-free survival, and overall survival in the group receiving bevacizumab.\textsuperscript{22} This trial excluded patients with squamous cell carcinoma because an earlier trial had shown increased bleeding and fatal bleeding in patients with squamous cell carcinoma. Bevacizumab produced increased toxicities, most importantly an increase in fatal complications including febrile neutropenia, bleeding, and cloting.\textsuperscript{23} Increased blood pressure requiring therapy was frequent. These toxicities were especially apparent in patients older than 70 years. A subsequent randomized trial from Europe comparing the gemcitabine/cisplatin combination to the same combination plus bevacizumab showed a higher response rate and longer progression-free survival for patients receiving bevacizumab but the survival was not significantly improved.\textsuperscript{24} Bevacizumab is approved by the FDA in combination with paclitaxel and carboplatin but only for patients with nonsquamous cell carcinoma. These studies of pemetrexed and bevacizumab reinforce the need to have an appropriate histologic diagnosis, as well as molecular analyses, before embarking on a course of treatment for patients with advanced non–small cell lung cancer. In some patients the tumor may be
extremely undifferentiated. In these cases additional analyses, such as immunohistochemistry with antibodies directed at thyroid transcription factor 1, cytokeratins, and p63, can be extremely useful in distinguishing squamous cell cancers from adenocarcinomas. Patients with squamous cell carcinoma are still treated with either paclitaxel/carboplatin or gemcitabine with either carboplatin or cisplatin. Patients with adenocarcinomas who have an EGFR mutation or an EML4/ALK fusion are first treated with erlotinib or crizotinib, respectively. Patients with adenocarcinomas lacking a molecular driver are treated with paclitaxel/carboplatin with or without bevacizumab or with pemetrexed/carboplatin with or without bevacizumab. In the coming few years it is likely that we will identify additional “actionable” molecular drivers treated with specific oral inhibitors and will identify mechanisms of resistance that should lead to improved therapy.

References