

Pulmonary and Critical Care Updates

Update in Lung Cancer 2005

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SMOKING CESSATION

The Lung Health Study randomized 5,887 participants with mild airway obstruction to a special intervention group consisting of a 10-wk smoking cessation program versus usual care (1). At 5 yr, the special intervention participants had a quit-smoking rate of 21.7% versus 5.4% of the usual care participants. After 14.5 yr, 731 individuals had died: 33% of lung cancer, 22% of cardiovascular causes, and 7.8% of respiratory disease (not cancer). The all-cause mortality was significantly lower in the special intervention group than in the usual care group ($p = 0.03$). The authors concluded that smoking cessation can have substantial effect on subsequent mortality even when successful in a minority of patients. This is just one more study (perhaps the best) showing that smoking cessation is worth the effort. Care providers should strongly consider referring current smokers to a smoking cessation program.

EPIDEMIOLOGY/GENETICS

Progress has been made in identifying the genetic basis of lung cancer susceptibility (2). Cote and colleagues have contributed to this by comparing lifetime risk of lung cancer in relatives of early-onset lung cancer cases and controls, demonstrating elevated odds ratios (1.91; 95% confidence interval [CI], 1.33–2.73) of lung cancer in first-degree relatives of early-onset cases (3). Surprisingly, the effect was greater in black than white individuals (odds ratio, 2.07; 95% CI, 1.29–3.32). The effects of race on lung cancer susceptibility are not fully understood, but increasing evidence is accumulating that ethnic disparities in treatment contribute to poorer lung cancer outcomes in minorities. Wisnivesky and colleagues used data from the Surveillance, Epidemiology, and End Results registry to evaluate outcomes of stage I non-small cell lung cancer (NSCLC) in Hispanics and whites (4). Hispanics had worse lung cancer-specific and overall survival than whites, likely explained by lower resection rates and higher incidence of stage IB tumors.

BIOLOGY

Finding the biologic determinants of tumor sensitivity to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) is the most exciting and rapidly moving area of translational research in lung cancer. In late 2004, two groups described

the presence of activating mutations in the EGFR of patients who had a marked clinical response to EGFR TKI therapy (5, 6). The story has now evolved further. Increases in gene copy number and EGFR protein expression are also highly associated with clinical response and improved survival, and mutations in the *K-ras* oncogene may be predictive of a lack of response (7, 8). Not all groups have confirmed these findings and there is a need for further analysis in well-designed prospective trials (9, 10). Clinically, the most important need is to develop tests that accurately predict which patients will and will not benefit from EGFR TKIs; we now have preliminary evidence that those without either gene amplification, mutation, or increased protein expression are unlikely to benefit from treatment. Acquired resistance to EGFR TKIs in some cases is caused by mutations within the EFGR (11). Interestingly, alternative strategies for EGFR inhibition may effectively treat these individuals (12). At present, lung cancer is at the leading edge of rationally targeted molecular therapy.

Gene expression profiling has been used to determine prognosis and the response to therapy, and to identify mechanisms of tumor biology. Borczuk and colleagues have used this approach to further delineate the role of the transforming growth factor- β pathway in tumor invasiveness (13).

Tumor hypoxia may have prognostic and therapeutic consequences for lung cancer. Bard and associates evaluated tumor hypoxia via bronchoscopy, using differential path length spectroscopy (14). Bronchial tumors are characterized by lower blood oxygen saturation and higher blood content than normal mucosa. Protein tyrosine nitration is elevated in lung cancer. Exhaled nitric oxide (NO) and NO₂ (nitrate) were increased in tumor regions compared with tumor-free regions. Proteomic evaluation of modified proteins provides evidence in favor of a role for reactive nitrogen and oxygen species in lung cancer (15). Rahman and coworkers attempted to identify a proteomic profile from bronchial biopsies that was predictive of normal, preinvasive and invasive lung cancer, and identified a profile with an accuracy of more than 90% (16). This line of investigation is an initial step toward characterization of lung cancer tumor genesis.

Dendritic cell-based immunotherapy is an area of intense research at present. In a murine model of malignant mesothelioma, dendritic cells pulsed with tumor lysate, and administered before tumor implantation, demonstrated protective antitumor immunity (17). This type of therapy may have a future role as an adjuvant to local therapies. The study by Chen and associates evaluated the presence of regulatory T cells in the pleural fluid or lavage of patients with lung cancer with or without malignant pleural effusions (18). They observed increased CD4⁺CD25⁺ T cells in malignant effusions and these cells express high levels of a transcription factor that may cause down-regulation of local antitumor response. Manipulation of this unique T-cell population (CD4⁺CD25⁺) could be an important component of future immunotherapy trials against lung cancer.

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SCREENING FOR LUNG CANCER

The current recommendation is that there is no role for routine screening of lung cancer even in high-risk individuals. That position is being challenged by a number of trials evaluating the role of low-dose (radiation) computed tomography (CT) screening. Swensen and associates reported the final results of their 5-yr prospective phase II trial, in which all participants were screened by spiral CT (19). Sixty-eight cancers were detected in 66 participants. There were 28 NSCLCs detected after the baseline CT scan (incidence cancers) and 17 (61%) were stage I. The mean tumor diameter was 14 mm (median, 10 mm). Noncalcified nodules (NCNs) were detected in 74% of all participants and required follow-up testing. It is impossible to determine whether CT screening decreased lung cancer mortality in this nonrandomized phase II trial. That question will have to be answered from the ongoing National Lung Cancer Screening Trial, which completes the third annual screening of participants in February 2006. A group from Pamplona, Spain, performed positron emission tomography (PET) scans on NCNs (≥ 10 mm) or nodules (≥ 7 mm) that were growing (20). These NCNs were detected in a CT screening study of high-risk individuals. Fluorodeoxyglucose (FDG)-PET was helpful for correct diagnosis of 19 of 25 indeterminate NCNs. The sensitivity, specificity, positive predictive value, and negative predictive value of PET for malignancy were 69, 91, 91, and 71%, respectively. The Lung Screening Study was a pilot trial of randomizing screening via CT or chest radiograph (21). The Lung Screening Study did not specify a dynamic algorithm for evaluation of abnormalities. Of 522 subjects with an abnormal screening CT, 12% underwent biopsy. Biopsy was more common (25%) with larger lesions (≥ 10 mm) than with smaller, 4- to 9-mm nodules (5%). The median time to first follow-up CT was 82 d.

MacMahon and colleagues from the Fleischner Society have offered clinicians some guidelines on the management of small pulmonary nodules detected on CT scans done for screening purposes or picked up on CT performed for other reasons (e.g., CT angiogram, CT abdomen, and coronary artery calcification studies) (22). These guidelines may take some of the medicolegal anxiety out of evaluations of NCNs.

FDG-PET is frequently used in the preoperative evaluation of a patient with lung cancer. Often the PET scan will reveal one distant abnormality other than the primary lung cancer. A report by Lardinois and coworkers evaluated 69 such patients (23). Fifty-four percent of these lesions were solitary metastases and 46% were unrelated to the primary cancer. This study further documents the necessity of tissue confirmation of isolated PET abnormalities before determining that a patient is unresectable.

New technologies are being developed and evaluated in the early detection of lung cancer. Machado and colleagues have described the use of an electronic nose to detect exhaled gases in lung cancer and control patients, reporting a 71% sensitivity and 92% specificity (24). This and other approaches to the use of exhaled breath analysis need to be further refined but show promise. DNA in exhaled breath condensate can be analyzed for the presence of microsatellite alterations (25). Antibodies to tumor antigens are produced in patients with lung cancer. Zhong and coworkers have explored the potential utility of these antibodies for lung cancer diagnosis and screening; in a preliminary study, 90% sensitivity and 95% specificity were found (26).

DIAGNOSIS AND STAGING

Mediastinoscopy or thoracotomy has been considered the "gold standard" for mediastinal staging of lung cancer, which is necessary to define optimal treatment strategies. Several reports have

described advances in both esophageal endoscopic ultrasound and endobronchial ultrasound to direct the transbronchial aspiration of mediastinal nodes (27, 28). Herth and colleagues have directly compared endoscopic ultrasound with endobronchial ultrasound for directed biopsy and found that they are comparable, with 78 and 85% success rates, respectively (29). Combining both modalities results in a 97% success rate. This and other studies suggest that mediastinal staging can be accurately determined endoscopically in many cases.

TREATMENT

The European Organization for Research and Treatment of Cancer performed a multicenter trial for patients with proven stage IIIA–N2 NSCLC (30). After induction of platinum-based chemotherapy, patients were randomized to surgery or radiotherapy. Of 167 patients randomized to the surgical arm, 147 (89%) had surgical resection. Of these 147, there were 74 (49.7%) who were completely resected. Pneumonectomy was performed in 69 patients (46%). The 30-d operative mortality was 4%. The authors conclude that the surgical morbidity and mortality were acceptable. However, the high rate of pneumonectomy and the substantial rate of incomplete resection would lead many to question this approach.

The National Cancer Institute Canada group reported the results of an adjuvant therapy trial in patients with total resected stage IB or II NSCLC randomized to observation or four cycles of vinorelbine plus cisplatin chemotherapy (31). Overall survival was significantly prolonged in the chemotherapy group (hazard ratio for death, 0.69; $p = 0.04$). The 5-yr survival rates were 69 versus 54% on the observation arm. This trial, along with two other trials that have been reported in abstract form, have established adjuvant chemotherapy for totally resected stage IB, II, and IIIA NSCLC as the new standard of care.

Tegafur-uracil (UFT) is an oral fluorouracil available in Japan (but not in the United States). Japanese investigators have conducted a number of adjuvant trials in completely resected stage IA and IB NSCLC. Hamada and colleagues performed a meta-analysis of six randomized trials of adjuvant therapy for 1 to 2 yr or no further treatment (32). The overall pooled hazard ratio was 0.74 ($p = 0.001$) and the 5-yr survival was 81.5 versus 76.5%, favoring adjuvant UFT. Many Japanese physicians consider adjuvant UFT their standard of care.

EGFR TKIs have been a major breakthrough in the management of selected cases of lung cancer. Gefitinib (Iressa) was the first in its class to receive U.S. Food and Drug Administration (FDA) approval in the United States and Japan, but the approval was based on phase II data. Erlotinib (Tarceva) was the second EGFR TKI to undergo evaluation. The National Cancer Institute Canada group performed a randomized phase III trial of erlotinib versus placebo in patients with previously treated stage IIIB or IV NSCLC. Patients were stratified by the number of prior treatment regimens they had received. The response rate was 8.9% in the erlotinib group. Median survival was 6.7 versus 4.7 mo, with a hazard ratio of 0.7 ($p < 0.001$) in favor of erlotinib treatment. On the basis of this trial, the FDA has approved erlotinib (Tarceva) for second- or third-line therapy of NSCLC. The FDA gave approval for gefitinib (Iressa) contingent on the performance of a phase III trial (endpoint of survival). Thatcher and coworkers reported the phase III trial results of gefitinib versus placebo in patients who were refractory or intolerant of their latest chemotherapy (33). The median survival time did not differ significantly between the two groups (5.6 vs. 5.1 mo for placebo), with a hazard ratio of 0.89 ($p = 0.087$). Subgroup analysis showed significantly longer survival in the gefitinib group than placebo for never-smokers ($p = 0.012$) and patients

of Asian descent ($p = 0.01$). However, overall the trial is considered to be negative and the FDA is no longer allowing gefitinib prescriptions for new patients. Further analysis of the data and additional trials are ongoing.

An in-depth overview of the pathogenesis and clinical features of lung cancer was presented in the Centennial Review series published this year in *AJRCCM* (34, 35). These articles represent an excellent overview of our progress in understanding of the biology and treatment of this abominable disease.

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