Current Strategies in the Management of Lung Cancer

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Lung cancer causes more deaths in American men and women than the total number of deaths from breast, prostate, and colon cancer combined. Recently the lung cancer death rate has reached a plateau in the United States, primarily because a significant number of American men have stopped smoking. However, smoking incidence in adult American women, as well as teenagers of both genders and of all ethnicities, has not decreased significantly.

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Screening and Imaging Technology
Currently, approximately 75% of lung cancer patients are diagnosed with locally advanced or widely disseminated disease, making them ineligible for potentially curative surgery. As Dr. Mulshine points out, recent nonrandomized trials have shown that approximately 80% of patients diagnosed with low-dose spiral CT scans are found to have stage I disease. A nationwide lung cancer screening trial in which individuals were randomly assigned to annual chest x-rays or annual spiral CT chest scans has completed accrual; it is estimated that results of this trial will be mature in approximately 2010. If the results of this trial show a similar rate of detection of stage I lung cancer with a concomitant reduction in lung cancer mortality, this will result in a major paradigm shift in lung cancer patients. Critics have argued that this approach won't be cost-effective, that there will be significant overdiagnosis (patients being diagnosed with lung cancer that will not result in death), and that there will be overtreatment (interventions being done for nonmalignant causes). So far the results of nonrandomized trials suggest that this will not be the case. Another concern is that imaging technology is changing so rapidly that the results that will be available from randomized trials in approximately 5 years will not be relevant to the pathology that will be available then. The relatively high rate of stage I lung cancer detected in the nonrandomized spiral CT scan studies is confirmed, it will, at least, result in a treatment paradigm shift with more patients being eligible for potentially curative surgery. This situation would pose interesting questions regarding patient selection and treatment selection for postoperative therapy. Adjuvant Therapy
Prior to 2003 there was relatively little information regarding postoperative adjuvant therapy. As Drs. Solomon, Mitchell, and Bunn have noted, the major available information came from a relatively small meta-analysis that revealed a 5% improvement in 5-year survival that was marginally significant ($P = .08$). More recently, a large adjuvant trial that included patients with stages I through III disease treated with a variety of cisplatin doublets showed results that were virtually identical to the chemotherapy was associated with a 4% improvement in 5-year survival rate, but in this case results were statistically significant ($P < .003$). Newer platinum doublets have improved the 5-year survival rate from 9% to 15% in patients with resulted stages IB through IIA non-small-cell lung cancer. However, two of the trials found no survival advantages in stage IB. Dr. Pisters suggests that perhaps a meta-analysis may clarify the role of adjuvant chemotherapy in stage IB patients. In their articles, Drs. Laskin, Sandler, Buter, and Giaccone comment about systemic therapy for stage IV non-small-cell lung cancer. There appears to be a therapeutic plateau with conventional chemotherapy. Doublets consisting of platinum and a newer chemotherapeutic agent provide similar efficacy with slightly different toxicity profiles. Biologic Targeted Therapies
A variety of biologic targeted therapies have been combined with chemotherapy with disappointing results until the recent trial in which bevacizumab (Avastin) was combined with paclitaxel and carboplatin. The study was limited to patients with adenocarcinoma, no brain metastases, and no history of hemoptysis. Adding bevacizumab to the chemotherapy doublets resulted in a modest survival advantage. This observation in lung cancer, as well as similar improvements in survival observed in breast cancer and colon cancer patients, suggests that the beneficial effect of combining chemotherapy with an effective antiangiogenic agent might have implications for many tumors.

**EGFR Inhibitors**

In contrast, anti-epidermal growth factor receptor (EGFR) agents seem to be more tumor-specific, with positive results being observed in colon cancer, lung cancer, and head and neck cancer. Two EGFR tyrosine kinase inhibitors, gefitinib (Iressa) and erlotinib (Tarceva) have been compared to best supportive care in previously treated small-cell lung cancer patients. Treatment with erlotinib was associated with a statistically significantly longer survival while gefitinib is associated with nonsignificant trend for improved survival. Drs. Buter and Giaccone discuss apparent reasons for the discordant results for gefitinib vs erlotinib, but it is unlikely that a decisive answer will be obtained. A relatively large number of investigators are trying to identify clinical and molecular parameters that might identify sensitive tumors within a specific type of cancer. Multiple investigators have observed that never-smokers, patients with adenocarcinoma, women, and Asians are more likely to respond to EGFR tyrosine kinase inhibitors. Approximately 18 months ago researchers in Boston identified activating mutations in the ATP binding site for EGFR protein in patients who had objective responses with EGFR tyrosine kinase inhibitors. Since that time, multiple reports of EGFR mutations in the same sites have been reported. It appears that approximately 80% of responding tumors contain these mutations. Other investigators have found that patients with tumors that have a high EGFR copy number are more likely to have objective responses and to live longer. **Conclusions**

With the ongoing work in lung cancer screening, the recent observations of improved survival with postoperative chemotherapy, the improvement in survival with EGFR tyrosine kinase inhibitors in patients with far advanced disease, and the improvement in survival with the addition of antiangiogenic therapy to chemotherapy, it appears that we may be on the verge of a paradigm shift for treatment and outcome for lung cancer patients.

**Disclosures:**

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