Lung Cancer: New Developments Point the Way to Reduced Mortality

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Ganti et al have described the most recent negative lung cancer chemoprevention trial, which compared selenium to placebo.[1] Interestingly, a recent meta-analysis showed that taking low-dose daily aspirin for 4 or more years was associated with a 30% reduction in lung cancer mortality, with the greatest effect occurring in mortality from adenocarcinomas.[2] In addition to reducing mortality from cardiovascular disease, it appears that long-term use of this relatively nontoxic, inexpensive treatment reduces the risk of death from another common tobacco-related disease. This review also discusses the recent National Cancer Institute (NCI) announcement that the National Lung Screening Trial (NLST) evaluating low-dose spiral CT scanning was stopped early because CT screening reduced lung cancer mortality by 20%.[3] Some experts believe that CT screening will reduce lung cancer mortality as much as 50% to 60%. Their argument is based on the fact that in the NLST only three annual CT scans were performed in each person screened, and it is likely that individuals who are at high risk for lung cancer will have annual scans for decades. Currently, the majority of lung cancer patients present with advanced disease and have a low chance of being cured. With increasing use of CT screening, the paradigm will change, with larger numbers of patients being candidates for curative local therapy.

The surprising results from the NCI Canada study that compared postoperative gefitinib (Iressa) to placebo in patients with stage IB-IIIA non–small-cell lung cancer (NSCLC) were reviewed.[4] This trial, which was stopped prematurely, produced survival results that are amazingly similar to those seen in the Southwest Oncology Group study in which significantly shorter survival occurred in stage III NSCLC patients who were treated with gefitinib following chemoradiation.[5] Why an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor would have a negative effect on survival in locally advanced disease and in early-stage lung cancer is not readily apparent. However, given these collective results, EGFR tyrosine kinase inhibitors should not be used outside of the clinical trial setting in these groups of patients. The authors also reviewed results of the IPASS trial, in which gefitinib was compared to paclitaxel/carboplatin in Asian never/light smokers who had adenocarcinoma of the lung.[6] This trial showed no significant difference in progression-free survival (PFS) in the unselected patients. However, in patients whose tumors had EGFR mutations, a superior response rate and PFS were seen in the patients who received gefitinib. Conversely, patients with EGFR wild-type tumors who were treated with paclitaxel/carboplatin had superior PFS and a higher response rate. The predictive value of EGFR mutations for PFS has resulted in many physicians changing their practice pattern for first-line treatment of stage IV NSCLC. Many are requesting EGFR mutation analyses, and if an activating mutation is detected, erlotinib is recommended as the initial treatment rather than a chemotherapy doublet. At this point, in IPASS as well as in similar studies, there has been no significant difference in overall survival between patients treated initially with an EGFR tyrosine kinase inhibitor and those initially treated with doublet chemotherapy. It is likely that this observation is due to the fact that EGFR tyrosine kinase inhibitors appear to be equally effective in previously treated and untreated patients. The recent phase III trial comparing carboplatin plus albumin-bound paclitaxel (nab-paclitaxel) to carboplatin plus paclitaxel revealed a higher response rate for the nab-paclitaxel regimen, with a particularly high response rate in squamous cancers.[7] This is an example of the different chemosensitivities of histologic subsets of NSCLC. The significantly longer survival seen in patients with nonsquamous tumors who were treated with pemetrexed/cisplatin as first-line treatment or with pemetrexed maintenance therapy was the first indication of the different chemosensitivities of cancers with squamous vs nonsquamous histology. Biomarker studies are being done in an attempt
to identify potential predictive molecular markers. Maintenance therapy was briefly discussed, but the phase III trials with maintenance pemetrexed or erlotinib which showed superior survival were not mentioned.[8,9] In both these trials, “switch” maintenance treatment was started in patients who had an objective remission or stable disease at the completion of four courses of a platinum doublet. The survival advantage seen with maintenance pemetrexed was limited to nonsquamous cancers. Erlotinib was associated with longer survival in unselected patients and in patients who had wild-type EGFR tumors.

Activating EGFR mutations are examples of oncogene addiction in NSCLC. Recently, EML4-anaplastic lymphoma kinase (ALK)-4 translocations and inversions have been identified as another instance of oncogene addiction in NSCLC.[10,11] These genetic abnormalities are found in approximately 4% of all NSCLC patients, and like EGFR mutations, ALK translocations are more common in never smokers, occurring in approximately 20% of these persons. Crizotinib, an oral ALK inhibitor, produced a response rate of 57% in patients whose tumors contained ALK translocations.[12] Additional data are needed regarding the duration of response, PFS, and overall survival in this group of patients treated with crizotinib.

Results of recently reported studies of new targeted therapies as single agents or in new combinations were reviewed. A MET tyrosine kinase inhibitor (ARQ197) and an anti-MET monoclonal antibody added to erlotinib resulted in longer PFS than did erlotinib alone in phase II trials.[13] Similarly, in phase III studies, afatinib, an irreversible dual EGFR and HER2 tyrosine kinase inhibitor, was compared to placebo,[14] and the combination of sunitinib (Sutent) and erlotinib was compared to erlotinib alone.[15] In each of these phase III trials, the experimental treatment produced superior PFS but did not have a significant impact on overall survival, raising questions regarding what the primary endpoints should be for trials in which overall survival might be influenced by subsequent treatment.

The provocative New England Journal of Medicine report that described longer survival in stage IV NSCLC patients who had early involvement of palliative care specialists was discussed.[16] Confirmatory studies, including analyses of concomitant medications and other therapies, are likely to follow.

In summary, we are entering an era in which we are using targeted therapies in patients with specific predictive molecular markers. This strategy, combined with increasing use of screening CT scans, is likely to result in a significant reduction in lung cancer mortality similar to the improved outcomes seen in breast cancer that have come from the widespread use of mammography and the development of more effective systemic therapy.

Also, it is possible that a treatment as simple as low-dose daily aspirin may have a significant preventive effect in former smokers.

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**References:**


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