Lung Cancer Management: Emerging Strategies

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This special “annual highlights” supplement to Oncology News International is a compilation of major advances in the management of lung cancer during 2004, as reported in ONI. Guest editor Dr. Roy Herbst discusses these advances in clinical management, with a focus on developments in adjuvant therapy for early disease, targeted therapy, and new chemotherapy findings.

Advances in treatment of non-small-cell lung cancer (NSCLC) and other lung cancers over the past year include demonstration of the benefit of adjuvant chemotherapy in early NSCLC; new indications for a number of chemotherapeutic agents and molecular targeted agents; and continued progress not only in efforts to identify early-stage disease through imaging, but also in determining optimal use of targeted therapies. **Adjuvant Chemotherapy for Early-Stage NSCLC** Two phase III trials reported last year have demonstrated a significant benefit of adjuvant chemotherapy in early-stage NSCLC, suggesting a new standard of treatment. In the Cancer and Leukemia Group B 9633 trial (CALGB 9633), 344 patients with stage IB NSCLC were randomized to paclitaxel (Taxol)/ carboplatin (Paraplatin) or no further treatment after complete surgical resection (see report on page 5). Adjuvant chemotherapy was associated with significant 38% and 49% reductions in risk for 4-year allcause mortality and lung cancer mortality, respectively. Chemotherapy was well tolerated; grade 3 or 4 neutropenia occurred in 36% of patients.

In the Canadian JBR.10 trial, 482 patients with completely resected stage I or II disease were randomized to adjuvant vinorelbine (Navelbine)/cisplatin (Platinol) or observation (see report on page 6). Adjuvant therapy was associated with a significant 30% reduction in risk for death over 5 years and a significant prolongation of median overall survival (94 vs 73 months). Adjuvant therapy was well tolerated in this trial, as well.

**Targeted Therapy** The U.S. Food and Drug Administration (FDA) approved Tarceva (erlotinib) as treatment for patients with locally advanced or metastatic NSCLC whose disease has continued to progress despite other therapies, including at least one prior chemotherapy regimen (see report on page 5). In a phase III doubleblinded, placebo-controlled trial in 731 patients from 17 countries, erlotinib treatment significantly improved overall survival, progression-free survival, and tumor response rate compared with placebo. Epidermal growth factor receptor (EGFR) status was not part of the study protocol, but was looked at retrospectively. Among patients with known EGFR status, erlotinib significantly improved overall survival in EGFR-positive patients but did not appear to improve survival in EGFR-negative patients. Adverse events were primarily rash and diarrhea. Interestingly, a significant survival benefit with erlotinib treatment was seen in EGFR-positive patients who had never smoked. While survival benefit was seen in all groups, it was especially high in neversmokers. The finding of survival benefit in never-smokers was also made in a subset analysis of the TRIBUTE trial of erlotinib in NSCLC; neversmokers tended to be younger and female and to have adenocarcinoma (see report on page 7). Molecular studies indicate that patients who are neversmokers have more mutations in the EGFR tyrosine kinase domain and that such mutations may confer sensitivity to treatment with EGFR inhibitors. A more definitive analysis of this will await the final analysis of the BR21 trial. Other molecular studies have indicated that mutations in the EGFR tyrosine kinase are significantly associated with response to the EGFR inhibitor gefitinib (Iressa), raising the possibility of screening for mutations that can identify patients likely to benefit from treatment (see report on page 8). Similar mutations affect the response to erlotinib. In the meantime, the post-accelerated approval clinical trial of gefitinib in lung cancer patients failed to show survival benefit vs placebo, despite an improved objective response rate; AstraZeneca has cautioned patients currently taking gefitinib to contact their physicians but to continue taking the agent (see report on page 10). EGFR inhibitors clearly provide benefit in some patients, and it has become a major initiative to identify markers that predict such benefit. **New Drug Findings and Approvals** The FDA approved Alimta (pemetrexed) for use in combination with cisplatin in patients with malignant pleural mesothelioma who are not candidates for curative surgery, making this drug the first to be approved in the treatment of this disease (see report on page 19). In a randomized, single-blind trial in 448 chemotherapy-naïve patients, pemetrexed plus cisplatin improved median survival by 30% compared with cisplatin alone (12.1 vs 9.3 months); 1-year survival was 50.3% vs...
38%. It is now recognized that pemetrexed must be given with folic acid and vitamin B12 supplementation; among patients receiving supplementation throughout the study, median survival was 13.3 months in the pemetrexed group and 10.0 months in the cisplatin alone group. Hematologic toxicity was more common in patients receiving pemetrexed. Pemetrexed has also been given accelerated approval by the FDA for single-agent treatment of locally advanced or metastatic NSCLC in previously treated patients (see report on page 12). Approval was based on a randomized, unblinded trial in 571 patients receiving second-line treatment with pemetrexed plus vitamin supplementation or docetaxel. In an as-treated analysis, there were no significant differences between the Alimta and docetaxel (Taxotere) groups with regard to response rate (9.1% vs 8.8%) or stable disease (45.8% vs 46.4%) or rates of on-study death or drug-related death. Pemetrexed treatment was associated with significant reductions in a number of toxicities, including neutropenia, diarrhea, and alopecia. In other studies in NSCLC, an Italian phase II trial of pemetrexed plus either carboplatin or oxaliplatin (Eloxatin) showed good response rates and favorable toxicity profiles for the combinations in chemotherapy-naive patients with resectable locally advanced or metastatic NSCLC (see report on page 14). Response rates were 31.6% in the pemetrexed/carboplatin arm and 26.8% in the pemetrexed/oxaliplatin arm, and median survival was 10.5 months in both arms. Hematologic toxicities were more common with pemetrexed/carboplatin. Nonhematologic toxicities were minimal. Investigation of inhalational therapy for lung cancer continues (see reports on page 16). The Sustained release Lipid Inhalation Targeting technology, or SLIT, developed to improve injectable or inhaled products by producing a targeted, prolonged effect that can reduce systemic and local toxicity and permit dose reduction, has been examined in a phase I study using cisplatin. No dose-limiting toxicity was observed in the study participants up to a maximum inhaled liposomal dose of 48 mg/m² every 2 weeks or 24 mg/m² every week. Preclinical studies using inhalational p53 indicate reduced tumor growth and longer survival in treated animals. Screening and Treatment Planning

- The National Lung Screening Trial has completed enrollment of 50,000 smokers or former smokers, who will be assessed to determine whether spiral computed tomography (CT) or chest x-ray to detect cancer prior to onset of symptoms can improve treatment outcome and reduce mortality (see page 20).
- The Early Lung Cancer Action Program (ELCAP) has tested CT screening over the last decade and has reported substantially improved cure rates when cancers are detected early. CT is capable of identifying tumors of much smaller size than are x-rays. Most recently, the technique of volume CT has been examined, which represents an improvement in resolution over that achieved with spiral or helical CT. Of cancers detected since 1993 in ELCAP, 80% were stage I disease, a marked improvement in diagnosis at this early stage compared with usual care, and the 8-year case fatality rate for all patients undergoing resection was 4%.
- Researchers in Germany found that fused positron emission tomography (PET)/CT scanning was more accurate in defining TNM stage in NSCLC than PET alone, CT alone, or side-by-side PET and CT images. Fused PET/CT resulted in modification of surgical treatment plans in a substantial proportion of patients compared with the other imaging approaches.
- Gated 4D PET/CT scanning has been shown to improve detection of tumor motion during respiration, permitting determination of which patients may require respiration-gated radiation therapy and improving the accuracy of radiation treatment.

Tobacco-Related Issues

- A working group of the National Cancer Institute (NCI) released “Women, Tobacco, and Cancer: An Agenda for the 21st Century,” a series of recommendations aimed at stimulating scientific research into tobacco-related cancers in women and developing evidence-based interventions to prevent the cancers worldwide (see page 23).
- The American Society of Clinical Oncology is setting up a commission comprising representatives from government, educational and scientific organizations, advocacy groups, and the private sector to assess tobacco-related social, medical, legal, and economic issues.
- The National Institutes of Health is funding seven new centers participating in the NCI's Transdisciplinary Tobacco Use Research Center program, designed to improve understanding of tobacco-related diseases and their control, as well as psychosocial factors that influence smoking. In less hopeful news, a House-Senate conference committee dropped a provision
that would have given the FDA regulatory powers over tobacco products, a provision the Senate had passed by a large margin as part of the 2004 Foreign Sales Corporation tax cut bill. Taken together, however, the research developments of the past year have been quite promising on several fronts, in terms of improvements in screening, diagnosis, staging, and treatment, and 2005 will likely continue to see further refinement in our understanding of how to optimize management of our patients with lung cancer through these state-of-the-art technologies and therapies. In all, 2004 was a very good year for lung cancer research.

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