Update in Lung Cancer and Oncological Disorders 2010

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Lung cancer remains the leading cause of cancer mortality in the world, with 157,000 deaths expected in the United States in 2010 (1). Despite the large death toll, there are reasons to be cautiously optimistic for a future with fewer lung cancer deaths. First, incidence and death rates are declining in U.S. men and are plateauing in women, following trends of declining smoking prevalence rates over the past 30 years (2). Second, recent studies of lung cancer screening, staging, drug development, and molecular diagnostics have demonstrated important advances that promise to decrease death rates over time (3). Third, epidemiological and bench science research have provided important insights into lung cancer susceptibility and pathogenesis. Recent advances in clinical and bench science directed toward diagnostics and therapy have had significant and often dramatic impacts on patient outcomes. These developments suggest that smoking prevention, chest computed tomography (CT) screening, and personalized approaches to treating lung cancer will significantly reduce lung cancer mortality. In this update, we present recent research findings and highlight future directions for lung cancer research and therapy.

LUNG CANCER EPIDEMIOLOGY

Following the paradigm of other major respiratory diseases, such as chronic obstructive pulmonary disease (COPD), tuberculosis, and diffuse parenchymal lung disease, lung cancer represents the cumulative effects of toxic exposures in susceptible individuals. For lung cancer, as in COPD, the major source of exposure is tobacco smoke, which accounts for 90% of lung cancer cases. Other exposures may contribute to regional variations in lung cancer rates, particularly in China and South Asia where 60 to 80% of lung cancer cases in women occur in nonsmokers. In-home coal and wood use in Asian countries was found to be associated with an odds ratio greater than 4 for lung cancer in women nonsmokers (4, 5). To determine if occupational exposure to diesel motor exhaust in Europe and Canada was associated with lung cancer risk, Olsson and colleagues pooled data from 11 case-control studies (6). Multiple models consistently showed an association of diesel motor exhaust exposure with an odds ratio of 1.31 (95% confidence interval, 1.19–1.43), thus indicating that individuals in occupations with high levels of diesel motor exhaust exposure (e.g., underground mining, tunnel construction) may have increased risk for disease.

Genome-wide association studies have found common susceptibility variants on chromosomal region 15q24–25.1 associated with lung cancer risk and nicotine dependence (7). Subsequent studies have been directed toward validating this observation and determining the functional consequences of gene variation at this and other loci on smoking behavior, lung cancer, and other tobacco-associated diseases. Thorgeirsson and colleagues detected variants in nicotine metabolizing enzyme CYP2A6 and CYP2B6 and nicotinic acetylcholine receptor subunit CHRNB3 and CHRNA6 genes associated with smoking behavior, measured by number of cigarettes smoked per day (8), as was shown for CHRNA5 SNP rs16969968 by Saccone and colleagues (9). The link between lung cancer and emphysema susceptibility was examined by Lambrechts and colleagues (10). The lung cancer and nicotine dependence gene variant rs1051730 on chromosome 15q24–25.1 was genotyped in two independent cohorts of smokers who underwent pulmonary function testing and CT of the chest. Independent of smoking, the A-allele was associated with increased risk and severity of emphysema as assessed by CT scan (10). Similarly, Young and colleagues showed that variants in 4q31 gene locus for HHIP and glycophorin A (GYPA) were associated with decreased risk for both COPD and lung cancer (11).

SCREENING

Early diagnosis remains an elusive goal for lung cancer. Currently, the American Cancer Society and the U.S. Preventive Services Task Force recommend no screening tests for lung cancer. The debate over the clinical usefulness of chest CT screening for lung cancer has been vigorous. Observational studies have shown that CT screening is sensitive; however, the specificity is low, with tumor being present in only approximately 1 to 3% of nodules detected by CT scan at screening. Recent research articles have presented conflicting predictions of survival benefit ranging from 80% 10-year survival in screen-detected cancers (12) to no benefit in screened versus unscreened patients (13). These discrepant results can be explained, in part, by the limitations of study designs used to estimate survival endpoints. The single-arm studies show the potential promise of CT screening, but they do not directly address key issues relevant to implementation of this technology. These issues include cost-effectiveness, overdiagnosis bias, risks, and the impact of comorbidities in smokers (14).

To address these issues in a robust, unbiased fashion, the National Cancer Institute and the American College of Radiology Imaging Network initiated in 2002 the National Lung Screening Trial (NLST). This large-scale randomized controlled trial assigned 54,000 current and former smokers aged 55 to 74 years to either low-dose helical chest CT or chest X-ray screening. In November, 2010, the National Cancer Institute announced initial findings from the NLST trial after notification from the data safety monitoring board that the data necessary for inference on the primary endpoint of lung cancer–specific mortality had been collected (15). The initial data showed a 20.3% reduction in lung cancer mortality among participants in the CT arm of the study. An ancillary finding, which was not the main endpoint of the trial's design, showed that all-cause mortality was 7% lower in those screened with chest CT. Approximately 25% of deaths in the NLST were due

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to lung cancer, whereas other deaths were due to factors such as cardiovascular disease. Publication of these findings is expected in 2011.

To maximize the potential benefits and to minimize the costs and risks of lung cancer screening, future efforts should be directed to: discrimination of false-positive benign nodules from malignant nodules (16, 17); use of biomarkers of disease risk (18–21) to potentially increase the positive predictive value of the examination; compliance with guidelines for nodule evaluation (22); assessment of radiation risk (23); cost-effectiveness; and generalizability to other populations, such as the European cohort being studied in the NEderlandsLeuvensLongkanker Screenings Onderzoek (NELSON) screening trial (24).

LUNG ADENOCARCINOMA CLASSIFICATION AND DIAGNOSIS

Lung adenocarcinoma, the most frequent histological type of non-small cell lung carcinoma, is heterogeneous. Studies from several groups across the globe have consistently shown that histologic subtypes of lung adenocarcinoma are associated with clinical outcome and with distinct molecular signatures, thus providing clinical rationale and biological plausibility for formal recognition of these subtypes. In a joint document sponsored by the American Thoracic Society, the European Respiratory Society, and the International Association for the Study of Lung Cancer, Travis and colleagues propose an evidence-based classification for lung adenocarcinoma (25). The document introduces the terminology of adenocarcinoma *in situ* and minimally invasive adenocarcinoma for subtypes of preinvasive lung adenocarcinoma, and it proposes that pathological annotation describe the nature and extent of the invasive component in the invasive tumors. Based on clinical trial results, it is recommended that epidermal growth factor receptor (EGFR) mutation testing be performed in advanced lung adenocarcinoma tumors. Also provided is an algorithm for immunostaining and molecular testing that is designed to provide clinically relevant histological subtype and molecular data for resected tumors and for small specimens acquired by biopsy.

STAGING

The role of the pulmonary physician in making the initial diagnosis of lung cancer by transbronchial lymph node aspiration is expanding. Annema and colleagues reported results from a randomized trial comparing endobronchial and endoscopic ultrasound to mediastinoscopy for mediastinal staging (26). The study showed that an approach that used endosonography for initial staging had sensitivity of 94% compared with 79% in patients staged by mediastinoscopy alone. The study is important because it confirms prior reports of the high sensitivity of endosonography and because it emphasizes that both endobronchial and endoscopic approaches have an important role, depending on location of the suspicious lymph nodes. Considering the importance of histology and molecular markers in directing lung cancer therapy, regardless of diagnostic approach, it is imperative that these procedures be performed in a manner that provides specimens sufficient for histological subtyping by morphology or immunostaining and for molecular testing (27–29).

LUNG CANCER PATHOGENESIS MODELS

Recent research has elucidated key inflammatory and immune pathways important for lung tumor initiation, progression, and metastasis (30–37). Berger and colleagues identified DOK 1, 2, and 3 as candidate tumor suppressor in lung cancer (38). These proteins serve as adaptor proteins and negatively modulate Erk signaling. In knockout mouse models, loss of these genes alone or jointly leads to a predisposition to lung cancer development as well as an expansion in alveolar type II and bronchioloalveolar stem cells. Takahashi and colleagues showed that activation of the IKKB and JNK signaling pathways in myeloid cells is important for tumor proliferation and progression in genetic and chemically induced lung adenoma in mice (39). DuPage and colleagues examined the immune response in murine models of lung cancer engineered to express exogenous antigens (40). The initial T-cell responses suppressed tumor progression but over time the responses became ineffective; thus the model provides insights into mechanisms important for tumor immune evasion. The therapeutic implications of these translational lines of research are demonstrated by drug studies in murine models. In these studies, Turke and colleagues (41), Carretero and colleagues (42), and Chang and colleagues (43) provide important *in vivo* feasibility data supporting clinical trials using drugs targeted to key tumor-signaling pathways (MET, LKB1, and EMT, respectively).

LUNG CANCER THERAPY FOR EARLY-STAGE DISEASE

Radiotherapy in Patients with Inoperable Disease

Many patients with relatively early-stage non-small cell lung cancer (NSCLC) cannot undergo curative surgery due to poor lung function or medical comorbidities. The historical standard for such patients with medically inoperable disease has been external beam radiotherapy, which is fraught with many issues, such as pulmonary side effects, fairly high rate of local recurrence, and inconvenience. Wisnivesky and colleagues (44) performed a Surveillance, Epidemiology and End Results (SEER)-based review of the efficacy of radiotherapy in elderly patients with stage I or II NSCLC who were not candidates for surgery. Overall 59% of 6,065 identified patients received radiotherapy, and this led to an improvement in overall and lung cancer–specific survival of treated patients (hazard ratio of 0.74 and 0.73) after appropriate adjustments for confounders.

Stereotactic radiosurgery (SRS) has been developed as an alternative strategy for providing high-dose radiotherapy in a very focused and dose-intense fashion. Timmermann and colleagues (45) reported the findings of RTOG0236, a phase II study of 55 evaluable patients (44 with T1 and 11 with T2 primaries) undergoing 54 Gy of SRS in three fractions. With a median follow-up of 34.4 months, only one patient had local recurrence, resulting in a 97.6% 3-year primary tumor control rate, 87% locoregional control rate, 48.3% disease-free rate, and 55.8% overall survival rate. Overall, treatment was well tolerated, with moderate pulmonary toxicity. The favorable toxicity profile along with the excellent rate of local control suggests SRS is an appealing alternative to conventional radiotherapy in inoperable patients; a randomized study is ongoing to compare these two modalities.

Grills and colleagues (46) compared outcomes of patients undergoing SRS versus wedge resection for the management of stage I NSCLC. Lung function was comparable between the two groups, but comorbidity scores were higher in the SRS group. At 30 months' median follow-up, local recurrence rates were 4% in the SRS group versus 20% in the wedge resection group. However, overall survival was better in the wedge resection group, which is as expected given fewer comorbidities in the wedge resection group.

Adjuvant Chemotherapy

The NSCLC Metaanalyses Collaborative Group reported on two analyses of a comprehensive systematic review of clinical trials data of 34 studies of surgery with or without chemotherapy and 13 trials of surgery plus radiotherapy with or without added

chemotherapy (47). Both metaanalyses confirmed an absolute 4% improvement in overall survival at 5 years. Interestingly, the data suggested similar estimated benefits for platinum-based chemotherapy in patients with node-positive cancers as well as stage IB tumors. Overall, these data confirm the significant but modest benefit of adjuvant chemotherapy in patients with NSCLC and also demonstrate similar benefits in patients receiving postoperative radiotherapy. Zhu and colleagues developed a 15-gene prognostic indicator that was able to distinguish high-risk and low-risk patients (as measured by overall survival) treated in the JBR.10 randomized controlled trial of adjuvant vinorelbine/cisplatin (48). Prospective validation of this classifier will support the potential promise of molecular testing to improve the efficacy of adjuvant chemotherapy by enhancing patient selection.

LUNG CANCER THERAPY FOR ADVANCED DISEASE

Palliative Care

A provocative study of Temel and colleagues (49) randomized 151 patients with advanced lung cancer to standard care versus early palliative care. In the early palliative care group, patients met with a palliative care team member at least once a month through the study with additional visits provided as necessary. Patients in both groups received standard therapy for their cancers (i.e., the receipt of systemic or other therapy was not restricted). Quality-of-life scores and depressive symptom rates were significantly better in the early palliative care group. Fewer patients in the early palliative care group received aggressive end-of-life care. Besides these expected results, the study surprisingly demonstrated a 2.7-month (8.9–11.6 mo) prolongation of life expectancy in the early palliative care group. These results suggest that early integration of palliative care for patients with advanced NSCLC is feasible and could lead to longer survival with better quality of life.

Chemotherapy in the Elderly

In the plenary session of the 2010 American Society of Clinical Oncology meeting, Quoix and colleagues (50) presented findings of a pivotal, randomized, phase III study comparing carboplatin/paclitaxel doublet chemotherapy for four cycles with single-agent chemotherapy vinorelbine or gemcitabine for five cycles in elderly patients (70–89 yr of age) with metastatic NSCLC. A very significant improvement in overall survival was noted in the doublet chemotherapy arm (6.2 vs. 10.3 mo) and progression-free survival (PFS) increased from 3 to 6.1 months. The attenuated doublet chemotherapy program was well tolerated overall despite being more toxic than single-agent chemotherapy. These results strongly argue for the use of doublet chemotherapy in fit elderly patients.

TARGETED THERAPY TO HISTOLOGY AND TO MOLECULAR ALTERATIONS

Histology Dependence

Although no major new clinical studies were reported on the topic of histology dependence of NSCLC therapy, several key follow-up analyses have been performed that suggest a major treatment-by-histology interaction in the responsiveness of NSCLC to pemetrexed. Scagliotti and colleagues (51) performed an interaction analysis of the three pivotal phase III studies leading to the approval of pemetrexed in the first-line, second-line, and maintenance settings. The results demonstrated clear-cut and very significant treatment-by-histology interactions regarding both PFS and overall survival (OS), thus confirming the superior efficacy of pemetrexed in patients with nonsquamous NSCLC. These findings strengthen the evidence base to the point that *de facto* it has become one of the major shifts in lung cancer management in 2010 (52).

Small Cell Lung Cancer

Jotte and colleagues (53) reported on a randomized phase II study of amrubicin versus topotecan in 76 patients with advanced, platinum-sensitive small cell lung cancer in the second-line setting. Amrubicin is a novel anthracycline analog, which is approved in Japan, with potent topoisomerase II inhibition but limited cardiotoxicity. Amrubicin treatment resulted in a higher response rate of 44 versus 15% with topotecan, and the PFS and OS rates also favored the amrubicin arm. Tolerability was similar between the two arms, with a higher rate of hematological toxicity with topotecan. Results of a pivotal phase III study comparing amrubicin with topotecan are awaited.

First-Line Tyrosine Kinase Therapy in EGFR-Mutant Lung Adenocarcinoma

Maemondo and colleagues (54) presented findings of the North-East Japan Study Group comparing first-line gefitinib with standard carboplatin-paclitaxel chemotherapy in patients with EGFR-mutant lung adenocarcinoma. This randomized study of 230 patients was terminated early after a planned interim analysis of the first 200 patients demonstrated significantly longer PFS (10.8 vs. 5.4 mo) and higher response rates (73.7 vs. 30.7%) in patients receiving gefitinib. Survival analyses suggested a trend for better overall survival in the gefitinib group as well, but this was not significant (30.5 vs. 23.6 months, $P = 0.31$); further updates are awaited as the data mature. The West Japan Oncology Group (55) reported nearly identical findings of a significant benefit of first-line gefitinib versus cisplatin/docetaxel in patients with advanced EGFR-mutant lung adenocarcinoma (median PFS of 9.2 vs. 6.3 mo). Further confirmation of the effectiveness of first-line EGFR TKI therapy was presented at the 2010 European Society for Medical Oncology meeting. In a phase III study (OPTIMAL), first-line erlotinib was compared with carboplatin/gemcitabine chemotherapy in 154 Chinese patients with treatment-naive advanced NSCLC harboring EGFR gene mutations (56). PFS of 13.1 versus 4.6 months was seen in favor of erlotinib therapy, and the greatest benefit was noted in patients with a good performance status. The overall response rate also strongly favored erlotinib therapy (83 vs. 36%). Together, these studies confirm that in patients with EGFR-mutated tumors, the use of first-line EGFR TKI therapy is a standard of care and they strongly support the use of molecular testing in lung adenocarcinoma for identification of EGFR mutant cancers (57).

Maintenance Therapy

Final results of the SATURN study (58), a randomized study of erlotinib or placebo as maintenance therapy after four cycles of platinum-based doublet chemotherapy for advanced NSCLC, demonstrated prolongation of PFS. More importantly, SATURN showed an improvement in overall survival (median survival of 11 vs. 12 mo) in the treatment arm that has led to Food and Drug Administration approval for erlotinib for this maintenance therapy indication. In the small number of patients with EGFR mutation–positive tumors, the PFS difference was marked, with a hazard ratio of 0.10.

Irreversible EGFR Inhibitors in Tumors Refractory to Tyrosine Kinase Therapy

Several reports last year addressed the usefulness of irreversible EGFR inhibitors, drugs that potentially circumvent common gefitinib or erlotinib resistance mechanisms, such as the EGFR-T790M

mutation. The LUX-1 study (59) compared the irreversible EGFR/ErbB2 inhibitor afatinib (BW2992) plus best supportive care with best supportive care alone in 585 patients with advanced lung adenocarcinoma that progressed after one or two lines of chemotherapy and at least 12 weeks of erlotinib or gefitinib therapy. A significant PFS difference was seen in favor of afatinib therapy (3.3 vs. 1.1 mo), but this did not translate into an OS benefit, the primary endpoint of the study (10.78 vs. 11.96 mo). Overall response rate was 11% for afatinib, and diarrhea and rash were common side effects. The complex biology of acquired resistance and the efficacy of posterior therapy might have confounded the ability to detect an OS difference, despite the evidence of drug activity in this setting. Another study (60) compared the irreversible pan-HER inhibitor PF299804 with erlotinib in 188 unselected patients with advanced NSCLC who had failed two prior chemotherapy regimens. Median PFS was prolonged from 8.3 weeks in the erlotinib group to 12.4 weeks in the PF299804 group, and the difference was even more pronounced in patients with K-ras mutant tumors. The objective response rate also favored PF299804 (17 vs. 6.4%).

New Targeted Therapeutic Approaches

Echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase translocation. Anaplastic lymphoma kinase (ALK) gene translocations, mainly Echinoderm microtubule-associated protein-like 4 (EML4)-ALK, were recently identified as a new oncogenic mechanism in NSCLC present in 3 to 5% of tumors, principally in patients with adenocarcinoma with limited or no smoking history. Kwak and colleagues (61) published the first human experience with ALK inhibition through the use of the dual ALK/MET inhibitor, crizotinib (PF-02341066) in patients with ALK-translocated, advanced lung carcinoma. In 82 patients in whom ALK translocations were confirmed by fluorescence *in situ* hybridization testing, crizotinib at a dose of 250 mg orally twice a day led to an outstanding 57% response rate and a 6-month PFS of 72%. Adverse effects overall were mild, composed of mild visual disturbances, gastrointestinal side effects, and hepatic dysfunction. A randomized, phase III registration trial comparing crizotinib with pemetrexed or docetaxel second-line chemotherapy is ongoing and is expected to complete accrual soon. Choi and colleagues have described acquired somatic mutations in the kinase domain that conferred resistance to ALK inhibitors in a single patient (62). Future data about the prevalence and clinical significance of these mutations should emerge from the clinical trials. Taken together, exciting data from the EGFR and ALK-targeted clinical studies have accelerated the widespread acceptance of molecular testing and targeted therapy of lung adenocarcinomas over the last year (63).

Insulin-like growth factor 1 receptor signaling. Insulin-like growth factor 1 receptor (IGF1R) overexpression is common in NSCLC and is associated with a poor prognosis. *In vitro* studies suggest that IGF1R blockade could be an effective strategy in NSCLC. Despite promising results reported from a randomized phase II study that showed previously unprecedented response rates in squamous cell tumors (64), the pivotal phase III study of carboplatin/paclitaxel with or without the anti-IGF1R monoclonal antibody figitumumab was closed prematurely due to an excessive number of deaths reported in the experimental arm (65). Overall survival favored the standard arm with deaths in the experimental arm primarily attributed to metabolic, cardiovascular, and infectious complications. High circulating plasma levels of free IGF1 were associated with improved PFS (66), but validated biomarkers to identify patients/tumors with a better chance of response are undeveloped. At present, the further development of IGF-targeted compounds for advanced NSCLC is in doubt.

MESOTHELIOMA

There are approximately 3,300 cases of mesothelioma in the United States each year, with the highest global incidence of disease presently being in the UK (67). Mesothelioma is caused by exposure to amphibole asbestos, with insidious disease onset and frequent presentation with locally advanced disease. Several groups have examined the performance of serum-based disease biomarkers to enhance early diagnosis and to distinguish mesothelioma from other pleural diseases (68, 69). Hollevoet and colleagues tested soluble mesothelin and megakaryocyte potentiating factor in 507 subjects (70). Receiver operator curve analysis showed similar performance in distinguishing patients with mesothelioma from control subjects, with area under the curve of soluble mesothelin equal to 0.87, and of megakaryocyte potentiating factor, with area under the curve of 0.85. Prospective validation studies will provide guidance into the role of these assays in screening and diagnosis, and ongoing efforts to sequence tumors will provide additional diagnostic assay targets (71).

The role of surgical treatment (i.e., extrapleural pneumonectomy, pleurectomy/decortication) in patients with malignant pleural mesothelioma remains controversial, with lower rates of surgical intervention in the community compared with tertiary referral centers (72). Van Schil and colleagues reported on a trimodality approach consisting of induction chemotherapy followed by extrapleural pneumonectomy and postoperative radiotherapy in early-stage disease (73). In this European Organization for Research and Treatment of Cancer (EORTC; protocol 08031) phase II trial, the success rate as measured by protocol completion and PFS at 90 days was only 42%, raising concerns about the feasibility of routine use of trimodal approaches in mesothelioma treatment.

Research has been directed toward novel approaches to mesothelioma treatment that include adjuvant immunotherapy and direct delivery of gene therapy (74). Hegmans and colleagues reported results of a phase I trial after their demonstration that dendritic cell–based immunotherapy induced protective immunity with prolonged survival in a syngeneic murine model (75). In the clinical trial, patients were treated with standard chemotherapy followed by autologous tumor lysate–pulsed dendritic-cell vaccination. The results showed that the approach was safe and effective in inducing an immunological response in patients with mesothelioma. To date, these novel approaches have not yet demonstrated clinical efficacy as measured by outcome, but recent translational studies using dendritic cell immunotherapy and "immuno-gene" delivery suggest that ultimately these strategies will deliver on their promise to impact clinical practice (76).

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