Advances in NSCLC

The era of targeted therapy has arrived for lung cancer and has made an unprecedented impact on outcomes, including survival, James R. Jett, MD, National Jewish Hospital, Denver, Colorado, USA, told attendees of the American Thoracic Society 2011 annual meeting. Choosing therapy on the basis of mutation testing has dramatically increased survival expectations from a few months with conventional chemotherapy to as much as 3 years with targeted agents.

"I have been doing this for a long time," said Dr. Jett. "In randomized clinical trials of stage IV non-small cell lung cancer, patients treated with chemotherapy or no therapy had a median survival of 4 to 5 months. Now, in patients with stage IV lung cancer associated with EGFR or ALK mutations, treatment with an appropriately targeted therapy results in survival on the order of 2 to 3 years. Is that progress? Absolutely."

The targeted therapy era in non-small cell lung cancer (NSCLC) began with the recognition that a substantial subgroup of patients have tumors with epidermal growth factor receptor (EGFR) mutations in the tyrosine kinase domain. Moreover, an exon 19 deletion and an exon 21 mutation account for 90% of EGFR mutations in NSCLC. Targeted therapy's potential to improve outcomes in NSCLC came to realization in the Iressa Pan-Asia Study (IPASS), conducted in East Asia [Mok TS et al. *N Engl J Med* 2009]. Never-smokers and former light smokers with advanced pulmonary adenocarcinoma were randomized to first-line therapy with the EGFR tyrosine kinase inhibitor gefitinib or to carboplatin-paclitaxel chemotherapy. The primary endpoint was progression-free survival (PFS), and the trial was statistically powered to test the noninferiority of gefitinib versus conventional chemotherapy.

An exploratory analysis focused on outcomes in patients with EGFR mutations. Of 436 patients who were tested, 261 (60%) were positive for EGFR mutations. Patients with EGFR mutation-positive tumors had a 52% reduction in the hazard for progression or death when treated with gefitinib (HR, 0.48; 95% CI, 0.36 to 0.64; $p<0.001$). In contrast, patients with EGFR-negative tumors fared better with conventional chemotherapy.

At about the same time as the IPASS study, Spanish investigators examined the distribution of EGFR mutations in a large population of patients with advanced NSCLC [Rosell R et al. *N Engl J Med* 2009]. Of 350 patients who were tested for mutations, women (69.7%), never-smokers (66.6%), and patients with adenocarcinoma (80.9%) had a significantly higher prevalence of mutations ($p<0.001$) compared with other subgroups that were analyzed.

In both the IPASS and Spanish trials, patients with EGFR mutations had an objective response rate of 70% with an EGFR inhibitor. Moreover, an additional 19% of patients in the Spanish study had stable disease with erlotinib, meaning that only about 10% of patients with EGFR mutations derived no benefit from treatment with an EGFR tyrosine kinase inhibitor.

Subsequently, other studies have corroborated the results of the IPASS and Spanish trials with respect to the activity of EGFR inhibitors in lung tumors with EGFR mutations. Other types of mutations that are associated with NSCLC have stimulated interest in the development of agents that target those mutations, including ALK, Met, KRAS, PI3K, and BRAF. Promising results have begun to emerge from preliminary studies of several investigational agents, such as crizotinib, an inhibitor of Met and ALK.

Highlights from the
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Ongoing trials are evaluating a wide range of therapeutics to determine their ability to block various signaling pathways.

Clinical trials are also being designed to take advantage of the new knowledge about the influence of mutations on response to therapy. For example, investigators from MD Anderson Cancer Center will perform pretreatment biopsies to test for 26 types of genetic mutations. Treatment will be adjusted on a case-by-case basis in response to changes in gene mutations in the individual cancer.

Under the old treatment paradigm, a biopsy would be obtained, labeled NSCLC, and treated with platinum-based chemotherapy, which would lead to responses in 20% to 30% of patients. Under the new paradigm, a good biopsy sample is obtained and molecular testing is performed. Patients with EGFR mutations will be treated with a tyrosine kinase inhibitor, and most of them will respond. If a tumor has mutations in ALK or Met, the patient will get an inhibitor (targeted therapy) of those pathways.

Updates in Personalized Medicine in COPD

Personalized medicine describes an individualized approach to treatment that takes into account the unique clinical, genetic, and molecular features of a disease for each patient. Blanca Camoretti-Mercado, PhD, University of Chicago, Chicago, Illinois, USA, described advances in the use of personalized medicine for patients with chronic obstructive pulmonary disease (COPD).

Effective management of COPD requires multidisciplinary care that may include smoking cessation, treatment with bronchodilators and glucocorticoids, oxygen therapy, pulmonary rehabilitation, and, in severe cases, surgical treatment with lung reduction or transplantation. Each of these components of therapy can be refined further according to individual patient factors. While few options for personalized medicine are available in current clinical practice, ongoing research on COPD susceptibility and pathogenesis has revealed potential therapeutic targets for specific subpopulations of patients with COPD.

Among smokers, certain single-nucleotide polymorphisms (SNPs) on chromosome 15, where the nicotinic receptor gene cluster resides, are associated with an increased risk of nicotine dependence and heavy smoking. One SNP, rs16969968, influences both nicotine dependence and the risk of lung cancer and COPD. In the future, this SNP may serve as a marker to identify smokers who need more intensive behavioral modification and pharmacological approaches to overcome nicotine dependence [Bierut LJ. *Trends Pharmacol Sci* 2010].

Alterations in the transforming growth factor (TGF)-beta signaling pathway have been implicated in the pathogenesis of COPD. Genetic differences that influence the expression of proteins along the TGF signaling pathway may have important implications for individualized COPD treatment. Most cells secrete TGF-beta as a complex that contains one of three latent TGF-beta binding proteins (Ltbp1, Ltbp3, and Ltbp4). Mutational inactivation of Ltbp4 causes defective TGF-beta signaling and an increased risk of the severe pulmonary emphysema phenotype of COPD. In a mouse model of COPD, mutational inactivation of the antioxidant protein sestrin 2 (sesn2) in Ltbp4-deficient mice reversed the emphysema phenotype. This suggests that patients with COPD that is due to altered TGF-beta signaling may benefit from treatment with antagonists of sestrin function [Wempe F et al. *Dis Mod Mech* 2010].

For patients with the emphysema phenotype of COPD, cell-based therapy is a promising option for restoring function to the pulmonary parenchyma. A recent proof-of-concept study examined the safety and efficacy of stem cell therapy in 4 patients with advanced COPD (stage IV dyspnea) [Ribeiro-Paes JT et al. *Int J Chron Obstruct Pulmon Dis* 2011]. All patients were treated with granulocyte colony-stimulating factor for 3 days immediately prior to bone marrow harvest. Autologous bone marrow mononuclear cells were isolated and infused into a peripheral vein. After 30 days, all patients showed a modest improvement in lung function, as measured by forced expiratory volume in 1 second (FEV_1). After 12 months, patients showed a significant improvement in quality of life and stable disease, suggesting a beneficial change in the natural history of COPD progression.

In summary, COPD is a heterogeneous disease, with major differences in risk factors, clinical features, and prognosis in different patient groups. Research in personalized medicine for COPD promises to provide effective treatment strategies that are tailored to the individual characteristics of each patient's disease. Genetic analysis, biomarker testing, and targeted therapy may soon be incorporated into the routine management of COPD.