Advances in Lung Cancer Therapy—Steady Progress in Personalized Therapy

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ABSTRACT

Recent improvements in our understanding of cancer pathogenesis have given rise to new treatment options, including targeted agents and cancer immunotherapy. This paradigm shift has created new hope, opportunities, and, at the same time, challenges in the fight against lung cancer.

Initially, cancer chemotherapies were identified from screens for compounds that killed rapidly dividing cells. These drugs remain the backbone of treatment; however, they are limited by a narrow therapeutic index and significant toxicities. In the early 1980s, evidence of mutated or abnormally functioning oncogenes and suppressor genes in human cancers began to accumulate, and we started to think of these genes and their products as targets for cancer therapy [1]. Consequently, cancer treatment has evolved from relatively nonspecific cytotoxic agents to selective, mechanism-based therapeutics and personalized medicine, defined by the National Cancer Institute as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”

Non-small-cell lung cancer (NSCLC) comprises multiple clinically relevant molecular subsets defined by specific driver mutations [2,3]. Such mutations result in constitutively active mutant signaling proteins and uncontrolled cellular proliferation. Interestingly, many of these mutant proteins can be targeted with specific kinase inhibitors, which can be more effective as a treatment modality than chemotherapy. There has been an acceleration both in research identifying genetic and molecular targets and in clinical trials using biomarkers that identify the presence of such targets in a patient’s cancer. This approach has been made possible both by increased knowledge of the genetic pathogenesis of cancer and by increased capacity to sequence genes and genomes in clinically useful timeframes and at a reasonable cost; this is thought to make the selection of appropriate targeted therapy for an individual patient possible. Thus, the standard of care for patients with advanced-stage NSCLC is shifting from empirically selected therapy based on a patient’s clinicopathologic features to biomarker-driven treatment algorithms based on the molecular profile of a patient’s tumor (personalized medicine).

Clinical application of single gene-based biomarkers has already proven successful in guiding the selection of molecularly targeted agents in NSCLC. The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib were the first molecularly targeted agents approved for the treatment of advanced NSCLC. Although these agents were initially approved for use in unselected patients with NSCLC, the presence of gain-of-function tyrosine-kinase-activating EGFR mutations was subsequently shown to be predictive of response. Recently, a new EGFR inhibitor, afatinib, has been tested clinically with promising results, and other EGFR inhibitors (such as dacomitinib, CO-1686, and AZD9291) are being developed. Similarly, gain-of-function tyrosine-kinase-activating anaplastic lymphoma kinase (ALK) gene rearrangements are valid biomarkers for predicting tumor response and progression-free survival with the first-in-class ALK-TKI crizotinib, and early results have shown the newly developed agents LDK378 and AF802 to have encouraging antitumor effects in ALK-positive lung cancers. In parallel, many other molecularly targeted therapies against genes such as HER2, ROS1, RET, BRAF, PIK3CA, FGFR1 and DDR2 are being developed for small subsets of patients with NSCLC [1,2].

Although not currently a standard part of our arsenal against lung cancer, immunotherapy may play a role in the future. By targeting the immune system rather than the tumor itself, it marks an entirely different way of treating cancer. The body’s immune response, if left unchecked, can result in autoimmunity; therefore, a number of immune “checkpoints” have evolved that work as braking mechanisms to counterbalance immune activation. Cancer takes advantage of these checkpoints to hide from the immune system. Improved understanding of the immune profile of cancer has led to immunotherapeutic strategies, including inhibition molecules responsible for abrogating an immune response such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) [4].

The CTLA-4 pathway is important in early T-cell activation, and ipilimumab is a fully human anti-CTLA-4 monoclonal antibody that blocks the interaction between CTLA-4 and its ligands CD80 and CD86; blocking this interaction promotes T-cell activation. Despite a high frequency of immune-related toxicity, ipilimumab, which was approved for clinical use in 2010, was the first agent to demonstrate a survival benefit in patients with advanced melanoma, and ipilimumab in combination with chemotherapy has shown some promise in patients with NSCLC.

In 1992, a young researcher in Japan, Dr Ishida, discovered a molecule expressed in dying T cells, which he called PD-1 and recognized as a "brake" on T cells [5]. In 1999, Nishimura et al. demonstrated that PD-1 downmodulated immune responses [6]. The PD-1/PD-L1 pathway is a primary method of tumor immune evasion, with upregulation of the pathway leading to immune tolerance and tumor progression. By upregulating ligands for PD-1 (PD-L1), tumor cells block anti-tumor immune responses in the tumor microenvironment. Currently, several agents targeting PD-1 are in clinical development, including nivolumab, lambrolizumab, MEDI4736 and AMP-224, and promising early data in NSCLC have been reported for nivolumab and lambrolizumab [4].

Further investigation is needed to identify patients who will benefit from immunotherapy, and to validate durable biomarkers of response. It is hoped that immunotherapy might consolidate the dramatic tumor responses that are achieved with targeted therapy into durable, long-lasting remissions in which sustained host immune responses targeting multiple cancer-associated antigens might reduce the risk of potentially lethal drug-resistant tumor cell clones. Recent advances in genomic technologies and drug development are bringing closer the dream of personalized therapy in lung cancer, with continued progress in the development of new biomarker-based therapies, although there are many barriers still to overcome.

CONFLICT OF INTEREST
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REFERENCES