New Approaches to Targeted Therapy in Lung Cancer

William Pao[1]

[1]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee

This brief report summarizes Dr. Pao's talk at the 54th Annual Meeting of the Thomas L. Petty Aspen Lung Conference, in Aspen, Colorado, on June 11, 2011. In this talk, Dr. Pao discussed three main topics: (*1*) DETECT (DNA Evaluation of Tumors for Enhanced Cancer Treatment), (*2*) MyCancerGenome.org (web-based decision support), and (*3*) DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment).

Keywords: lung cancer; driver mutations; targeted therapy; MyCancerGenome

Lung cancer causes the most cancer-related deaths in the United States and worldwide (1). Five-year overall survival rates are poor, and the maximal benefit of existing chemotherapy has reached a plateau (2).

In the past, the disease has been treated according to histologic criteria (small-cell lung cancer versus non–small-cell lung cancer [NSCLC) (3). However, over the past 40 years, investigators have discovered several key biological principles. First, cancers arise from an accumulation of gain-of-function mutations in oncogenes and loss-of-function mutations in tumor suppressor genes (4). Second, mutations that occur in signaling proteins, most notably kinases, can leave them "stuck" in the "on" position. Finally, despite the presence of multiple mutations in cancer cells, turning "off" a specific "driver" mutant kinase with small molecule inhibitors can be highly effective antitumor therapy (5). This phenomenon has been called "oncogene addiction," conveying the notion that cancer cells have become so "addicted" to signaling from a mutant oncoprotein that they die when the signaling is inhibited (6). Oncogene addiction underlies the move toward rational treatment of cancers with targeted therapies according to the genetic makeup of individual tumors.

NSCLCs harbor many driver mutations (7). Adenocarcinomas can be classified according to "driver mutations" in multiple genes, including EGFR, HER2, KRAS, BRAF, PIK3CA, AKT1, MEK1, ROS1, and ALK. Most of these mutations are mutually exclusive, so a tumor with a mutation in one gene rarely harbors a mutation in another. Mutations within individual genes can be associated with primary drug sensitivity, primary drug resistance, or secondary drug resistance.

Multiple studies have shown that a genotype-driven approach to lung cancer treatment has benefits over the one-size-fits-all approach. This is best exemplified in metastatic EGFR mutant lung cancer. Patients whose tumors harbor EGFR mutations have improved responses rates (~70%), prolonged progression-free survival, and improved quality of life on an EGFR tyrosine kinase inhibitor versus chemotherapy. Conversely, patients whose tumors are wild-type for EGFR display minimal response rates to EGFR tyrosine kinase inhibitors (TKIs) (~1%) and have better progression-free survival with chemotherapy (8). With this approach, the overall survival of patients with EGFR mutant tumors treated first-line with EGFR TKIs is about 27 to 30 months (9). By comparison, the overall survival of patients with metastatic unselected NSCLC on first-line chemotherapy is 10 to 12 months (10). Analogous observations have been made for patients whose tumors harbor ALK fusions treated with the ALK TKI crizotinib (11).

East Asian never smokers with lung adenocarcinoma have a very distinct tumor mutation profile. Approximately 90% of these tumors harbor a "driver" mutation in just one of five genes: EGFR, HER2, ALK, ROS1, and KRAS, of which EGFR, HER2, ROS1, and ALK are treatable with kinase inhibitors (12–14). By contrast, more than half of NSCLCs lack a known driver mutation.

At Vanderbilt, starting in July 2010, we adopted a genotype-driven approach to lung cancer treatment in a program called DETECT (DNA Evaluation of Tumors for Enhanced Cancer Treatment). Lung cancers are reflexively screened for more than 40 mutations in 10 genes using a variety of molecular methods (SNaPshot, sizing assay, and FISH) in the CLIA- and CAP-certified laboratories (15). (Given an analogous situation, we also began testing for 43 mutations in six genes in melanoma.) From July 1, 2010 to March 31, 2011, we tested tumors from 204 patients, demonstrating about the expected distribution of known mutations. The results have been placed in the electronic medical record in ways that are useful and easy to find for practicing clinicians. This approach has enabled rapid enrollment of patients on various clinical trials with specific targeted therapies. It has also allowed us to more rationally prioritize therapy for our patients.

We launched a website called MyCancerGenome (www.mycancergenome.org) to enable a genetically informed approach to cancer medicine. At this freely accessible website, users can learn about what mutations make cancers grow, what therapies are possibly effective against specific mutant gene products, and what clinical trials are available that target specific mutant gene products. Content is written by physicians and physician-scientists from all over the world in a collaborative manner for clinicians at the point of care, so that busy practitioners no longer have to worry about keeping track of the information explosion on their own. From January 2011 to December 2011, the website was accessed by users from more than 110 countries and all 52 US states and territories. Currently, the web-based decision support tool is accessed by about 1,400 individual users per week. As a point of reference, there are only approximately 8,500 medical oncologists in the United States (16).

We also launched a separate but related program called DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment) (17). We realize that personalized cancer medicine will

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Correspondence and requests for reprints should be addressed to William Pao, M.D., Ph.D., Vanderbilt-Ingram Cancer Center, 2220 Pierce Avenue 777 PRB, Nashville, TN 37232. E-mail: william.pao@vanderbilt.edu

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require large databases with patient information annotated by tumor mutation status and therapy outcomes. As a start, we reviewed more than 1,000 papers and found 115 that contained data on 1,152 individual patients with EGFR mutant tumors. There were 154 different EGFR mutations reported: 48% were exon 19 deletions, 27% were L858R, 3% were G719X, 1% were L861Q, and 21% were other. This database is searchable, allowing users to ask, "What happens to patients with EGFR mutation 'x' or 'y'?" We routinely receive requests from clinicians across the United States asking for this information.

In summary, lung cancers are highly heterogeneous at the molecular level. "Driver" mutations define subsets that can benefit significantly from targeted therapies. To take advantage of this knowledge, we started routine multiplex cancer genotyping in Vanderbilt CLIA labs as of July 1, 2010, where we perform "DETECT to select" therapy. Molecular results are reported in ways useful to clinicians and patients in our own electronic medical record and at www.MyCancerGenome.org. Finally, we are building a large database, DIRECT, to further accelerate a genotype-driven approach to cancer medicine. We hope that MyCancerGenome and DIRECT can become international resources for all because no one person can keep up with the explosion of knowledge generated over the past few years in efforts to map and genetically annotate human cancers.

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