The EGFR mutation and precision therapy for lung cancer

Outcomes in advanced lung cancer have seen meaningful improvement in the past decade thanks to new precision drug therapies. Because tumors usually develop resistance to the drugs, scientists are pursuing second-generation agents to regain control.

Background

No form of cancer is as deadly to Americans as lung cancer, which is expected to cause 159,260 deaths in 2014 with an estimated 224,210 new diagnoses of the disease. In patients with advanced lung cancer, surgery, radiation, and chemotherapy have failed to significantly improve the results.

In the late 1990s, researchers began to develop a new strategy that identified specific alterations, such as mutations, in the genetic code of tumors that allowed cancer cells to survive and grow. These DNA alterations became the focus of “targeted” drugs that blocked the cancer-driving effects of the mutations, slowing their growth or shrinking the tumor. Unlike chemotherapy, these new drugs limited their attack to cancer cells carrying the mutations – sparing normal cells and reducing toxic side effects.

In 2004, researchers at Dana-Farber and elsewhere identified vulnerability in some patients’ lung cancers – and began exploiting that weakness with designer cancer drugs. It was the opening of precision “targeted therapy” for lung cancer, and for certain patients in advanced stages of the disease, these treatments have made a meaningful difference.

Targeting EGFR

One of the early targets in lung cancer was the epidermal growth factor receptor (EGFR), a component of the molecular signaling pathway that controls proliferation and growth of cells. The EGFR protein sits on the surface of the cell, where it responds to stimulation by several different proteins (ligands), setting off a chain of signals inside the cell all the way to the nucleus, turning on growth genes when needed.

The mutation in the EGFR gene leads to overactivation, and activation independent of the ligand, of the EGFR protein in the cancer cells. The effect is to prod cells in the lungs to surge with uncontrolled, dangerous division and spread. At the same time, the mutation blocks signals that normally cause unwanted cells to self-destruct.

Iressa (gefitinib), a drug that selectively inhibits EGFR, had been tried against
non-small cell lung cancer (NSCLC) without much success—except, that is, with a small minority of patients whose lung tumors were dramatically beaten back by the drug. Often, these patients were nonsmokers.

These “exceptional responses” were interesting, but too rare in most experts’ opinion to pursue Iressa as a lung cancer treatment in the United States. Yet in Japan, Iressa was more successful and an approved lung cancer treatment there.

Delving into this disparity, Dana-Farber scientists analyzed the DNA of NSCLC tumors from American and Japanese patients. The gene that makes the EGFR protein, they found, was mutated in lung tumors from 15 Japanese patients but only in one patient from the United States.

Another part of the puzzle dropped into place when a Dana-Farber team identified the same EGFR mutation in a tumor from a woman with the adenocarcinoma type of NSCLC. These patients with the EGFR mutation—never smokers, Japanese, women, and those with adenocarcinoma—were the very same group where Iressa treatment had succeeded. A further study found EGFR mutations in lung tumors that had shrunk with Iressa treatment. Tumors from patients who hadn’t responded to the drug lacked the EGFR mutation.

The Dana-Farber scientists published these results in 2004, along with similar reports from other researchers. Using a new gene test, physicians could now identify the 10-15 percent of NSCLC patients in the United States and Europe who were likely to respond to Iressa. (In Asia, the mutant EGFR protein is present in the tumors of about 40 percent of patients with NSCLC.) EGFR mutation testing is now part of every single treatment guideline in oncology and is endorsed by major cancer organizations including the American Society of Clinical Oncology.

It was the first demonstration that a targeted therapy could be an effective treatment in lung cancer. A different oral EGFR-inhibitor drug, Tarceva (erlotinib) has since been approved for first-line treatment for advanced patients with EGFR-mutant NSCLC, and for second or third-line treatment for patients whose cancer has continued to spread after chemotherapy. A second agent, Afatinib (Gilotrif) is also now approved for first-line treatment for advanced EGFR mutant NSCLC.

Bruce Johnson, MD, Dana-Farber’s chief clinical research officer, co-led the 2004 study along with colleagues Pasi Jänne, MD, PhD; Matthew Meyerson, MD, PhD, and William Sellers, MD (now at the Novartis Institutes for Biomedical Research). Prior to matching targeted drugs to the EGFR mutation in patients’ tumors when present, chemotherapy was the only option for patients with advanced, metastatic lung cancer, with only 20 to 40 percent of such patients responding to the traditional treatment.

The outlook is much better for patients whose tumors test positive for the EGFR mutation and receive a targeted drug. Remissions, and average survival, is much longer.
Beyond EGFR

Researchers at Dana-Farber and elsewhere have identified other genetic subsets of lung cancer that may be targeted, as well. About five percent of non-small cell lung cancers have a glitch in a gene called ALK that fuels their growth. The oral drugs Xalkori (crizotinib) and Zykadia (ceritinib) can shrink these tumors in many cases.

Dana-Farber/Brigham and Women’s Cancer Center has, for several years, tested patients with adenocarcinoma of the lung – which accounts for about 40 percent of all lung cancers in the United States – for nearly a dozen mutations that can potentially be targets of precision drugs. In 2013, scientists introduced targeted next generation sequencing which increased the number of genes evaluated to about 300. Today, all patients with lung cancer are offered this detailed testing which has vastly increased our ability to both study genetic alterations in lung cancers and use this information to guide therapy.

Today, about half of all lung cancer patients at Dana-Farber/Brigham and Women’s Cancer Center are cared for with targeted drugs. In addition, investigators in the Thoracic Oncology Program, led by Geoffrey Oxnard, MD, are evaluating whether genetic mutations can be identified from small pieces of DNA that tumors have shed in the blood. This “liquid biopsy” approach allows real-time monitoring of changes that may be occurring within a tumor as a result of treatment with targeted therapies. In addition, it may offer an alternative approach to tumor-based genotyping.

Unfortunately, the most common tumor-driving mutation in lung adenocarcinomas has proved the toughest. Mutations in the oncogene KRAS are present in about 30 percent of these adenocarcinomas; no drugs can block KRAS because of its particular configuration.

Rather than aim drugs at mutant KRAS directly, scientists are testing new strategies that attack other parts of the overactive KRAS signaling pathway. In early 2014, researchers led by David Barbie, MD, and Kwok-Kin Wong, MD, Ph.D. of Dana-Farber reported that two drugs that inhibit the action of proteins, including MEK, “downstream” from the KRAS protein -- that is, they help carry out orders from KRAS -- shut down growth of lung tumor cells in the laboratory and in mice. These results, researchers feel, merit clinical testing in lung cancer patients. Another MEK inhibitor, selumetinib, is currently being evaluated in a DFCI-led phase 3 clinical trial in conjunction with the chemotherapy drug docetaxel for patients with KRAS-mutant lung cancer. This is the first and largest phase 3 trial conducted specifically with patients who have KRAS mutant lung cancer.

Over time, targeted drugs may lose their effectiveness when tumor cells develop resistance. It may take months or years, but inevitably the cancer will “learn” to grow again.

Resistance can develop when additional mutations cause the original target protein to shape-shift: its configuration changes so the drug molecules no longer bind with it effectively. In addition, the tumor may develop new growth signaling
Scientists and clinicians are already combining EGFR inhibitors with drugs that inhibit other critical cancer cell signaling proteins, or with immunotherapy pathways that don’t depend on the mutated pathway that the drug had blocked.

Dana-Farber scientists led by Jänne were the first to show how NSCLC tumors change to escape the grip of EGFR inhibitor drugs like Iressa or Tarceva. After a year or more on these drugs, the scientists found, tumors in 50 percent of patients acquired an additional mutation that opened another route to growth. Moreover, tumors in 20 percent of the patients revealed that the cells had amplified — made extra copies of — another gene, MET. When amplified, this protein can promote cancer cell survival. In some cases, the scientists reported, a small number of these resistant lung cancer cells were present in the tumor even before treatment with Iressa or Tarceva, strengthening the tumor against the EGFR-targeted drugs. The findings suggest that a combination of drugs from the very start of therapy can produce longer remissions in these patients.

Dana-Farber scientists are developing second-generation treatments for EGFR-mutant lung cancers that have acquired resistance to the original inhibitors. Jänne, Nathanael Gray, PhD, and colleagues reported in 2009 that they had designed a compound that binds to a “resistance mutation” in the EGFR protein in lung tumors that are resistant to Iressa and Tarceva. The compound showed encouraging activity in EGFR inhibitor-resistant mouse models of lung cancer.

Early clinical studies of similar compounds (including AZD9291 and CO-1686) have shown encouraging activity with patients who have developed resistance to current EGFR inhibitors and whose cancers harbor a specific resistance mutation (called EGFR T790M). These agents, currently in late-stage clinical trials, have been granted breakthrough therapy status by the Food and Drug Administration based on their encouraging early clinical efficacy.

Scientists from Dana-Farber and elsewhere have shown that therapies targeting EGFR mutations constitute a new weapon against deadly lung cancer. But cancer’s ability to evolve and escape these precision treatments means continued persistent and innovative research is needed to stay one step ahead. Scientists and clinicians are already combining EGFR inhibitors with drugs that inhibit other critical cancer cell signaling proteins, or with immunotherapy. These approaches are now in early-stage clinical development and researchers are hopeful that they will vastly improve outcomes.

Selected References


Jänne PA1, Gurubhagavatula S, Yap BY, et al. Outcomes of patients with


