Ceritinib: A potent second-generation ALK inhibitor for non-small-cell lung cancer

Will ceritinib prove to be a breakthrough therapy?

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in the United States, yet until recently it had no effective treatments. Now, however, by gaining a better understanding of the molecular biology of NSCLC, researchers have identified genetic subtypes that can be targeted with selected inhibitors. The Massachusetts General Hospital Cancer Center has led many of the studies and trials of first- and second-generation targeted therapies for specific NSCLC subtypes. The latest results concern NSCLCs driven by chromosomal rearrangements in the anaplastic lymphoma kinase (ALK) gene that have become resistant to the first-generation ALK inhibitor, crizotinib.

In a phase I trial, ceritinib caused marked tumor shrinkage in patients with advanced cancer who had developed resistance to crizotinib as well as in those who had received other treatments, according to Alice Shaw, MD, PhD, a thoracic oncologist at the Mass General Cancer Center and lead investigator of that trial. Trial results appeared in the March 27 New England Journal of Medicine, while the March 27 Cancer Discovery published a molecular analysis of the treatment. (continued on page 4)

PET scan showing response to ceritinib in ALK-rearranged non–small-cell lung cancer (NSCLC). Positron-emission tomographic scans taken at baseline (left) and after 3.5 weeks of ceritinib treatment (right) in a patient with crizotinib-resistant disease. Subsequent computed tomographic scans after six weeks of ceritinib treatment showed a 52 percent reduction in tumor burden.

Lung Tumor Shrinkage

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ALK CHROMOSOMAL REARRANGEMENT IN NSCLC
Chromosomal ALK rearrangements create a fusion protein with potent oncogenic properties. The resulting cancer cells, however, are highly sensitive to ALK inhibition. Following the 2007 discovery that about 5 percent of NSCLCs harbor ALK rearrangements, Mass General Cancer Center led a trial of the ALK inhibitor ceritinib specifically for NSCLC patients with ALK rearrangements 1. A 60 percent response rate led to U.S. Food and Drug Administration approval of the drug for this subset of patients in 2011, a treatment that is now the standard of care. Despite excellent initial responses, however, patients develop resistance to ceritinib and relapse in one to two years. Chemotherapy, the only other treatment option for patients with advanced NSCLC, has shown modest benefit.

To identify a potentially potent next-generation ALK inhibitor, Dr. Shaw teamed up with Jeffrey Engelman, MD, director of the Center for Thoracic Cancers at Mass General Cancer Center, and other colleagues to characterize the molecular nature of ceritinib resistance in cell lines and patient biopsies. Seven acquired mutations, together with ALK fusion gene amplification, accounted for about a third of the resistance cases. In another third, the tumors activated alternative signaling pathways, including EGFR (epidermal growth factor receptor) and c-KIT (a receptor tyrosine kinase that transmits growth signals into the cell). The resistance mechanisms for the remaining third of the cases are unknown.

Dr. Shaw’s team evaluated the efficacy of four investigational ALK inhibitors in cellular and animal models of ALK cancers with and without acquired ceritinib resistance. Ceritinib (LDK378, developed by Novartis Pharmaceuticals) proved the most potent and selective inhibitor. Ceritinib also suppressed downstream cancer-promoting pathways (PI3K/AKT, MEK/ERK, mTOR). In animal models, ceritinib induced a more durable response than ceritinib.

TRIAL RESULTS
The preclinical results provided a strong rationale for a multi-center phase 1 trial of ceritinib in patients with locally advanced or metastatic NSCLC, which was open to patients who had or had not previously been treated with ceritinib. The dose escalation phase of the trial enrolled 59 NSCLC patients and established a maximum tolerable dose of 750 mg/day of this oral drug. Side effects involved mainly gastrointestinal issues that resolved when treatment was reduced or stopped. Another 71 patients enrolled in an expansion phase to assess response rate and progression-free survival (PFS).

Among the 114 patients who received at least 400 mg/day, the overall response rate was 58 percent and the median PFS was seven months. Those results included patients with various resistance mechanisms and those with brain metastases. Response rates and PFS were better for patients who had not previously been treated with ceritinib. Because some patients are continuing to respond to ceritinib, data on overall survival are not available.

The positive responses to ceritinib among ceritinib-resistant NSCLC patients stand in contrast to the situation with EGFR-mutated cancers, in which fewer than 10 percent of patients with acquired resistance to first-line EGFR inhibitors respond to second-generation inhibitors.

Preliminary data from this trial led the FDA to give ceritinib a “breakthrough therapy” designation one year ago, and to grant accelerated approval to ceritinib in April 2014.

Dr. Shaw is also involved in two phase II clinical trials of ceritinib that have completed enrollment. There are also two ongoing phase III trials that are enrolling patients. Information about these “LDK378” trials is available on clinicaltrials.gov.

Can the genes of cancer cells unlock better treatments?

Brain cancer researchers face two difficult challenges that have hindered progress. One concerns the dearth of information about how to treat rare tumors with high morbidity or mortality, such as craniopharyngioma, which affects fewer than two in one million people per year. The second involves a lack of knowledge about how common cancers that have metastasized to the brain differ from the original primary tumors.

At the Massachusetts General Hospital Cancer Center, neuro-oncologist Priscilla Brastianos, MD, has developed new approaches to overcome both challenges.

FORMIDABLE CRANIOPHARYNGIOMAS

In 1939, Harvey Cushing, the father of neurosurgery, declared craniopharyngioma “the most formidable of intracranial tumors” because of the extreme sensitivity required to remove them surgically. The tumors wrap around structures at the base of the brain, including the pituitary gland, hypothalamus, cranial nerves, ventricular system, visual pathways and major blood vessels. The standard therapy (surgery, if possible, or radiation or both) itself can be debilitating.

Craniopharyngiomas are grouped into two subtypes reflecting tumor locations: the adamantinomatous form affects children and the papillary form occurs predominantly in adults. But researchers have not known whether the subtypes differ in their genetic mutations or just in their location or the patient age of onset.

Dr. Brastianos notes that it required “an amazing international collaborative effort” to collect sufficient tumor samples for (continued on page 6)