The current state of lung cancer treatment

December 11 2012

A review in the December issue of the journal *Archives of Pathology & Laboratory Medicine* by Paul Bunn Jr, MD, University of Colorado Cancer Center investigator and past president of ASCO, IASLC and AACI describes the current state of lung cancer care.

"We're in a new paradigm in which we realize this top cause of cancer deaths is actually a number of related diseases, each potentially with its own cause and cure," Bunn says.

The review describes the shift from blanketing lung cancer with radiation and chemotherapy, to targeting the specific genetic mutations that cause lung cancer's many varieties. The first of these oncogenic lung cancer mutations to be exploited by a drug was the epidermal growth factor receptor (EGFR), described in 2004 and targeted by the drugs erlotinib and gefitinib. Then in 2007 the oncogenic ALK/EML4 fusion protein was described, and is now targeted by the drug crizotinib, which earned FDA approval in 2011. Drugs in the development pipeline target a handful of additional lung-cancer-causing mutations including KRAS, HER2/neu, BRAF, NRAF, and ROS.

"Pathologists used to define lung cancer as one of four types, based on its appearance," Bunn says, "but it's much more heterogenous than that. Some of these driver mutations may only be present in 1 or 2 percent of the lung cancer population, and mutations in combination may make for hundreds of species of the disease, each with its own response characteristics to targeted drugs and drug combinations."

"Whole exome sequencing shows there are about 300 mutations in the average lung cancer," Bunn says. "You may have an EGFR mutation driving the cancer, but then the other 299 mutations may help define who will do well on an EGFR inhibitor."

Bunn points out that in the lung cancer varieties whose driver oncogenes can be matched with targeted therapy, we tend to see 70-80 percent patient response as opposed to 20-30 percent response to traditional chemotherapies, and with much reduced side effects.

But with this great promise of picking off cancer varieties one-by-one according to their oncogenes comes the challenge of testing drugs that are effective in perhaps only one of every 100 lung cancer patients. The challenge is twofold: enrolling enough patients on a clinical trial to make the results meaningful, and securing funding for a trial in which the drug will only be marketable to a small slice of the lung cancer population.

"How do you get drug approvals for what we'd normally call orphan diseases?" Bunn asks.

Then, Bunn points to the major challenge of staying ahead of lung cancer as it mutates in response to these targeted first-line drugs. "Targeted therapies don't cure patients yet," Bunn says. Instead, lung cancer eventually mutates around the drug's effectiveness. "And so we have to discover the most rational combinations and see if these combinations allow complete response," Bunn says.

In addition to therapies targeting oncogenes, Bunn describes completely new approaches to treating the disease, including Phase III clinical trials of lung cancer vaccines that aid the body's immune response against the cancer, and the search for ways to promote the function of tumor-suppressor genes that are commonly turned off in cancers.

What is clear is that after many years of chemotherapy and radiation, we're in the midst of an explosion in novel lung cancer treatment options.

"In the coming few years it is likely that we will identify additional 'actionable' molecular drivers treated with specific oral inhibitors," Bunn says. "We're already up to 30 or 40 percent of lung cancers that are susceptible to targeted therapies. I don't know if we'll reach 100 percent but the number is certain to grow."

Provided by University of Colorado Denver