MedicalXpress

New drug successfully treats crizotinib-resistant, ALK-positive lung cancer

March 26 2014

Although the targeted cancer treatment drug crizotinib is very effective in causing rapid regression of a particular form of lung cancer, patients' tumors inevitably become resistant to the drug. Now a new drug called ceritinib appears to be effective against advanced ALK-positive non-small cell lung cancer (NSCLC), both in tumors that have become resistant to crizotinib and in those never treated with the older drug. The results of a phase 1 clinical trial conducted at centers in 11 countries are reported in the March 27 *New England Journal of Medicine*.

"Crizotinib has become a standard treatment agent for patients with advanced, ALK-rearranged NSCLC, but patients invariably develop resistance, leaving their treatment options limited," says Alice Shaw, MD, PhD, of the Massachusetts General Hospital (MGH) Cancer Center, lead author of the report. "We found ceritinib to be highly effective in the majority of crizotinib-resistant patients, as well as those who had never received the drug, with mostly mild and manageable side effects."

NSCLC is the leading cause of cancer death in the U.S., and around 5 percent of cases are driven by mutations in the ALK gene, which lead to uncontrolled tumor growth. In 2011, crizotinib received accelerated approval to treat ALK-positive NSCLC, but as with other drugs directed against cancer-driving gene mutations, its effectiveness proved to be temporary. Laboratory studies indicated that ceritinib, which has a different molecular structure than crizotinib, could be as much as 20 times stronger; and animal studies suggested it would be effective against

both crizotinib-sensitive and crizotinib-resistant tumors. The current study was designed to assess the drug's safety and tolerability, along with giving a first look at its antitumor activity, in human patients.

The study's first phase was designed to determine the maximum tolerable dose of ceritinib and enrolled 59 NSCLC patients, who received escalating daily doses ranging from 50 to 750 mg. Adverse events – mostly gastrointestinal – were generally mild and resolved when treatment stopped or the dose was reduced. The second phase enrolled another 71 participants, eight of whom had other forms of cancer driven by ALK mutations, for a total of 130 participants in the overall study. Participants took daily oral doses of ceritinib as long as the drug was effective in suppressing tumor growth, with dosage levels being adjusted to reduce side effects.

As in trials of crizotinib, ceritinib produced often-dramatic shrinkage in the size and number of tumors in around 60 percent of study participants, with similar effectiveness in those who had and in those who had not previously been treated with crizotinib. But also as with the earlier drug, resistance to ceritinib developed for most patients after an average of around seven months. Patients whose tumors have kept responding to ceritinib treatments are still receiving the drug, some after two years.

Another MGH-led study published on-line in Cancer Discovery finds that ceritinib is able to overcome several known ALK mutations that confer crizotinib resistance and identifies two additional mutations that cause tumors to become resistant to both drugs. "These findings help us understand both the benefit and limitations of ceritinib and the need to develop ALK inhibitors that can overcome these more recalcitrant mutants," says Jeffrey Engelman, MD, PhD, of the MGH Cancer Center, senior author of both the Cancer Discovery and the *NEJM* papers.

Shaw explains that preliminary data from the *NEJM* study led to ceritinib's receiving 'breakthrough therapy' designation from the FDA last year. The drug's manufacturer, Novartis Pharmaceuticals, has applied for accelerated FDA approval based on results from this study. Shaw is the principal investigator for two phase 2 clinical trials that are now underway, and two phase 3 trials – one being offered at the MGH – are currently enrolling patients. Information on these trials is available by searching for LDK378 on http://www.clinicaltrials.gov.

Provided by Massachusetts General Hospital

Citation: New drug successfully treats crizotinib-resistant, ALK-positive lung cancer (2014, March 26) retrieved 24 April 2023 from https://medicalxpress.com/news/2014-03-drug-successfully-crizotinib-resistant-alk-positive-lung.html