With early, obvious benefit of a targeted cancer drug, should expensive clinical testing continue?

August 8 2013

Generally, FDA-approved clinical trials progress through three phases: the first shows safety, the second starts to explore effects and the third seeks to prove a drug's superiority over existing treatments. But when a drug's benefit is obvious in the first or second phase, is the third, costly phase needed? The question is posed in a recent edition of the journal *Nature Reviews: Clinical Oncology* by Robert C. Doebele, MD, PhD, investigator at the University of Colorado Cancer Center and assistant professor of medical oncology at the CU School of Medicine.

Doebele points out the example of the drug crizotinib, which is used to treat a subset of lung cancer patients with a specific gene mutation known as an ALK-EML4 rearrangement. For these "ALK+" patients, crizotinib can be extremely beneficial – both the phase I and phase II clinical trials of the drug showed dramatic response in the majority of ALK+ patients treated, even in those with advanced disease who had received prior chemotherapy. In light of these results, the FDA approved the drug in 2011.

But testing continued. Specifically, a phase III trial of crizotinib known as PROFILE 1007 screened 5,000 lung cancer patients and randomly assigned 347 ALK+ patients to treatment with crizotinib or chemotherapy. As everyone expected, crizotinib proved superior in this subset of ALK+ patients, with a progression-free survival of 7.7 months on crizotinib compared to 3 months on chemotherapy, and an overall

response rate of 65 percent on crizotinib compared to 20 percent for chemotherapy.

"The question is whether the phase III trial was needed at all," says Doebele.

In addition to continued testing requiring that some patients be randomly assigned to a treatment that most involved expect to be less effective, a phase III clinical test is hugely expensive. "This expense can deter some manufacturers from pursuing promising drugs," Doebele says. For example, imagine a strong candidate drug existed that targeted only 1-2 percent of lung cancer patients – knowing the expense of a phase III clinical trial, a drug sponsor may be unlikely to push for approval because the small, eventual market may not justify the cost of testing.

Such is the case for the gene ROS1, which is mutated in 1-to-2 percent of lung cancers. In a phase I clinical trial, lung cancer patients positive for ROS1 fusion showed responses to crizotinib that are nearly identical to those of ALK+ patients. Doebele argues that with genetics showing similarities in the cancer-causing abilities of ALK and ROS1 and with phase I results for crizotinib in the treatment of ROS1 lung cancer so closely matching results in ALK+ lung cancer, the bar for drug approval should be lower. Perhaps a phase II or III trial of crizotinib for ROS1 lung cancer is unneeded?

"This would put some of the burden of monitoring a drug's long-term effects onto clinicians," Doebele says, pointing out that a colleague at the CU Cancer Center noticed the side-effect of low testosterone in some crizotinib patients only after using the drug in clinical practice. "But it streamlines the approval process and gets drugs that are all but proven into the lives of patients who desperately need them."

If the science behind a drug shows it to be rationally targeted at a cancer-

causing genetic mutation, and if early clinical trials show the drug is safe and happens to be especially effective, should the drug be held to the same time-consuming and expensive testing standards of traditional chemotherapies? Or is the clinical trials process a relic from the time of earlier, highly toxic therapies? It's an open question.

Doebele writes that, "Targeted therapy for oncogene-positive lung cancer has been proven to induce remarkable tumor responses that are durable and have relatively few adverse effects. Therefore, it is imperative that we develop clinical trials that will accommodate this new paradigm and allow the expedient study and rapid approval of these therapies for patients with oncogene-positive lung cancer."

More information: www.nature.com/nrclinonc/journ … onc.2013.135.html#B1

Provided by University of Colorado Denver