TAK-733 shows challenge of using a promising drug in the human body

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Christopher Lieu, MD, and University of Colorado Cancer Center phase I clinical trials team show strong activity but challenging 'pharmacokinetics' of the new drug, TAK-733. Credit: CU Cancer Center

A University of Colorado Cancer Center study recently published online ahead of print in the journal *Oncotarget* reports "robust antitumor activity" of the drug TAK-733 in cells and mouse models of colorectal cancer. In all, 42 of 54 tested cell lines were sensitive to the drug, as were 15 of 20 tumors grown on mice from patient samples. Nine of these patient-derived tumors showed regression, meaning that tumor tumors shrank in response to the drug.

"This was a large preclinical study that showed good activity for the drug and gave preliminary evidence for a potential biomarker that could predict which tumors would respond best to the drug," says Christopher Lieu, MD, investigator at the CU Cancer Center and assistant professor of medical oncology at the University of Colorado School of Medicine.

Specifically, the drug intercedes in the MAPK signaling pathway, a cascade of cellular communication that controls cell growth and survival and is frequently altered in many cancers (especially including melanoma, non-small cell lung cancer, and colorectal cancer). The drug does this by silencing an essential link in this signaling chain, namely the molecule MEK. Without activity of the MEK kinase, MAPK signaling cannot occur and instead of surviving and proliferating, cancer cells dependent on this pathway die.

A handful of successful MEK kinase inhibitors exist, including trametinib and selumetinib.

"The preclinical results for TAK-733 were fairly impressive. We had high hopes that TAK-733 could be a next-generation MEK inhibitor that might support or replace the use of current drugs," Lieu says.

The study seemed a perfect precursor to a human clinical trial of TAK-733 in colorectal cancer.

"However, as dramatic as some of the responses were, the drug has had some challenges in development when used in the context of a real, human body," says Lieu.

Some promising cancer drugs are derailed by the existence of harmful side-effects. This is not necessarily the case for TAK-733. Instead, another necessary step for drugs seeking human clinical trials that could lead to approval is the consistency of the drug's "pharmacokinetics".

"When you give a patient 'x' amount of a drug, we need to know that 'y' amount of it will become bioavailable to cells," Lieu says.

In this study, it seemed as if the drug's path through the body was uneven. To Lieu's point, "x" amount of the drug did not always lead to "y" amount of absorption or bioavailability, nor to a specific process the body used to metabolize and excrete the drug.

In Lieu's opinion, targeting the MAPK signaling pathway in colorectal cancer remains extremely promising and doing so by silencing the MEK kinase remains an attractive target. In fact, Lieu hopes to push forward with research into possible uses of MEK inhibitors in combination with other targeted therapies for the treatment of colorectal cancer. However, as is so frequently the case in cancer science, the road from this drug's preclinical promise to its possible clinical success appears as if it will be longer and more winding than researchers hoped.

"It's not just the activity of a drug that matters, it's the safety and tolerability and bioavailability," Lieu says.

More information: Christopher H. Lieu et al. Antitumor activity of a potent MEK inhibitor, TAK-733, against colorectal cancer cell lines and patient derived xenografts, *Oncotarget* (2014). DOI: 10.18632/oncotarget.5949

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