Lung cancer patients with pockets of resistance prolong disease control by 'weeding the garden'

December 1 2012

The central skill of cancer is its ability to mutate – that's how it became cancerous in the first place. Once it's started down that path, it's not so difficult for a cancer cell to mutate again and again. This means that different tumors within a single patient or even different areas within the same cancerous deposit may develop different genetic characteristics. This heterogeneity helps cancer escape control by new, targeted cancer therapy drugs.

Two of these targeted drugs are crizotinib and erlotinib – they do wonders for the patients whose cancers depend on the basic mutations that these drugs exploit. That is, until pockets of the cancer mutate again, pivoting their dependence away from the original, targeted mutation. Due to continuing mutation, the unfortunate reality is that while crizotinib and erlotinib extend patients' lives, the drugs eventually, inevitably, inexorably stop working.

A University of Colorado Cancer Center study published in the December issue of the International Association for the Study of Lung Cancer's (IASLC) Journal of Thoracic Oncology shows that when pockets of resistant cancer develop, it's often possible to zap these resistant pockets with focused, targeted radiation while continuing crizotinib or erlotinib to maintain control of the majority of the disease that continues to depend on the primary mutation.

"We liken this to weeding the garden," says Andrew Weickhardt, MD, senior clinical fellow at the CU Cancer Center. "In nearly half of patients, when these drugs stop working, they stop working only in a limited number of sites. Given how well these people tolerate the medication, it made sense to us to treat these isolated spots with radiation (or in one case, surgery), and continue the same drug, which was obviously working elsewhere."

This study of 65 patients showed that continuing either crizotinib or erlotinib after the treatment of resistant pockets was associated with more than half a year of additional cancer control.

The benefit was especially robust when the metastatic lung cancer progressed in the brain. The brain is unfortunately a common site of progression because the molecules of crizotinib and erlotinib have difficulty in passing from the bloodstream into the brain, across the so-called blood-brain barrier. Cancer cells sit in the brain as in a robber's cave, hidden away from the drugs.

"We expect using radiation to zap these pockets of cancer in the brain, and then continuing the targeted therapy to become the standard of care," says CU Cancer Center investigator, Ross Camidge, MD, PhD, director of the thoracic oncology clinical program at University of Colorado Hospital.

There was also a smaller but still significant progression-free survival benefit for using this approach in patients whose cancers progressed first outside the brain.

If and when pockets of crizotinib- or erlotinib-resistant lung cancer are detected, "Clinicians should consider using radiation in the body and especially in the brain to weed the garden while continuing the drug, when there is good ongoing control of the cancer in other sites in the

body," Weickhardt says.

Provided by University of Colorado Denver