Early treatment with lorlatinib improves survival in some lung cancer patients

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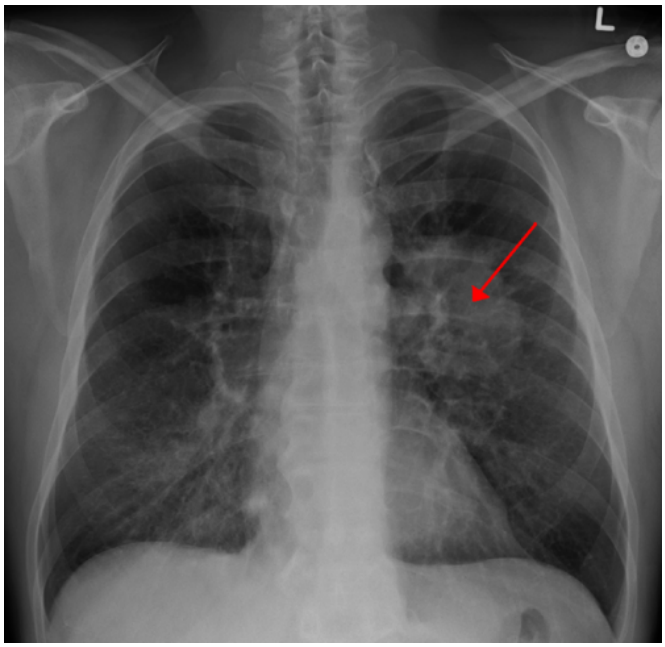

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Lung cancer patients with a specific genetic alteration lived longer and were protected against metastasis to the brain when treated early with the drug lorlatinib (Lorbrena), according to a study led by researchers at Massachusetts General Hospital (MGH), published in the *New England Journal of Medicine* (*NEJM*).

Non-small-cell lung cancer (NSCLC) accounts for 87% of all cases of lung cancer. Some 5% of NSCLC cases are ALK-positive, which means they have a genetic abnormality in the anaplastic lymphoma kinase gene. ALK-positive NSCLC, which is not associated with smoking, is a particularly aggressive form of lung cancer.

"When ALK is turned on abnormally, it's like stepping on the gas pedal—it drives uncontrolled proliferation and survival of cancer cells," says investigator Alice Shaw, MD, Ph.D., who was formerly director of the Center for Thoracic Cancers at MGH and led the NEJM study. Notably, ALK-positive patients tend to be 10 to 15 years younger than other lung cancer patients. They are also at high risk for developing brain metastasis.

A new class of drugs that block ALK, known as ALK inhibitors, was discovered in 2008. "Turning off ALK with an ALK inhibitor is like putting on the brakes," agrees Justin Gainor, MD, of the Mass General Cancer Center, who worked with Shaw on the study. "It can lead to rapid killing of cancer cells and cause tumors to shrink dramatically." Both first and second generation ALK inhibitors have been developed, including crizotinib (Xalkori), alectinib (Alecensa), and brigatinib (Alunbrig), which can be very effective, but patients eventually relapse. What's more, patients treated with these drugs can still develop metastatic spread of cancer to the brain.

Lorlatinib belongs to a third-generation of this drug class and is even more effective at blocking ALK. It's currently approved by the Food and Drug Administration for treating ALK-positive patients whose cancer has progressed despite taking older-generation ALK inhibitors.

Shaw and her co-investigators wanted to know if lorlatinib improved the likelihood of long-term remission in ALK-positive patients when administered as first-line therapy. To find out, she and colleagues at 104 medical centers in 23 countries recruited 296 patients with advanced, previously untreated ALK-positive NSCLC. Half of the patients received lorlatinib, while the remainder were treated with crizotinib, which was the standard of care for these patients when the trial began.

The results were striking. Compared to patients who received crizotinib, those given lorlatinib had a 72% reduction in the risk of cancer progression or

death. Importantly, lorlatinib also reduced the risk of new or recurrent brain metastases by 93%. Serious side effects were more common in the lorlatinib group, but more than half were increases in blood cholesterol and triglycerides, which were manageable with medication.

The investigators will continue to follow patients in this study to track their long-term outcomes, but "these results support lorlatinib as a potential first-line option for ALK-positive patients," says Shaw.

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