Intratumoral heterogeneity may be responsible for chemotherapy resistance in patients with small cell lung cancer

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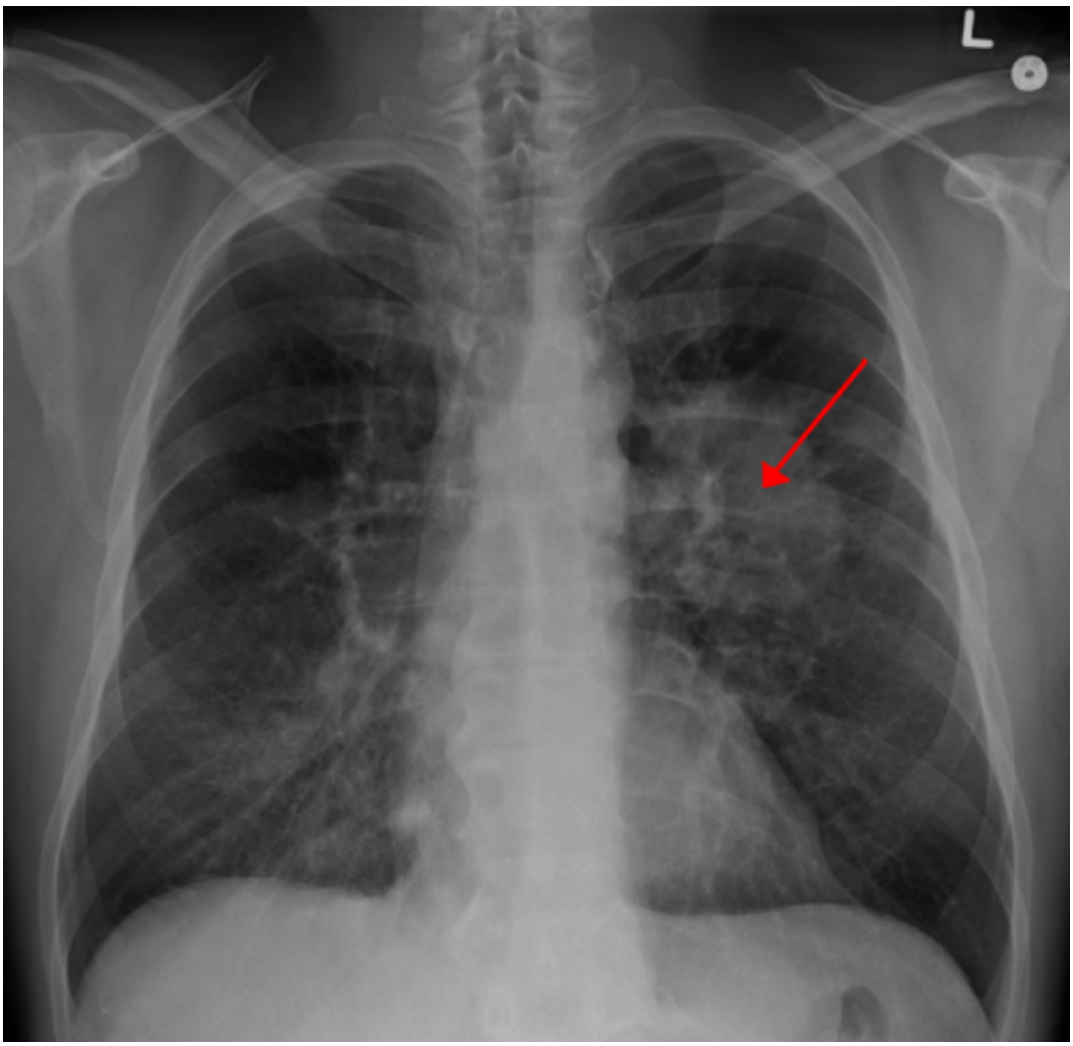

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Small cell lung cancer (SCLC) accounts for 14% of all lung cancers and is often rapidly resistant to chemotherapy, resulting in poor clinical outcomes. Treatment has changed little for decades, but a study at The University of Texas MD Anderson Cancer Center found that chemotherapy results in increased heterogeneity within the tumor, leading to the evolution of multiple resistance mechanisms.

The research team, led by Lauren Averett Byers, M.D., associate professor of Thoracic/Head & Neck Medical Oncology, published their findings today in *Nature Cancer*. Early results were presented at the American Association for Cancer Research Annual Meeting 2018 in Chicago.

"There have been few therapeutic advances in the past 30 years, and platinum-based chemotherapy remains the backbone of the standard of care. As a result, five-year survival is less than 7% across all stages," Byers said. "Most patients respond well to platinum chemotherapy initially, but relapse within a few months. There are no highly effective second-line therapies when the tumor recurs."

The team found that after treatment, SCLC tumors rapidly evolve. Before treatment, SCLC is largely homogenous, with the same type of cells found throughout the tumor. Within weeks to months of treatment, many new and different types of cells appear; this diversity within the tumor is called intratumoral heterogeneity.

"Because you end up with a cancer that has multiple resistance mechanisms turned on at the same time in different cells, the cancer becomes much harder to treat," Byers said. "Some cells might be resistant through one mechanism or pathway, and other cells might be resistant through a different one. Treatment targeting one type of resistance will only kill a subset of cancer cells."

A novel method

One challenge in studying why and how SCLC chemoresistance occurs is due to the fact that biopsy or surgery isn't required to confirm cancer recurrence for most patients. This leaves investigators with few SCLC samples with which to conduct genomic and biomarker analyses of drug-resistant tumors.

To overcome the lack of recurrent SCLC samples, the team developed novel disease models by isolating circulating tumor cells (CTCs) from a simple blood draw. The cells, placed under the mouse's skin, develop tumors representative of the patient from whom they were derived. These SCLC models, called circulating tumor cell-derived xenografts (CDX), are unique to each patient and provide an opportunity to assess treatment response to therapy, as well as changes that may occur after therapy.

The investigators performed single-cell RNA sequencing on 14 CDX models to identify gene expression differences between individual cells from chemotherapy-sensitive CDX tumors compared to those that remain resistant. They also performed single-cell sequencing directly on circulating tumor cells retrieved from one patient before treatment, during treatment and after relapse.

"To our knowledge, this is the first time in solid tumors that this type of approach has been applied directly to patient blood samples with RNA sequencing analysis of individual circulating tumor cells," Byers said. "We looked at the tumor model grown from the same patient at the single-cell level before and after treatment, and we saw the same cell diversity in the circulating tumor cells from the patient."

Clinical implications and future research

Byers' lab is beginning to study what causes SCLC to evolve and develop intratumoral heterogeneity to see if the evolution can be stopped or prevented. Clinically, they hope to investigate aggressive early treatment approaches that bring new drugs to patients in the maintenance phase of treatment, before their cancer comes back. Currently, most clinical trials for SCLC enroll patients after their tumor recurs and has become chemoresistant.

"If you look at a lot of the available treatments for relapsed small cell lung cancer, it's really a minority of patients where you see any response—this study may explain why," Byers said. "The next step is to design trials that get drugs to patients earlier, before the cancer has a chance to evolve and become more complex and harder to treat."

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