Drugs create balancing act for patients with non-small cell lung cancer

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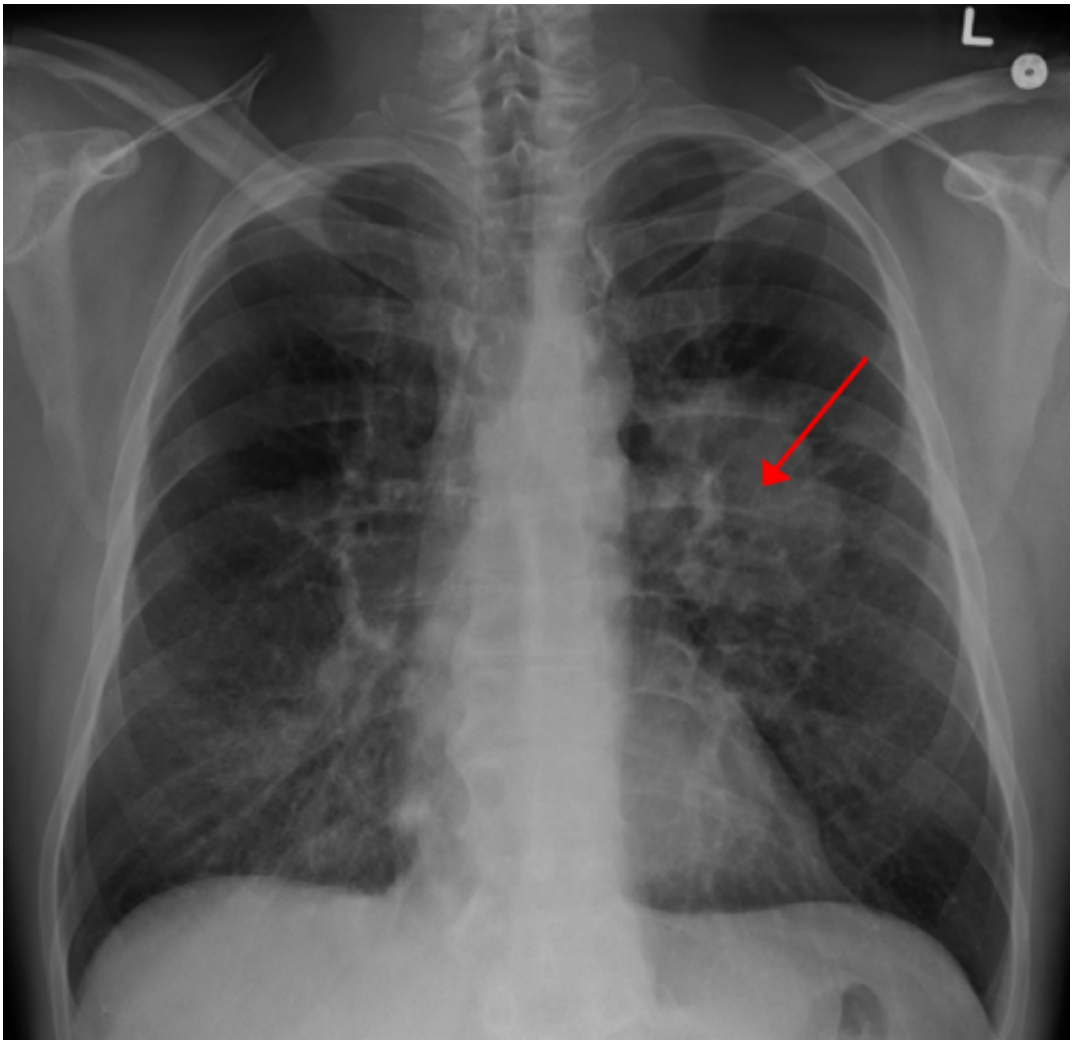

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

The results of a large, retrospective study of patients who received a form of immunotherapy for non-small cell lung cancer (NSCLC) revealed that patients may get more than one immune-related side effect, and identified a correlation between these multisystem immune-related adverse events (irAEs) and improved patient survival. In fact, patients who developed two irAEs did better, in terms of delaying the time to cancer progression and overall survival, than those who developed only one irAE. According to the researchers, this new information will be helpful in discussing with patients the spectrum of immune side effects that may occur from immunotherapy and the implications for their survival.

The findings were published online Oct. 29 in the journal *JAMA Oncology*.

The researchers analyzed data from 623 patients with NSCLC from five academic medical centers: The Johns Hopkins Hospital, Baltimore, Maryland; East Carolina University, Greenville, North Carolina; the Ohio State University-James Comprehensive Cancer Center, Columbus, Ohio; the University of Perugia, Perugia, Italy; and Sendai Kousei Hospital, Miyagi, Japan.

Patients diagnosed with stage III/IV NSCLC and treated with anti-PD-1/anti-PD-L1 immune checkpoint inhibitors (alone or in combination with other treatments) between January 2007 and January 2019 were included in the study. Of the 623 participants, 148 (24%) developed a single irAE. The most common four irAEs were inflammation of either the lungs, thyroid, liver or skin (pneumonitis, thyroiditis, hepatitis and dermatitis, respectively). Fifty-eight patients (9.3%) sequentially developed two single-organ irAEs, dubbed "multisystem irAEs." Patients with higher health scores—in the best overall health—who were treated with immune checkpoint inhibitors tended to be treated for a longer period of time, and were more likely to

develop multisystem irAEs.

"While it makes sense that people who are fitter may be treated longer and have a higher risk of irAEs, this study accounted for treatment duration, and the association between irAEs and survival remains statistically robust," says Jarushka Naidoo, M.B.B.Ch., an adjunct professor at the Johns Hopkins Kimmel Cancer Center and a Bloomberg~Kimmel Institute for Cancer Immunotherapy investigator. Naidoo was an assistant professor of oncology at the time of the study.

The higher risk seems to come with a benefit, as patients showed incrementally improved survival outcomes based on the number of irAEs they developed. Those with no irAEs lived a median of 8.7 months after diagnosis versus 12.3 months and 21.8 months for those with one or two irAEs, respectively. A similar trend was seen in patients' progression-free survival (PFS) time, which is the time from diagnosis until tumor growth as seen on a CT scan. The median PFS for those with no irAEs was 2.8 months versus 5.1 months and 10.9 months for those with one and two irAEs, respectively.

Immunotherapy is a relatively new type of drug therapy that targets the interactions between cancer cells and cells from the immune system, causing immune cells to kill cancer cells. A subset of these drugs is called immune checkpoint inhibitors. These drugs bind to specific molecules—in this study, PD-1 and PD-L1—found on the surface of cancer cells. When PD-1 and PD-L1 connect with receptor molecules on immune cells, the immune cell response to the cancer is shut down. Anti-PD-1/PD-L1 immune checkpoint inhibitors break the communication between PD-1 and PD-L1, reigniting the immune response against the cancer.

Immune checkpoint inhibitors generally have fewer side effects than standard chemotherapeutic drugs, but a subset of patients develop irAEs,

which can be complicated and difficult to manage, the researchers report. Since immune checkpoint inhibitors work by temporarily releasing the brakes on the immune system, this heightened immune response can sometimes cause an attack on healthy organs and tissue.

"IrAEs are tricky because they are characteristically unpredictable. They can develop within days—but also after many years of treatment, so patients and oncologists have to always be on the lookout for symptoms," says Naidoo. They usually respond well to steroids, but can occasionally become chronic and even be fatal, she says. "At the Kimmel Cancer Center, we started noticing that some patients developed multiple irAEs, so I thought we might learn something helpful by characterizing them, seeing what patterns might exist and the implications on survival," she says.

The incidence of severe immune side effects depends on the type of immunotherapy received or what it combined with, and may be as low as about 5%-10% in patients receiving a single immune checkpoint inhibitor or as high as 35%-40% in those who receive a combination, says Naidoo. "We know that the outcome for most advanced cancers is poor, so the balance usually favors treatment with immune checkpoint inhibitors. However, it is important for patients to be aware of immune side effects, that they may experience multiple immune side effects, and the implications on survival," Naidoo says.

NSCLC is the most common type of lung cancer, comprising 80% of cases. It is also the most common cancer in men and the leading cause of cancer deaths in men and women worldwide. Naidoo says that, until five or six years ago, the average survival for those diagnosed with NSCLC was about one year. Two new treatment options—targeted therapy and immunotherapy—have led to dramatic improvements in survival for the patients in whom these treatments are effective.

More information: Bairavi Shankar et al. Multisystem Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors for Treatment of Non–Small Cell Lung Cancer, *JAMA Oncology* (2020). DOI: 10.1001/jamaoncol.2020.5012