Uncovering Why Cancer Immunotherapy Leads to Heart Inflammation

Immune checkpoint inhibitors—especially a new combo treatment—are linked to rare cardiac issues. UCSF researchers explore the cause.

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Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by using a patient's own T-cells to target tumors. However, they can cause rare but potentially fatal cardiac inflammation known as ICI-myocarditis. This is particularly true in the most recent ICI combination treatment, according to new research.

In a study led by UC San Francisco researchers that published January 7 in Circulation, the researchers found that anti-LAG-3/anti-PD-1 combination therapy shows a higher risk of myocarditis compared to other ICI treatments.

Using Vigibase, a pharmacovigilance database, the team first determined that anti-LAG-3/anti-PD-1 therapy increased the risk of ICI myocarditis four-fold in human patients compared to anti-PD-1 therapy alone. Investigating further using mice with anti-LAG-3/anti-PD-1 myocarditis, the researchers saw that the resulting severe cardiac inflammation was associated with spontaneous arrhythmias.

Importantly, in mice with anti-LAG-3/anti-PD-1 myocarditis, researchers discovered that the cardiac T-cells expressed CXCR6, a protein that directs cell movement and regulates immune responses and inflammation. By targeting CXCR6 with an antibody, researchers were able to reduce cardiac inflammation and spontaneous arrhythmias. With this new knowledge, the researchers turned back to patients. Using available patient data, they were able to show CXCR6 T-cells also increased in the hearts of patients who developed ICI-myocarditis — meaning CXCR6 could be a possible target for treatment.

"These data are particularly exciting and help us understand the signals that recruit and position T-cells in the heart," said study co-first and co-corresponding author Amir Munir, MD, a cardiologist and instructor in the UCSF Section of Cardio-Oncology and Immunology. "The results help define the specific type of cardiac T-cells that lead to myocarditis and may serve as a potential therapeutic target for treating ICI-myocarditis in the future."

Munir adds that while the investigators studied ICI-myocarditis in the current study, it is possible that this same T-cell population may drive other forms of cardiac inflammation. “An important next question to address will be understanding the role CXCR6 T-cells in anti-tumor immunity, especially if we think this could be a possible therapeutic option for patients with ICI myocarditis,” said Munir.

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