Studies show how to boost immunotherapy effectiveness for patients with oral-cavity squamous cell carcinoma

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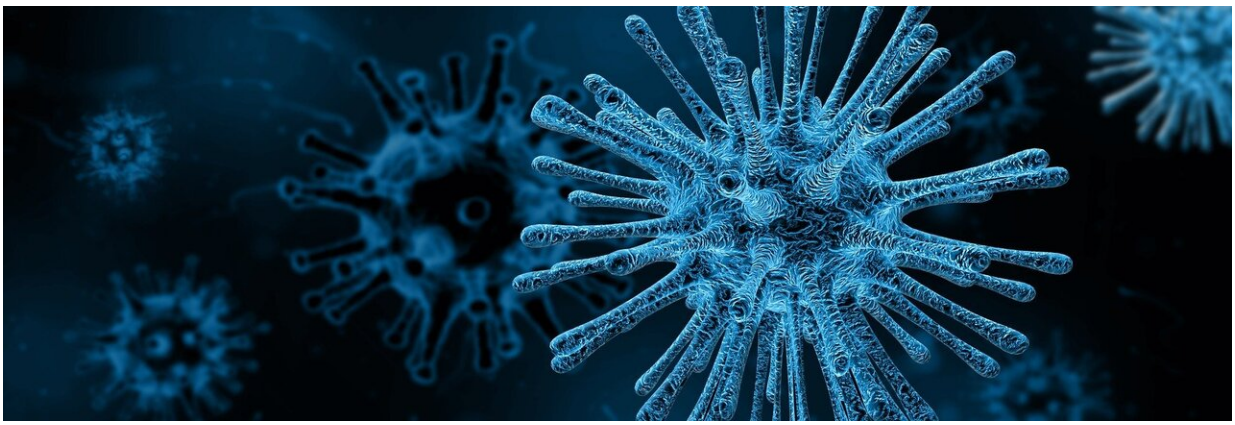

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Two new studies revealed that anti-PD-1 immunotherapy given before surgery was safe and effective for patients with oral-cavity squamous cell carcinoma (OCSCC) and identified potential molecular biomarkers in the blood and tumors of patients that would show how likely it is that someone would respond to immunotherapy.

The studies, recently published in *Cell Reports Medicine*, were a collaborative effort between MUSC Hollings Cancer Center, UCLA Jonsson Comprehensive Cancer Center and Winship Cancer Institute of

Emory University. Due to the highly invasive and resistant nature of OCSCC, researchers looked to anti-PD-1 immune checkpoint inhibitors to improve outcomes as this type of immunotherapy has revolutionized the way patients with advanced malignancies are treated.

OCSCC, a subset of head and neck cancer, is prevalent in South Carolina due to the history of tobacco use. These cancers oftentimes require complicated surgeries that may be disfiguring, as treatment may involve removing all or a portion of the jawbone and tongue. David Neskey, M.D., a Hollings head and neck cancer specialist and co-senior author of the studies, said 50% of these patients will have a recurrence, and only 60% of patients are alive five years later.

"This cancer can impact a patient's ability to talk and breathe," Neskey said. "It can impact a patient's ability to go out to a restaurant or socialize with friends and family. It's one of the reasons so many head and neck cancer doctors are seeking ways to improve outcomes for these patients."

Leveraging the immune system

The researchers' studies were based on a phase two clinical trial of nivolumab, an anti-PD-1 antibody, that was given to 12 patients in South Carolina with stage 2 to stage 4A OCSCC, prior to surgery. Patients were evaluated by how their tumors responded to treatment. Patients who responded to treatment that caused their tumors to shrink were given the antibody four times every two weeks, before surgery. Those patients who didn't show a response went directly to surgery.

Of the patients who took part in the study, Neskey said four showed a positive response to treatment, four had stable disease and four had a disease that progressed. The results demonstrated feasibility and safety for the incorporation of nivolumab in a neoadjuvant setting for OCSCC

patients. Neoadjuvant treatment, such as chemotherapy, radiation therapy and hormone therapy, is often used prior to the main treatment, like surgery, to increase the likelihood of success.

"What was really interesting was that for patients who were responding to treatment, we almost always saw the response within the first two antibody doses," Neskey said. "That told us that the additional two doses, which prolonged the patient from getting surgery, may not be necessary."

Researchers compared the effectiveness of programmed death 1 (PD-1) blockade immunotherapy given prior to surgery against traditional chemotherapy. PD-1 and PD-L1 are part of the immune checkpoint pathway that suppresses the response of T-cells in the immune system. Neskey said some cancer patients with OCSCC have tumors that express PD-L1, which communicates and binds with PD-1 proteins to prevent the immune system from attacking it. By blocking this interaction between PD-1 and PD-L1 by using immunotherapy, Neskey said the immune system would be able to recognize the tumor correctly as foreign and attack it.

John Kaczmar, M.D., a Hollings medical oncologist who oversaw the antibody treatments in the study, said he was pleased with the response some patients had. He believes that immunotherapy is the future for head and neck cancer treatment as well as other cancers. Unlike chemotherapy that attacks rapidly dividing cells, whether they are cancerous or not, immunotherapy can be targeted to kill the tumor itself without having dramatic impacts on healthy cells.

"This study isn't the be-all, end-all. Thirty three percent of patients responding well to treatment isn't good enough for us," Kaczmar said. "We need to keep finding ways to improve treatment so more patients can benefit and have better outcomes."

Kaczmar said the study does lay important groundwork for future studies to build off of to develop a treatment regimen that will work for more patients and improve overall survival rates. "One of the benefits of a study like this is that we have tissue samples from patients to do further research afterward to determine why some responded and others didn't."

Finding biomarkers

Following the completion of the clinical trial in April of 2020, researchers began a correlative study to explore the mechanism of response patterns, survival and post-operative recurrence by analyzing blood and tumor tissue that were collected from patients over the course of the clinical trial and during follow-up, if and when patients relapsed.

The researchers used omic, disciplines with the '-omics' suffix—like genomics—and multiplex molecular tools to analyze the tissues deeply to discover markers associated with favorable or unfavorable outcomes. By making large-scale measurements longitudinally, the team was able to track immune and tumor cell co-evolution.

Researchers detected biomarkers at three points in time: before neoadjuvant anti-PD-1 therapy; after neoadjuvant anti-PD-1 therapy; and after surgery, if and when patients relapsed. They uncovered potential biomarkers in the blood and in the tumors that indicate the types of T-cells present and genetic changes inside the tumors.

Inside the tumors, they identified mutations in specific genes, such as CDKN2A, FLT4 and YAP1, which can explain either initial tumor response patterns or post-surgical relapses. In the blood before treatment, researchers found a high ratio of two distinct T-cell types, regulatory T-cells and Th17 cells, associated with a lack of tumor response. The researchers also found that tumor shrinkage elicited by neoadjuvant anti-PD-1 therapy tracks with not only clonal proliferation

of T-cells after treatment but proliferation of specifically those T-cells that were present before treatment.

Roger Lo, M.D., Ph.D., a researcher with the UCLA Jonsson Comprehensive Cancer Center and a senior co-author of the correlative study, said this type of immunotherapy allows doctors to target a patient's cancer more effectively.

"The studies open a new way to help improve precision management of patients with resectable oral-cavity squamous cell carcinoma, a subset of mostly HPV-negative head and neck cancers that tend to have a far worse prognosis compared to HPV-positive head and neck cancers," Lo said. "If we can intervene more effectively earlier in the natural history when the disease is still amenable to surgery, then we have a chance of improving survival or the prognosis of this disease."

Kaczmar said a larger study is needed to examine the impacts of tailored immunotherapy treatment for head and neck cancer patients. However, he is optimistic that this study will help to further Hollings' mission to reduce the burden of cancer in South Carolina.

"We have a lot of patients who are smokers, so we see this type of cancer here at Hollings. If we can help our patients, then we prove we can help the state as a whole, and that is really the mission at MUSC—to improve the health of people in South Carolina."

More information: Sixue Liu et al, Response and recurrence correlates in individuals treated with neoadjuvant anti-PD-1 therapy for resectable oral cavity squamous cell carcinoma, *Cell Reports Medicine* (2021). DOI: 10.1016/j.xcrm.2021.100411

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