MedicalXpress

Immune analysis of on-treatment longitudinal biopsies predicts response to melanoma immunotherapy

August 10 2016

Immune response measured in tumor biopsies during the course of early treatment predicts which melanoma patients will benefit from specific immune checkpoint blockade drugs, researchers at The University of Texas MD Anderson Cancer Center report in the journal *Cancer Discovery*.

Analysis of biopsies before treatment did not indicate who would respond in this unique longitudinal study of 53 melanoma patients treated with two immune checkpoint inhibitors between October 2011 and March 2015.

"Before treatment, analyzing samples with a 12-marker immune panel or a 795-gene expression panel, you can't tell who will respond with any degree of certainty. On treatment, there were night-and-day differences between responders and non-responders," said study senior author Jennifer Wargo, M.D., associate professor of Genomic Medicine and Surgical Oncology.

Their findings, if confirmed in larger studies, could help guide treatment with drugs that block PD-1, a protein on T cells that shuts down those specialized immune system attack cells. PD-1 inhibitors, and another drug that blocks a protein called CTLA-4, remove separate brakes on T cells, unleashing the immune system to attack cancer.

Response rates range from 8 to 44 percent of patients given the drugs separately, with many having complete responses that last for years. Identifying biomarkers to help determine who should receive these drugs has been the subject of much research, but the team noted that biomarkers have not strongly or exclusively predicted response.

Their research suggests that assessment of adaptive immune responses should be considered in early on-treatment biopsies after initiation of therapy, Wargo said, and may provide far more value than analysis of pretreatment samples, at least until better pre-treatment biomarkers are identified.

The study is part of MD Anderson's Cancer Moon Shots Program, designed to reduce cancer deaths by accelerating the development of new approaches based on scientific discoveries. This project of the Melanoma Moon Shot demonstrates the approach of the Adaptive Patient-Oriented Longitudinal Learning and Optimization (APOLLO) platform, which uses serial biopsies and deep molecular analyses (See sidebar) to understand tumor response to treatment.

Serial biopsies identify signature of success

The researchers assembled a cohort of longitudinal tumor samples from patients and analyzed each biopsy for gene expression and the presence of certain types of T cell and protein markers such as expression of PD-1 and PD-L1, the ligand found on tumor and other cells that activates PD-1.

Patients were treated with the CTLA-4 inhibitor ipilimumab (Yervoy). Biopsies followed, when feasible, after the second or third treatment and at progression. Seven (13 percent) of 53 patients had a clinical benefit, defined as either absence of disease, tumor shrinkage or stable disease for at least six months.

There were no immune biomarker differences between responders and non-responders before treatment. After treatment began, the presence of killer T cells was significantly higher in the tumors of responders.

The remaining 46 patients proceeded to treatment with the PD-1 inhibitor pembroluzimab (Keytruda). Thirteen (28 percent) of the 46 responded. Before treatment, three immune markers were slightly elevated in responders compared to non-responders, but values overlapped the two groups.

T cells in tumor and checkpoint molecules tell the tale

"Profound and highly statistically significant" differences between responders and non-responders were found in nearly all of the 12 immune markers in the early anti-PD1 on-treatment biopsies. These included the density in the tumor of killer CD8 T cells, CD4 helper T cells, and CD3 T cells that also assist killer cells, as well as the presence of PD-1, PD-L1 and the immune checkpoint molecule LAG-3.

In this study, tumor samples were collected when technically feasible and safe to perform at multiple time points after written informed consent was obtained under IRB-approved protocols. For example, for those undergoing anti-PD1 treatment, 24 patients had pretreatment biopsies (seven responders, 17 non-responders), 11 had on-treatment biopsies (five responders, six non-responders) and 12 provided tumor samples at progression.

The team's findings have implications for treatment and further research to understand how melanoma responds to or resists treatment. "We could start by treating with anti-PD1, do an early on-treatment biopsy and, based on that, either continue or add ipilimumab or another agent," Wargo said.

Such a strategy has the potential to more accurately apply these drugs to patients who will benefit and avoid the cost and potential side effects for patients who won't benefit and need alternative therapies.

Immune response analysis was conducted by the moon shots Immunotherapy Platform, led by Jim Allison, Ph.D., chair of Immunology and executive director of the platform, and Padmanee Sharma, M.D., Ph.D., scientific director and professor of Immunology and Genitourinary Medical Oncology. Allison invented immune checkpoint blockade as a potential cancer treatment and was honored with the 2015 Lasker-DeBakey Clinical Medical Research Award for his pioneering work.

Gene profiling identifies resistance mechanisms

As with the immune profiling, the gene expression panel turned up significant differences between responders and non-responders only at the on-treatment biopsy for anti-PD1. Significant differences were found in 411 differentially expressed genes in responders.

Most differences involved increased expression in the responding patients of genes involved in immune response. Only six genes were lower in responders, including the vascular endothelial growth factor (VEGFA), which is involved in the generation of new blood vessels, or angiogenesis.

This suggests a targetable mechanism for resistance to treatment, Wargo said, which is consistent with findings by others. Anti-PD1 therapy is being tested with VEGF inhibitors in clinical trials now.

Potential mechanisms of therapeutic resistance to PD-1 based therapy were also identified through defects in interferon signaling and altered antigen processing and presentation - essentially allowing tumors to

"hide" from killer T cells. Another paper will more fully report genomic results.

Provided by University of Texas M. D. Anderson Cancer Center