A serum biomarker may predict response to immunotherapy drugs that target immune checkpoints

December 22 2016

Serum levels of ANGPT2, a protein related to angiogenesis (blood vessel formation), was found to predict response to and influence the outcomes of treatment with a class of immunotherapeutics called immune checkpoint inhibitors in patients with advanced melanoma, according to a study published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research.

Immune checkpoint inhibitors are a type of drugs that block certain proteins in order to release the "brakes" on certain immune cells, enabling them to attack the cancer cells.

The study found that ANGPT2 may also serve as a target for combination therapies of inhibitors of immune checkpoint and angiogenesis.

"In this study, we found ANGPT2 to be a predictive and prognostic biomarker of response to the inhibitors of immune checkpoints CTLA-4 and PD-1," said F. Stephen Hodi, MD, director of the Melanoma Center at Dana-Farber Cancer Institute, professor of medicine and investigator at the Ludwig Center at Harvard Medical School in Boston. "We found additional evidence suggesting a role for angiogenic fators in immune regulation and the possibility of targeting the immune system and angiogenic factors with combinations in the treatmtent of cancer."

Specific aspects of tumor cells, immune cells, and other components of the tumor microenvironment contribute to the complexity of the biology of cancer, which make identifying tissue biomarkers that can predict response to immune checkpoint inhibitors a huge challenge, Hodi explained. One way to tackle this is by identifying serum biomarkers that can be measured and monitored with ease, he said.

In this study, Hodi and colleagues studied the role of the angiogenic factor ANGPT2 in immune regulation and its potential role as a biomarker for immune checkpoint inhibitors. ANGPT2 is a regulator of blood vessel maturation and enables angiogenesis. In prior studies, this protein was associated with resistance to treatment with bevacizumab (Avastin), an antibody therapeutic that targets another angiogenesis factor, VEGF.

The investigators studied serum samples collected before and within three months of treatment initiation from 48, 43, and 43 patients with advanced melanoma treated with the anti-CTLA-4 antibody ipilimumab (Yervoy), ipilimumab plus bevacizumab, and an anti-PD1 therapeutic (nivolumab [Opdivo] or pembrolizumab [Keytruda]), respectively. Patients were from three different clinical trials in which survival data were available.

About 17, 20, and 37 percent of the patients in the three studies had complete or partial responses, and the median follow-up time for all of them combined was 33 months.

The researchers found that among patients treated with ipilimumab alone, the median overall survival (OS) in those with high versus low levels of pretreatment serum ANGPT2 was 12.2 months and 28.2 months, respectively. In those treated with ipilimumab plus bevacizumab, the median OS was 10.9 versus 19.3 months.

In patients treated with an anti-PD1, the median OS was 7.3 months among those with high pretreatment ANGPT2; median OS had not yet been reached in those from the low-group as more than half of the patients were alive at the time of this report.

In order to understand how changes in serum ANGPT2 levels with treatment influenced clinical outcomes, the researchers computed the fold change of the protein levels before and during treatment and found that in patients who received ipilimumab alone, those with ANGPT2 levels below and above the fold-change cutoff of 1.25 had OS of 12.4 and 28.1 months, respectively. They made similar observations in patients from the ipilimumab plus bevacizumab study, but the difference was not statistically significant.

All patients in these two studies whose ANGPT2 levels increased by at least 25 percent either had stable or progressive disease, except for one patient who had a partial response.

When the investigators combined the data from patients in the three groups, those with high pretreatment ANGPT2 levels and large fold changes had the worst survival, and those with low pretreatment protein levels and small fold changes had the best survival. Patients with high pretreatment ANGPT2 levels and small fold changes and those with low pretreatment ANGPT2 levels and large fold changes had intermediate survival. This correlation between the dynamic ANGPT2 levels and survival consolidates the role of this protein as a prognostic biomarker.

In order to understand the mechanism by which ANGPT2 influences clinical outcomes, the investigators conducted laboratory-based tests using a specific subset of macrophages (a type of immune cells) that are present in the tumor microenvironment and found that ANGPT2 increased the expression of PD-L1 on these cells. PD-L1 is a protein that plays a role in immune suppression, and some immune checkpoint

inhibitors target the PD-1/PD-L1 axis.

"These in vitro studies suggested that angiogenic factors not only play a role in blood vessel formation in tumors but also have immune-regulatory effects; therefore, therapeutics that inhibit angiogenesis could synergize with immune checkpoint blockade," Hodi said. "We would, however, like to confirm the findings from this study in a larger patient population in the future," he added.

The investigators are conducting a phase I trial testing a combination of tremelimumab (another anti-CTLA-4 agent) and an ANGPT2 antibody in patients with advanced melanoma.

Limitations include modest sample size and the retrospective nature of the study, Hodi noted.

More information: X. Wu et al. Angiopoietin-2 as a Biomarker and Target for Immune Checkpoint Therapy, *Cancer Immunology Research* (2016). DOI: 10.1158/2326-6066.CIR-16-0206

Provided by American Association for Cancer Research