New combo of immunotherapy drugs is safe, shrinks tumors in metastatic melanoma patients

20 April 2015

Once again, researchers at Penn's Abramson Cancer Center have extended the reach of the immune system in the fight against metastatic melanoma, this time by combining the checkpoint inhibitor tremelimumab with an anti-CD40 monoclonal antibody drug. The first-of-its-kind study found the dual treatments to be safe and elicit a clinical response in patients, according to new results from a phase I trial to be presented at the AACR Annual Meeting 2015 on Sunday, April 19.

Researchers include first author David L. Bajor, MD, instructor of Medicine in the division of Hematology/Oncology, and senior author Robert H. Vonderheide, MD, DPhil the Hanna Wise Professor in Cancer Research.

"We've had wonderful success with immunotherapies, but we are barely scratching the surface," Bajor said. "Checkpoint inhibitors are just the beginning. When they are thoughtfully combined with immune-stimulating compounds like CD40 or drugs targeting other facets of the immune system we hope to be able to increase the response rate to previously approved therapies."

Known as a checkpoint inhibitor, tremelimumab is an investigational monoclonal antibody that "cuts the brakes" of the immune system by targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), a protein that can switch off a patient's immune response. Anti-CD40 drugs (in this trial, CP-870,893) antagonize the CD40 receptor, and effectively "push the gas" on the immune system to make it work harder.

Today, new immunotherapy drugs have shown great promise in melanoma, but many patients fail to respond, underscoring the need to further improve the drugs' abilities. There have been trials investigating the CTLA4 and CD40 pathways separately, but none have targeted melanoma with both of these agents simultaneously.

For the new study, researchers enrolled 24 patients with metastatic melanoma who had never been treated with either drug nor any CTLA-4 or PD-1/PD-L1 inhibitor. Patients received doses of tremelimumab every 12 weeks and doses of anti-CD40 every three weeks. They were followed for side effects continuously, and response was evaluated every three months.

After a median follow-up of 22 months, the team found that the drugs were safe and shrank tumors in a subset of patients, with an overall response rate of 27 percent, which included complete responses in two patients and partial responses in four patients. The median progression-free survival was 2.5 months and the median overall survival was 26.1 months.

"There was clear, clinical evidence of response to this combination, even in some patients with highly morbid, visceral disease," Bajor said. There was concern that stimulating the immune system while "cutting the brakes" with checkpoint inhibition could lead to increased incidence or severity of side effects, but that was not the case.

The researchers also analyzed specific immune cells called cytotoxic T cells isolated from the patients' blood and found increases in biomarkers indicative of immune activation.

However, there was still a dampening of the immune response in many cases, according to the researchers. Part of the body's natural response to activation of the immune system is to produce a compensatory immunosuppressive signal. Tumors use this to their advantage by expressing

molecules such as PD-L1, which cause T cells to become less active or "exhausted". The researchers saw evidence of this phenomenon, which may suggest future combinations with PD-1/PD-L1 inhibitors.

The next step at Penn is to combine anti-CD40 with chemotherapy in operable pancreatic cancer and to test new anti-CD40 compounds.

Provided by University of Pennsylvania School of Medicine