Concurrent treatment with OX40- and PD1-targeted cancer immunotherapies may be detrimental

28 August 2017

Concurrent administration of the T-cell stimulating anti-OX40 antibody and the immune checkpoint inhibitor anti-PD1 antibody attenuated the effect of anti-OX40 and resulted in poor treatment outcomes in mice.

"While immune checkpoint inhibitors, such as anti-PD1 and anti-CTLA4, are already in clinics and are used mainly as single agents, there are currently almost a thousand clinical trials that are testing a combination of anti-PD1 with other therapies," said Khleif. The investigators from the two studies wanted to test whether a combination of anti-OX40 and anti-PD1 could produce outcomes that are better than either treatment alone.

In the study published in *Clinical Cancer Research*, researchers found that concurrent treatment of mice bearing tumors that are refractory to anti-PD1 with anti-OX40 and anti-PD1 immunotherapies suppressed the therapeutic effect of anti-OX40 antibody, produced a cytokine storm-like event that made the mice lethargic, resulted in enlargement of their spleens, and led to an increase in the levels of the immune checkpoint proteins CTLA-4 and TIM-3 on T cells.

In the study published in *Cancer Immunology Research*, researchers found that in tumor-bearing mice, the simultaneous addition of anti-PD1 and anti-OX40 therapies inhibited the T-cell specific positive effects of anti-OX40 and suppressed its therapeutic efficacy. They found that the detrimental effect of the combination was a result of the induction of antigen-specific T-cell death (apoptosis).

The study by Fox and team also showed that sequential treatment with anti-OX40 followed by anti-PD1 (but not in reverse order) significantly improved the therapeutic efficacy of the combination, resulting in delayed tumor progression, including complete regression of tumors in about 30 percent of the mice. This is unprecedented in this model of human breast cancer, Fox noted.

Given that the majority of patients do not respond to anti-PD1 therapies, Fox and colleagues used a mouse model that is refractory to anti-PD1 to study if stimulating the T cells with anti-OX40 would make PD-1 blockade effective in an anti-PD1 refractory population.

Khleif and team, however, found that the therapeutic efficacy of continuous treatment with anti-OX40 with delayed addition of anti-PD1 was not superior to the outcomes with continuous anti-OX40 alone.

"The complexity of combination immunotherapy is enormous, because there are potentially many different ways it could work," said Fox. "Our study suggests that treating patients with anti-OX40 followed by anti-PD1 needs to be tested as it may be the best sequence to increase T-cell proliferation, reduce T-cell death, and maintain the T-cell numbers without upregulating as many inhibitory molecules."

"Moving forward, it is important to carefully study the patients, evaluate whether they have any pre-existing immunity, and follow their peripheral blood very closely over the early course of treatment to understand the biological effects of immunotherapy combinations," Fox noted. He added it is critical that more effort be invested in evaluating the contribution of each agent administered to patients in clinical trials.

"With chemotherapy, you hit the tumor with one hammer, then you hit it with another hammer, and we know that the outcome is better in most cases,"

Khleif said. "But treating a patient with one immunotherapy could change the tumor microenvironment and the biology of T-cell signaling in such a way that when you give another immunotherapy it might work very differently than what is expected and could exhibit the exact opposite outcome than it was supposed to.

"Our findings are very important because current clinical trials are testing this combination," Khleif noted. "Our studies show that preclinical testing of immunotherapy combinations prior to taking it to clinical trials is very important, and we need more of that research," headded.

Provided by American Association for Cancer Research