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Immunotherapy combination safe and 62 percent effective in metastatic melanoma patients

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Immunotherapy is a promising approach in the treatment of metastatic melanoma, an aggressive and deadly form of skin cancer; but for most patients, immunotherapy drugs so far have failed to live up to their promise and provide little or no benefit. In a phase 1b clinical trial with 21 patients, researchers tested the safety and efficacy of combining the immunotherapy drug pembrolizumab with an oncolytic virus called T-VEC. The results suggest that this combination treatment, which had a 62% response rate, may work better than using either therapy on its own. The study appears September 7 in the journal *Cell*.

"We had a hypothesis about how these treatments would work together, and when we did biopsies of patients' tumors we found that they were cooperating in just the way we thought they would," says lead author Antoni Ribas, director of the Immunology Program at the UCLA Jonsson Comprehensive Cancer Center.

Pembrolizumab is in a class of drugs called checkpoint inhibitors. They are designed to get around one of the ways that cancer protects itself from the immune system: tumors can activate the body's natural protective response from autoimmunity, called a checkpoint, and thereby thwart cytotoxic T cells. The drugs work by taking the brakes off the checkpoint and allowing T cells to attack the tumor.

"Some people put tumors into the categories of either 'hot' and 'cold,'"

Ribas explains. "Hot tumors, also called inflamed tumors, have a lot of immune cells in and around them, but cold tumors do not." Drugs like pembrolizumab boost the response in tumors where immune cells are present but don't work in tumors where there is no immune response to boost.

This is where T-VEC comes in. T-VEC, also called talimogene laherparepvec, is a human herpes simplex virus that is genetically engineered to bring T cells into a tumor and induce an antitumor response. It is FDA-approved for treating melanoma tumors in the skin and lymph nodes. By injecting T-VEC into the patients' tumors, even those that were located deeper in the body, the researchers were able to transform cold tumors into hot ones, which in turn allowed pembrolizumab to deliver a beneficial enhancement.

The phase 1b multicenter trial included 21 patients on three continents, all of whom had metastatic melanoma. The researchers report that 62% had an overall response to the drug combination, meaning that their tumors decreased in size. One-third had a complete response, meaning that their tumors were undetectable. These responses are much higher than what would have been expected with either treatment alone—usually about 35%-40%

The side effects in the study were no worse than what is observed when either drug is used on its own, and included fatigue chills, and fever. Three patients had more serious autoimmune side effects, which are sometimes seen after pembrolizumab treatment.

At the start of the trial, the patients were given two injections of T-VEC into their tumors three weeks apart. Starting at six weeks, they began receiving pembrolizumab every two weeks, at the same time as additional T-VEC injections.

When the researchers took biopsies of the patients' tumors during the trial, they confirmed that their hypothesis about how the tumors would respond was correct. At six weeks, after two treatments with T-VEC but before the checkpoint drug was started, most tumors were infiltrated with T cells. At 30 weeks, the T cells remained in the area, but the majority of the tumor cells were gone.

The investigators have already begun recruiting for a ohase III trial that will include 660 patients at more than 100 institutions around the word. This randomized, controlled trial will compare pembrolizumab plus T-VEC with pembrolizumab plus an injected placebo in patients who have not previously received either treatment.

More information: *Cell*, Ribas et al: "Oncolytic Virotherapy to Reverse Absence of Intratumoral T-1 Cell Infiltration and Improve Anti?PD-1 Immunotherapy." www.cell.com/cell/fulltext/S0092-8674(17)30952-2 , DOI: 10.1016/j.cell.2017.08.027

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