MedicalXpress

Targeted antibody, immune checkpoint blocker rein in follicular lymphoma

December 11 2013

One drug attacks tumor cells directly, the other treats the immune system by taking the brakes off T cell response. Together, they put half of the patients with relapsed follicular lymphoma into complete remission in a phase II clinical trial at The University of Texas MD Anderson Cancer Center.

"Most drugs target only the tumor, this combination is complementary, treating both the lymphoma cells directly and the T cells in a manner that activates them against cancer cells," said senior author Sattva Neelapu, M.D., Ph.D., associate professor of Lymphoma/Myeloma at MD Anderson and senior author of the paper out in *The Lancet Oncology*.

"The combination of the established antibody drug rituximab with the experimental drug pidilizumab so far also has a remarkably mild side effect profile," Neelapu said.

Of 29 study participants at a median follow-up of 15.4 months, 19 (66 percent) had either a complete or partial response, with 15 (52 percent) having a complete response.

There were no grade 3 or 4 adverse events, with all effects at the less serious grade 1 and 2 levels. Patients had no indicators of autoimmunity, which can be an issue in the class of drugs that blocks immune system checkpoints and activate T cells. Such mild effects are particularly important for follicular lymphoma patients, who are diagnosed with the disease at a median age of 60.

"Rituximab treatment alone usually achieves a 40 percent overall response rate and about 11 percent complete responses," Neelapu said. "And the side effect profile of the combination is about the same as rituximab alone. Adding pidilizumab greatly improves responses so far at little cost in additional side effects."

Drug targets PD-1 receptor to unleash immune response

The immune system usually recognizes and destroys abnormal cells, in addition to viral and bacterial infections, but cancer relies on immune checkpoints to evade attack. One of these is the programmed cell death 1 (PD-1) receptor, which stymies T cell function when activated by ligands highly expressed in tumor cells. Pidilizumab blocks PD-1, and like other drugs that impair immune checkpoints, should unleash T cells to attack cancer cells.

Immune checkpoint blockade was pioneered by James Allison, Ph.D., now chair of MD Anderson's Department of Immunology. He worked out the basic science of checkpoints and developed the first drug to block one. Ipilimumab (known commercially as Yervoy) blocks CTLA-4, another checkpoint.

Neelapu grew interested in checkpoint blockade after years of research developing vaccines to treat cancer. "Vaccines induce an immune response to cancer, but we don't see objective response in the tumors," Neelapu said.

Research showed PD1 is highly expressed on T cells in the bloodstream and tumors of follicular lymphoma patients and also is associated with impaired T cell function. Pidilizumab is a monoclonal antibody that targets PD1. A phase 1 trial had shown it to be safe, so Neelapu and

colleagues combined it with rituximab (known commercially as Rituxan), another monoclonal antibody that hits CD20, a surface protein on immune system B cells. Follicular lymphoma is a cancer of B cells.

No dose reductions or treatment halt required

Patients had gone through 1-4 previous treatments before enrolling in the clinical trial between January 2010 and January 2012. Of 32 patients enrolled, two were ineligible to proceed and were not treated and one withdrew from the trial after one infusion of pidilizumab and received alternate treatment.

None of the 29 remaining patients received a dose reduction or discontinued treatment due to adverse events. Median progression-free survival for all patients was 18.8 months but had not been reached for the 19 responders. Median response duration for responders was 20.2 months, with only seven having disease progression as of May 2013.

The research team examined blood samples and tumor biopsies to identify possible risk factors and genes that might indicate response to treatment and survival.

Gene expression predicts progression-free survival

"Gene expression analysis of tumor samples from 18 patients before treatment showed that progression-free survival increased for patients when their gene signature included genes that are highly active during T cell response or repressed in regulatory T cells that dampen T cell activation," said Eric Davis, M.D., associate professor of Lymphoma/Myeloma and co-senior author of the paper.

The team also identified 41 genes that are more highly expressed in

effector T cells with anti-tumor effects compared with follicular helper T cells, thought to have pro-tumor effects. Low expression of the 41-gene signature predicted less tumor shrinkage and shorter progression-free survival at 12.7 months. Median progression-free survival was not reached for patients with high signature expression.

"These findings indicate that patients who already have an active immune response before treatment do better on this combination," said co-first author Jason Westin, M.D., assistant professor of Lymphoma/Myeloma.

Core-needle biopsies from eight study participants after treatment showed increased expression of T cell activation genes, which was associated with longer progression-free survival.

When the researchers analyzed the 41-gene signature in 191 cases of follicular lymphoma patients treated with chemotherapy alone, it did not predict a significant difference in overall survival. It's likely, the researchers noted, that the signature only has predictive power for the combination treatment.

Randomized trial, new combinations

Since patients received only the combination therapy, the next step would be a randomized, double-blind trial comparing it to rituximab alone.

A commentary by two French oncologists also published in The Lancet Oncology noted: "The demonstration of activity in relapsing diffuse large B cell lymphomas suggests that anti-PD1 antibody therapy might have a therapeutic role in all lymphomas."

"Our findings indicate rituximab and pidilizumab together are safe and

highly active in follicular lymphoma," Neelapu said. New combinations might add other checkpoint blockade drugs, such as ipilimumab, the B cell receptor inhibitor ibrutinib or lenalidomide, which also activate immune system.

Chemotherapy could be added as well, Westin said, but that would likely increase side effects.

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