'Reprogrammed' treatment-resistant lymphomas respond to cancer drugs

August 16 2013

A phase I clinical trial showed diffuse, large B-cell lymphomas (DLBCLs) resistant to chemotherapy can be reprogrammed to respond to treatment using the drug azacitidine, according to a study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

Patients whose lymphomas recur after initial chemotherapy are treated with a combination of approaches, including high-dose chemotherapy followed by a stem cell transplant. However, some patients have tumors that do not respond to these extensive second treatments, and many of these patients die within two years of diagnosis.

"When lymphomas are formed, they shut down the cellular programs that sense that something is wrong in the cells. Once these fail-safe mechanisms that trigger cell death are shut down, it becomes difficult to kill the tumor with chemotherapy," said Leandro Cerchietti, M.D., assistant professor at the Hematology and Oncology Division of Weill Cornell Medical College in New York. "Our study showed that using low concentrations of the DNA methyltransferase inhibitors decitabine or azacitidine, these fail-safe mechanisms can slowly be awakened to induce lymphoma cell death when chemotherapy is administered."

Cerchietti and colleagues conducted a phase I trial in patients with newly diagnosed DLBCL. Eleven of the 12 patients enrolled were more than 60 years old when diagnosed, which meant that they were at high risk for tumor recurrence after initial treatment. The patients were treated with

azacitidine, in escalating doses, eight days prior to initiation of six cycles of standard chemotherapy. Side effects from pretreatment with azacitidine were minimal. Two patients who were treated with the maximum dose of azacitidine had dose-limiting toxicities.

Of the 12 patients, 11 had a complete response and 10 remained in complete remission for up to 28 months.

"We showed that aggressive lymphomas can be reprogramed to a more benign disease," said Cerchietti. "We think this work has the potential to change the standard of care for patients with aggressive lymphomas."

The researchers conducted the clinical trial based on the results of their extensive preclinical experiments to determine the mechanisms by which lymphomas evade chemotherapy drugs. They found that compared with normal cells, all DLBCLs possess a high degree of aberrant DNA methylation, a process which "silences" certain genes, causing resistance to treatment.

Using DLBCL cells and mice bearing human lymphoma xenografts, the researchers showed that DNA methyltransferase inhibitors are most effective if administered prior to chemotherapy, but not concurrently. They also found the gene SMAD1 to be silenced in the unresponsive tumors.

When the researchers looked for SMAD1 status in the biopsy specimens collected from patients enrolled in the phase I trial, they found that after treatment with azacitidine, there was a decrease in SMAD1 methylation and increase in SMAD1 protein, providing proof of principle.

Cerchietti and colleagues are currently conducting clinical trials with patients with lymphomas whose tumors failed to respond to standard therapies. They are in the process of conducting larger, multicenter trials

to extend this treatment to other cancers as well.

Provided by American Association for Cancer Research