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Drug-antibody pair has promising activity in non-Hodgkin lymphoma

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A toxin linked to a targeted monoclonal antibody has shown "compelling" antitumor activity in patients with non-Hodgkin lymphomas who were no longer responding to treatment, according to a report from Dana-Farber Cancer Institute.

The ongoing open-label phase 2 study presented at the American Society of Hematology (ASH) meeting was designed to test the activity of brentuximab vedotin (Adcetris) in relapsed or refractory non-Hodgkin lymphoma (NHL) including B-cell cancers such as diffuse large B cell lymphoma (DLBCL).

The antibody-toxin compound has been approved for treatment of relapsed or refractory Hodgkin lymphoma and anaplastic T cell lymphoma, and its success prompted the trial in NHL, said Eric Jacobsen, MD, of Dana-Farber, senior author of the study. First author is Nancy Bartlett, MD, of Washington University School of Medicine.

To date, the trial has enrolled 62 patients with B-cell lymphomas, including 44 diagnosed with DLBCL. Most the patients were no longer responding to previous therapy, and 23 percent had never responded to any treatment.

Forty percent of the 43 evaluable DLBCL patients had an objective response to the drug with a median duration of 36 weeks, including some of more than eight months. Seven had complete remissions and 10 had partial remissions. In the other B-cell lymphoma patients, 22 had an

objective response.

"In this interim analysis of 62 patients with highly refractory B-cell lymphomas, compelling antitumor activity has been observed with brentuximab vedotin," the authors wrote.

"It was more active than many expected," noted Jacobsen. "In my opinion, these results are encouraging enough to take the drug forward in diffuse large B cell lymphoma."

Brentuximab is a monoclonal antibody that binds to CD30, a molecule found on cells in Hodgkin lymphoma and anaplastic T cell lymphoma. The frequency of CD30 expression varies in other subtypes of lymphoma but is estimated to be present in one-quarter to one-third of B cell NHL cells. In the compound brentuximab vedotin, the targeted antibody is linked to a potent toxin that interferes with cell division and blocks cell growth. Like a chemical Trojan horse, the antibody-toxin compound is swallowed by cancer cells that carry the CD30 molecule on their surface. Once inside the cell, the poisonous cargo separates from the antibody and disables the cell.

Some of the patients' lymphoma cells strongly expressed the CD30 molecule, but in others the expression was less, and in some patients CD30 expression wasn't detected at all.

Surprisingly, the strength of CD30 expression by the patients' cancer bore no relationship to how they responded to the drug. "In fact, although the trend was not statistically significant, there was almost an inverse correlation. Some patients with the weakest CD30 expression had the most positive responses," said Jacobsen.

This is puzzling, he admitted: How did the antibody recognize and bind to the lymphoma cells that lacked the CD30 molecule? Possibilities

include binding to another target, although preclinical tests suggested this was not the case. Other possibilities is that brentuximab vedotin binds more effectively to CD30 than the antibody used to detect CD30 in the lab or that different cells have differing abilities to ingest brentuximab once the antibody binds to the cell. There is no clear answer from the study but further laboratory tests are ongoing. Jacobsen said the trial is beginning to evaluate the drug's activity in a cohort of patients whose lymphomas have no measurable CD30 expression.

The drug caused an array of adverse events, leading to discontinuation in six patients. Among the toxicities were fatigue, nausea, low white blood counts, fever, diarrhea, peripheral sensory neuropathy, vomiting, anemia and constipation. The researchers said this profile was consistent with that seen previously with brentuximab vedotin.

Provided by Dana-Farber Cancer Institute