Personalized vaccine for lymphoma patients extends disease-free survival by nearly 2 years

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A personalized vaccine is a powerful therapy to prevent recurrence among certain follicular lymphoma patients, according to the latest results of ongoing research led by the University of Pennsylvania School of Medicine. The new findings show that when these patients – whose tumors are marked by a specific protein that may be present in up to half of people with this type of cancer -- receive a vaccine made from their own tumor cells, disease-free survival is improved by nearly two years, compared with patients who receive a placebo. Based on the new analysis, the team thinks they can explain why the results of previous trials of similar therapeutic cancer vaccines were not as strong as expected.

"The treatment effect of the personalized vaccine is stunning in our trial," says Stephen J. Schuster, MD, an associate professor in the division of Hematology-Oncology and director of the Lymphoma Program at Penn's Abramson Cancer Center. Schuster will present data from a randomized, double-blind, phase III multicenter clinical trial on Monday, Dec. 6 at the annual meeting of the American Society of Hematology (ASH). "Our work stands to revolutionize the approach to personalized vaccine development in lymphoma, and bring new hope to patients who are diagnosed with all types of the disease. This is paradigm changing," Schuster says.

The majority of follicular lymphoma patients – who make up about 30

percent of the 66,000 patients diagnosed with non-Hodgkin lymphoma each year -- initially respond to monoclonal antibody therapy and chemotherapy but later suffer a relapse. They may be helped by subsequent rounds of chemotherapy, but eventually their disease becomes resistant to these drugs.

Each patient's lymphoma tumor carries a unique protein on the cell surface, called an idiotype protein. The idiotype protein is part of a larger protein on the cell's surface which can be one of several so-called "isotypes", usually either the IgG or IgM isotype. Only the tumor cells – not healthy cells – carry the idiotype protein, making it an ideal anti-tumor vaccine target. Researchers have used a variety of techniques to manufacture idiotype vaccines. To generate the vaccines used in their trial, Schuster and his colleagues fused the complete idiotype-isotype protein from each patient's tumor cells to a carrier called keyhole limpet hemocyanin protein, which helps attract the attention of immune system. The team used the carrier protein alone as a placebo vaccine.

In the current study, individuals who responded to initial chemotherapy and remained in remission for at least six months were eligible to continue in the trial, and received either a personalized idiotype vaccine plus an immune-stimulating agent called GM-CSF, or placebo vaccine plus GM-CSF. When researchers analyzed the patients who received at least one dose of personalized vaccine, they saw a 14-month improvement in disease-free survival, compared to those who received the placebo. The 76 patients treated with the vaccine had a median disease-free survival of 44.2 months, compared to 30.6 months for the 41 patients treated with the placebo. (The trial was designed so that two patients would receive the vaccine treatment for every one who received the placebo.)

Following a hunch and some earlier observations in the literature, Schuster and co-workers decided to reanalyze the data after dividing the

patients based upon the type of isotype protein on their tumor cells' surface. He found that patients whose tumors had an IgM-idiotype protein had a robust response to the vaccine, with an increase in median disease-free survival from 28.7 months in placebo-treated patients to 52.9 months in vaccine-treated patients. By contrast, the impact of the vaccine on patients whose idiotype protein was part of an IgG-type antibody was negligible, with a non-significant increase from 32.4 months to 35.1 months.

"There is some evidence in the scientific literature that IgG is not as immunogenic or causes immune suppression or tolerance, compared with IgM," Schuster says, "but no one has tested this hypothesis in a clinical trial." Although this new analysis was not included in the original trial design, Schuster thinks its importance is clear. "What this analysis is doing is telling us potential ways to make better vaccines," he says. "And it tells us that we should continue efforts to develop vaccines as part of our treatment for lymphoma."

In fact, the new analysis may reveal the very reason that previous attempts to make an effective idiotype vaccine have not produced encouraging results. The technology used to develop idiotype vaccines in other trials engineered all the idiotype proteins into an IgG-type. By contrast, this trial used a technique that didn't restrict idiotype vaccine production to IgG, but rather included whatever protein was native to the patients' tumors.

To confirm their novel results, Schuster's team plans to launch a new trial next year using the same vaccine approach, but this time they will divide patients at the outset, according to whether their idiotype protein is an IgM- or IgG-type.

Provided by University of Pennsylvania School of Medicine