MEDCO FORUM®

PRESENTING INNOVATIVE PRODUCTS & SERVICES TO HEALTHCARE PROFESSIONALS

VOLUME 11 NUMBER 28 JUNE 2004

REPRINT

GENITOPE CORPORATION IS DEVELOPING PERSONALIZED IMMUNOTHERAPY FOR NON-HODGKIN'S LYMPHOMA

A type of immunotherapy called **MyVax® Personalized Immunotherapy** is being developed by **Genitope Corporation** (Redwood City, CA) as a potential treatment for non-Hodgkin's lymphoma (NHL). MyVax Personalized Immunotherapy for NHL has not yet been approved by the U.S. Food and Drug Administration (FDA), but a large Phase 3 clinical trial and a Phase 2 rollover trial are currently underway that will provide information about the safety and efficacy of this new type of therapy. "This is the largest vaccine trial ever conducted for lymphoma," explains one of the principal investigators, Julie M. Vose, MD, Chief of the Section of Hematology/Oncology and Professor of Medicine, Nebraska Medical Center (Omaha, NE). "The Phase 3 study includes about 700 patients at 34 medical centers across North America. We expect to see the first set of interim data in mid-2005. If the data look favorable, Genitope could seek approval from the FDA at that point."

This pivotal Phase 3 trial is designed to test whether the company's patient- and tumor-specific immunotherapy can delay or even prevent recurrence of disease in previously untreated patients with follicular NHL. The trial includes patients with Stage III/IV follicular NHL who are in remission following their first course of CVP chemotherapy (cyclophosphamide, vincristine, and prednisone). Patients who have had a partial or complete tumor response (at least a 50% decrease in tumor volume) are eligible for the immunotherapy portion of the trial. Researchers hope to demonstrate a significant improvement in the progression-free survival time in those treated with the investigational therapy, compared with the control group.

The Phase 2 rollover trial is available for patients who enter the Phase 3 trial, but fail to achieve at least a partial response after eight cycles of CVP chemotherapy, or who progress during the mandatory rest period. This trial explores the use of Genitope's MyVax Personalized Immunotherapy following the use of the anti-CD20 monoclonal antibody rituximab (Rituxan®; Genentech, Inc., South San Francisco, CA).

Passive and Active Immunotherapy

The goal of immunotherapy is to activate the patient's immune system to identify and attack cells that cause diseases, including tumor cells (*1*). Two forms of immunotherapy—passive and active—are currently used to treat various diseases. Passive immunotherapy involves administration to patients of laboratory-produced antibodies specific for a particular antigen. Passive immunotherapies, such as Rituxan, have shown clinical benefits in some cancers, but they have two main drawbacks: 1) they require repeated infusions for continued activity, and 2) they bind to any cell that expresses the targeted antigen, not just to cancer cells.

An active immunotherapy is designed to generate an active, long-lasting immune response to an antigen by administering the antigen itself (or an active component of the antigen) to the patient, often along with other agents that enhance the immune reaction. The specific immunity generated by active immunotherapy can include both humoral (B-cell) and cell-mediated (T-cell) responses, as well as the formation of memory cells that respond upon subsequent exposure to the antigen.

Personalized Immunotherapy for NHL

Personalized immunotherapy (also known as idiotype immunotherapy, idiotype vaccine, and patient-specific vaccine therapy) is an example of active immunotherapy that is specific for tumor cells from each individual patient (*2*). B-cell lymphoma arises from a single malignant B lymphocyte, so that all tumor cells in any given patient bear the same cell-surface immunoglobulin. The idiotype is the unique portion of the variable region of the cell-surface immunoglobulin that determines to which antigens it can bind.

MyVax Personalized Immunotherapy consists of the idiotype protein derived from each individual patient, conjugated to a foreign carrier protein (keyhole limpet hemocyanin; KLH) and administered in conjunction with an adjuvant (granulocyte-macrophage colony-stimulating factor; GM-CSF). The KLH and GM-CSF serve to enhance the immune reaction to the patient-specific idiotype protein.

To manufacture this idiotype immunotherapy for NHL, a sample of the patient's tumor is removed before the patient undergoes chemotherapy. The genetic coding for the idiotype of the malignant B-cells is identified from the tumor biopsy, and large quantities of the antigen are produced using recombinant molecular biology and cell culture techniques. After the recombinant version of the idiotype protein is purified and conjugated to the KLH, the quality of the final product is tested and the frozen immunotherapy is shipped to the physician to administer the series of immunizations subcutaneously.

To date, the known side effects of personalized immunotherapy are minimal, consisting mainly of injection-site responses and minor flu-like symptoms that disappear within a few days to a few weeks after each series of injections. Side effects generally associated with chemotherapy, such as hair loss, nausea, fatigue, and mouth sores, do not occur.

Results of Clinical Trials

The results of early clinical trials of personalized immunotherapy in patients with NHL suggest that personalized immunotherapy may induce long-term remission and improve survival (*3*). In a study conducted at Stanford University (Stanford, CA), the median survival time was significantly longer for patients who received personalized immunotherapy following chemotherapy than it was for patients who received chemotherapy alone. In addition, those patients who mounted an immune response to their tumor cells after personalized immunotherapy had a longer median time to disease progression than did those who did not mount an immune response.

Clinicians treating patients with NHL have great hopes for this new type of therapy. "Personalized immunotherapy is an exciting new approach to the treatment of indolent lymphoma," says Mort Coleman, MD, Chair of the Lymphoma and Myeloma Department at the Weill Medical College of Cornell University (New York, NY). "And if the results of the ongoing clinical trials are positive, this could serve as a paradigm for the treatment of other cancers."

This article was supported by an unrestricted medical education grant from Genitope Corporation.

For more information concerning MyVax Personalized Immunotherapy, call 1-866-GENITOP (436-4867); contact a Genitope representative at ASCO, booth #3849; or visit Genitope's Web site at www.genitope.com.

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