Therapeutic melanoma vaccine improves response rate, progression-free survival

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A vaccine for one of the most lethal cancers, advanced melanoma, has improved response rate and progression-free survival for patients when combined with the immunotherapy drug Interleukin-2, according to research led by scientists from The University of Texas MD Anderson Cancer Center and Indiana University Health Goshen Center for Cancer Care.

The findings, published in the June 2 *New England Journal of Medicine*, mark the first vaccine study in the disease – and one of the first in cancer overall – to show clinical benefit in a randomized Phase III clinical trial. It's also the first cancer vaccine to show an improved response rate in patients.

The research was first presented on the plenary session of 2009 American Society of Clinical Oncology.

According to the American Cancer Society, melanoma has one of the fastest growing incidence rates of all cancers. In 2010, more than 68,130 people in the U.S. were diagnosed with melanoma and 8,700 died from the disease. The five-year survival rates for those with regional and metastatic disease are 65 percent and 16 percent, respectively.

"Obviously, this is a disease, in its advanced setting, in need of better therapies for patients," said Patrick Hwu, M.D., professor and Chair of the Department of Melanoma Medical Oncology and the study's senior author. "This study serves as a proof-of-principle for the role of vaccines

in melanoma and in cancer therapy overall. If we can use the body's own defense system to attack tumor cells, we provide a mechanism for ridding the body of cancer without destroying healthy tissue."

During their tenure at the National Cancer Institute NCI), Hwu and Douglas Schwartzentruber, M.D., the medical director of the Goshen Center for Cancer Care, were involved in the vaccine's development and early basic and clinical studies. The peptide vaccine, known as gp100:209-217 (200M), works by stimulating patients' T cells, known for controlling immune responses.

"This vaccine activates the body's cytotoxic T cells to recognize antigens on the surface of the tumor. The T cells then secrete enzymes that poke holes in the tumor cell's membrane, causing it to disintegrate," explained Schwartzentruber, the study's principal investigator and corresponding author.

After an NCI-led Phase II study combining the vaccine with Interleukin-2 (IL-2) showed response rates of 42 percent in metastatic melanoma patients, a Phase III randomized trial with the two agents opened more than a decade ago.

Conducting a large, multi-institutional trial with IL-2, however, had its own set of unique challenges, explained Hwu, as not all cancer centers and community hospitals are capable of administering the immunotherapy. A highly specialized therapy associated with such significant side effects as low blood pressure and capillary leak syndrome, which poses risks to the heart and lung, IL-2 is often delivered in intensive care units. MD Anderson is one of the few centers with a dedicated in-patient unit exclusively designed for the drug's delivery; before, the institution was offering the therapy in its ICU.

In the Phase III trial, 185 patients at 21 centers across the country were

enrolled in the study. All had advanced metastatic melanoma and were stratified for cutaneous metastasis, a known indicator of response to IL-2. Patients were randomized to receive either high dose IL-2, or IL-2 and vaccine. In the IL-2 arm, 94 patients were enrolled and 93 were treated and evaluated for response; 91 were enrolled and 86 treated and 85 were evaluated for response in the IL-2 and vaccine arm. The primary endpoint of the study was clinical response; the secondary endpoints were toxic effects and progression-free survival.

The study found that those who received the vaccine had a response rate of 16 percent, and progression-free survival of 2.2 months, compared to 6 percent and 1.6 months respectively in those that did not. The study was not powered to look at overall survival, but for those receiving the vaccine, it trended positive, 17.8 months vs. 11.1 months.

"This is one of the first positive randomized vaccine trials in cancer and the findings represent a significant step forward for treatment of advanced melanoma," said Schwartzentruber. "However, the vaccine only can be given to half of those with melanoma because it has to match a patient's tissue type, or HLA. A major priority for us is to figure out ways to broaden our approach and use mixtures of peptides, for example, so that more patients are eligible."

The researchers would like to improve upon it by including other immune-stimulatory agents, such as newer vaccine adjuvants, other cytokines and antibodies that further activate immune cells.

"This is a very exciting time for the field of melanoma. During the last few years, the entire landscape has changed – with the addition of targeted therapies such as those that target BRAF as well as those that stimulate the immune system. Still, these drugs work in a small number of patients, and/or resistance often develops," said Hwu. "Now, our focus will need to turn toward studying these novel therapies in

combination and continue our quest for better vaccines, as well as researching ways to make the study inclusive of more metastatic melanoma patients."

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