Targeted immunotherapy shows promise for metastatic breast, pancreatic cancers

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Early trials using targeted monoclonal antibodies in combination with existing therapies show promise in treating pancreatic cancer and metastatic breast cancer, according to research that will be presented by investigators from the University of Pennsylvania's Abramson Cancer Center at the 2010 meeting of the American Society of Clinical Oncology June 4 through 8. One study uses an antibody to enhance the effectiveness of a breast cancer vaccine developed at Penn to treat women with advanced breast cancer, while a pancreatic cancer trial uses an immune-enhancing antibody to increase the effectiveness of a current standard drug used to treat pancreatic cancer.

In the first new study, investigators used an antibody previously approved by the FDA to enhance the effectiveness of a therapeutic vaccine for women with advanced breast cancers. ("Phase I study of anti-CD25 mAb daclizumab to deplete regulatory T cells prior to telomerase/survivin peptide vaccination in patients with metastatic breast cancer" -- Oral Abstract #2508) The antibody, known as anti-CD25 mAb dacluzimab, targets T regulatory cells (Tregs), naturally occurring cells which tumors harness to dampen the body's normal immune response. Until now, these cells have represented an obstacle to cancer immunotherapy. The Penn Medicine team's approach uses the antibody to turn off the Treg cells' function in the immune system and boosting the effectiveness of a telomerase/survivin peptide vaccine made to tackle the cancer.

The study demonstrated that a single infusion of the antibody given a

week before patients received the vaccine results in "rapid, marked and prolonged" loss of Tregs without toxicity in patients with metastatic breast cancer. Six of the 10 patients who received the treatment exhibited a stabilization of their disease. Data for overall survival is not yet available, but the Penn researchers say the results represent significant promise for treating the patient population that does not respond to standard therapies.

"Many of these women have already been treated with and failed several chemotherapy regimens, but using this approach they were able to receive multiple doses of the vaccine without experiencing any of the toxicities that often accompany chemotherapy," says senior author Robert H. Vonderheide, MD, DPhil, an associate professor in the division of Hematology/Oncology. "For this group of patients, an extended period of stable disease represents an encouraging result." He and his team plan to begin much larger studies in the near future, and ultimately, to expand the new combined approach to women who are currently in remission but at very high risk of relapse.

Tregs play an important role in the body's normal immune response. When they are absent or severely depleted, the result is autoimmune problems. To date, however, research has not shown any long-term effects of this targeted immune suppression in the treated patients, which is an important consideration in expanding the trials to women without known active disease.

"Ten years ago, we didn't even know Tregs existed," Vonderheide says. "Our lack of knowledge about the intricacies of the normal immune system and the ways in which tumors can exploit the immune response severely limited the success of previous attempts at cancer immunotherapy. The early results were quite modest and very transient. It has taken five years to develop an understanding of how these cells work, but we have now reached the point where we are on the cusp of a

whole new era in cancer immunotherapy."

In second immunotherapy-related study, Penn researchers utilized CP-870,893, a CD40 agonist monoclonal antibody produced by Pfizer that enhances anti-tumor cellular immunity by activating tumor antigens and triggering the release of inflammatory cytokines. ("Phase I study of CD40 agonist monoclonal antibody (CP-870,893) with gemcitabine in pancreatic cancer" -- Poster Presentation #2539). The antibody was combined with the chemotherapy agent gemcitabine to treat pancreatic cancer patients who had not received any previous chemotherapy. The Phase I study demonstrated that the combined therapy produced promising results without causing any significant toxicity. Three of the first 21 patients treated experienced partial regressions of their tumors, and 11 patients' diseases stabilized, with the positive effects of the treatment observed in both the primary and metastatic tumors. Additional studies are underway to evaluate this treatment approach in larger groups of patients.

"The model for this research moves from the lab to the clinic and then back to the lab," says Hematology/Oncology physician Gregory Beatty, MD, who led the study with Peter O'Dwyer, MD, a professor of Hematology/Oncology. "With this approach, we cannot only measure the effects of the treatment, but also understand exactly what is going on at the cellular level and then use that information to develop our next generation of clinical interventions. Our goal is to re-educate the immune system to mount a specific inflammatory response to the tumor. By killing the cancer cells, the chemotherapy in effect alerts the immune system to the location of the tumor and provokes an immune response aimed at the cancer cells."

Currently, fewer than 10 percent of pancreatic cancer patients respond to gemcitabine alone, and most combination therapies studied have not produced more encouraging results - responses, when they do occur,

generally only last for about two months. The new combination therapy, however, appears to produce a significantly higher response rate, with an average duration of five to six months.

"This is an encouraging result against a cancer for which the outlook has been so grim for so long," says Vonderheide, who is also a co-author of the pancreatic cancer study. "We can honestly say now that the prospects for patients with pancreatic cancer are beginning to improve. What we are seeing, though, is just the tip of the iceberg. Patients and their families need to know this is no longer a disease against which we are helpless, and physicians must help their patients to seek clinical trials at the earliest point."

The breast cancer study will be presented as an oral abstract at the Developmental Therapeutics Clinical Pharmacology and Immunotherapy session on June 8 from 9:30 to 12:30 p.m. The pancreatic cancer study will be presented at the poster session on Developmental Therapeutics on June 7 from 8 a.m. to 12 p.m.

Provided by University of Pennsylvania School of Medicine