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Two-Step Immunotherapy Attacks Advanced Ovarian Cancer, Penn Medicine Researchers Report

Personalized Vaccine Made from Patients' Own Tumors Spurs Immune System

PHILADELPHIA — Most ovarian cancer patients are diagnosed with late stage disease that is unresponsive to existing therapies. In a new study, researchers from the Perelman School of Medicine at the University of Pennsylvania School of Medicine show that a two-step personalized immunotherapy treatment — a dendritic cell vaccine using patients' own tumor followed by adoptive T cell therapy — triggers anti-tumor immune responses in these type of patients. Four of the six patients treated in the trial responded to the therapy, the investigators report this month in *OncoImmunology.*

"What we proved in this study is that this is a safe treatment strategy," says co-first author **Lana Kandalaft, PharmD, MTR, PhD**, research assistant professor of Obstetrics and Gynecology and director of clinical development in the Ovarian Cancer Research Center. "It is a walk in the park for patients, especially compared to standard chemotherapies and surgical treatments for ovarian cancer – literally, some patients left the clinic and went for a walk in a nearby park after their treatment."

The findings follow research by the study's senior author, **George Coukos, MD, PhD**, director of the Ovarian Cancer Research Center at Penn, who showed in 2003 that women whose ovarian tumors were infiltrated by healthy immune cells, called T cells, tended to live longer than women whose tumors were devoid of T cells. That observation and other subsequent ones suggest the patient's immune system is trying to fight off the disease but can't quite muster the strength to beat it. Therefore, investigators have been trying to find ways using patients' own tumor cells to boost the immune system's power.

In the current study, Coukos, Kandalaft, co-first author **Daniel J. Powell Jr., PhD**, research assistant professor of Pathology and Laboratory Medicine, and colleagues treated six women with advanced ovarian cancer in a two-staged immunotherapy protocol in which they utilized a dendritic cell vaccine created from tissue in the patients' own tumor, which was stored at time of surgery. All of these women's cancers had progressed on standard of care chemotherapy.

In the first segment of the study, the team prepared an individualized dendritic cell vaccine for each patient. They harvested dendritic cells from each patient using apheresis, the same process volunteers go through when they donate platelets or other blood products such as those collected for stem cell transplants. Kandalaft and colleagues then exposed each patient's dendritic cells to tumor extract produced from the woman's own tumor, which teaches the dendritic cells who the enemy is. After this priming, the investigators vaccinated each patient with her own

dendritic cells and gave them a combination chemotherapy regimen of bevacizumab and cyclophosphamide. Because dendritic cells are like the generals of the immune system, they then induce other immune cells to take up the fight.

Of the six patients who received the dendritic cell vaccine, four developed an anti-tumor immune response, indicating that the approach was working. One of those patients had no measurable disease at study entry because all of it had been successfully removed during surgery. She remains in remission today, 42 months following vaccine treatment. The other three who had an immune response to the vaccine still had residual disease and went on to the second segment of treatment.

The team harvested T cells from each of these three women. Using a technique developed at Penn, they grew the cells in the laboratory, expanding their numbers exponentially, and then reintroduced them into each patient after she underwent a lymphodepleting chemotherapy regimen. Because the T cells had already been trained by the dendritic cell vaccine to attack the tumor cells, the adoptive T cell transfer amplifies the anti-tumor immune response.

Two of the women showed a restored immune response after the T cell transfer. One of the women continued to have stable disease, whereas the other had a complete response to the therapy.

The researchers say it is too early to say whether this type of therapy will be effective in a large number of ovarian cancer patients, but the early results are promising. First, and foremost, she notes, the two-step approach appears safe and well tolerated by the patients. Additionally, the team saw a correlation in both treatment steps between immune responses and clinical benefit, suggesting that it is, in fact, the immune response that is holding the disease in check.

With these encouraging results in hand, the team has opened a larger trial in which they have already enrolled about 25 women and aim for up to 30 more. The new protocol uses an improved vaccine platform and an optimized adoptive T cell transfer protocol. The PI of this study is Janos Tanyi, MD, PhD.

“Large clinical trials have shown that intensifying chemotherapy doesn't improve outcomes for women with advanced ovarian cancer,” Coukos says. “So we need to explore other avenues. We think the combinatorial approach of both immune and chemotherapy is the way to go.”

Other co-authors from Penn include Cheryl L. Chiang, Janos Tanyi, Sarah Kim, Kathy Montone, Rosemarie Mick, Bruce L. Levine, Drew A. Torigian, and Carl H. June. Co-author Marnix Bosch is from Northwest Biotherapeutics in Bethesda, MD.

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