

OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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Immunotherapy in Ovarian Cancer: Where Are We Now, and Where Are We Going?



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H&O What types of immunotherapy have been investigated for use in women with ovarian cancer?

AJ The 3 broad areas of immunotherapy that have been investigated in patients with ovarian cancer are T-cell therapies, checkpoint inhibitors, and therapeutic vaccines.

In T-cell therapy, which is sometimes called adoptive cell therapy, physicians remove T cells from the body, send them to a lab for expansion, then return them to the patient. T-cell therapy can consist of unmodified T cells, such as tumor-infiltrating lymphocytes (TILs), or T cells that have been genetically modified, such as chimeric antigen receptors (CARs) or target-specific T-cell receptors (TCRs).

In TIL therapy, the T-cell source consists of those cells that have made it to a patient's tumor. The TILs are expanded several thousand-fold in the laboratory and infused back into the patient. Before TIL infusion, patients require high doses of chemotherapy to knock down nonspecific and inhibitory immune cells in the body and make room for the transfused cells. Patients also receive interleukin 2 to help the T cells expand in the body. Like many different types of immunotherapy, this type has shown the greatest success in melanoma—it is still considered investigational in ovarian cancer.

In CAR T-cell therapy, T cells from the patient are genetically modified—reprogrammed to recognize specific antigens, such as CD19, on the surfaces of cancer cells. This approach has had the greatest success in B-cell leukemia and lymphoma, and the first US Food and Drug Administration (FDA) approval for this type of therapy has been for tisagenlecleucel (Kymriah, Novartis)

in certain patients with acute lymphocytic leukemia. The use of CAR T cells is being actively investigated in ovarian cancer and other solid tumors.

Checkpoint inhibitors are another active area of research in ovarian cancer. These agents work to remove the “brakes” on the immune system that tumors exploit to evade the immune system. Studies are being conducted to investigate agents that block cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) in

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ovarian cancer. Several other checkpoint inhibitors and other classes of immune-modulating drugs are under active clinical development, both alone and in combination with drugs that target PD-1 or PD-L1.

The term *therapeutic vaccine* refers to vaccines that are used to treat—as opposed to prevent—cancer. Therapeutic vaccines exist in many different forms, such as proteins,

peptides, DNA, immune cells, and radiated tumor cells. Typically, vaccines are delivered with a nonspecific immune-stimulating substance—the *adjuvant*—that enhances the immune response to the vaccine. Although therapeutic vaccines have a long track record in ovarian cancer and show evidence of being immunogenic, they have not produced clinically significant responses thus far. Many trials are looking at developing more effective vaccines, or at combining vaccine therapies with checkpoint inhibitors.

Cancer cells themselves can be used as a vaccine. The investigational vaccine Vigil (Gradalis) is made by harvesting cells from an ovarian tumor at the time of diagnosis. The cancer cells are modified to increase their immunogenicity and radiated to make them incapable of cell division and growth. The vaccine is injected after the patient has completed frontline surgery and chemotherapy. A phase 1 study by Senzer and colleagues has demonstrated safety and suggested improved survival, and confirmatory studies are ongoing (Trial of Adjuvant FANG Vaccine for High Risk Stage III/IV Ovarian Cancer; NCT01309230).

H&O What makes immunotherapy a good choice for treating ovarian cancer?

AJ A great deal of research has documented the immunogenicity of ovarian cancer. In 2003, research by Dr George Coukos and colleagues (first author, Zhang) showed that in ovarian cancer, the prognosis of patients whose tumors have high levels of TILs is better than that of patients whose tumors have low levels—and this applies when patients are treated with conventional chemotherapy drugs. This observation serves as a strong rationale for using treatments that will enhance tumor infiltration with immune cells, or otherwise remove immunosuppressive aspects of the ovarian tumor environment.

H&O What are the disadvantages and limitations of immunotherapy for patients with ovarian cancer?

AJ Immunotherapy drugs have significant side effects, including the possibility of immune-related side effects such as rash, diarrhea, colitis, hepatotoxicity, neurotoxicity, and endocrinopathies. These occur just as often in patients with ovarian cancer as they do in patients with other types of cancer. What is different about patients with ovarian cancer is that they tend to be older than those with other forms of cancer; their median age at ovarian cancer diagnosis is 62 years. Do older patients respond as well to immunotherapy as younger patients? That is one of the things we are learning.

H&O What are the most important studies to look at immunotherapy and ovarian cancer?

AJ We are still in the infancy of having good clinical trial information about the efficacy of immunotherapy drugs in ovarian cancer. Notable trials include a phase 2 study of nivolumab (Opdivo, Bristol-Myers Squibb) by Hamanishi and colleagues, which was published in the *Journal of Clinical Oncology* in 2015, and phase 1 and 2 studies of PD-1 or PD-L1 inhibitors such as pembrolizumab (Keytruda, Merck) and avelumab (Bavencio, EMD Serono/Pfizer), which were reported at the 2015 annual meeting of the American Society of Clinical Oncology by Dr Andrea Varga and Dr Mary Disis, respectively. These studies have shown response rates of 10% to 15% for immunotherapy in ovarian cancer, and stable disease in an additional 20% to 45% of patients.

To improve these results, there is a lot of interest in combining checkpoint inhibitors with a second checkpoint inhibitor or with another immune-related drug. For example, our group is planning a phase 1 trial of PD-1 inhibition plus the antibodies anti-OX40 and anti-4-1BB.

Genentech/Roche is sponsoring a phase 3 trial called ATALANTE (Atezolizumab vs Placebo Phase III Study in Late Relapse Ovarian Cancer Treated With Chemotherapy + Bevacizumab; NCT02891824) that is combining carboplatin, paclitaxel, and bevacizumab with the anti-PD-L1 agent atezolizumab (Tecentriq, Genentech).

Another phase 3 trial, JAVELIN Ovarian 200 (A Study Of Avelumab Alone Or In Combination With Pegylated Liposomal Doxorubicin Versus Pegylated Liposomal Doxorubicin Alone In Patients With Platinum Resistant/Refractory Ovarian Cancer; NCT02580058), is looking at the use of avelumab with or without liposomal doxorubicin.

H&O Are certain patients with ovarian cancer better suited to treatment with immunotherapy?

AJ Right now, the jury is out. Endometrioid and clear cell ovarian cancers tend to have elevated rates of microsatellite instability; it's worth testing for microsatellite instability because pembrolizumab is approved for use in these patients. Right now, we do not have any way to determine which patients with high-grade serous ovarian cancer—the most common histologic type of ovarian cancer—are most likely to respond to immunotherapy. So far, there is no evidence that PD-L1 expression predicts response to immunotherapy in ovarian cancer. The study of pembrolizumab that Dr Varga presented required that participants' tumors have elevated expression of PD-L1,

and the response rates were not appreciably different from those in studies that did not limit enrollment by PD-L1 status.

H&O How can results be improved with immunotherapy in ovarian cancer?

AJ Our focus is on combination therapy, and on ways to improve it. At MD Anderson, we are very interested in learning what happens to tumors that are exposed to immunotherapy agents, so many of our trials include on-treatment biopsies. If we can learn what immune-evasive mechanisms may be activated when a tumor is exposed to a drug, we should be able to devise more rational combinations of agents.

An interesting aspect of ovarian cancer is that it tends to grow and recur in the peritoneal cavity. Could a local approach, in which immunotherapy is delivered to the abdominal cavity, play a role in this type of cancer? We are planning to conduct a phase I study at MD Anderson of intraperitoneal immunotherapy with the CTLA-4 inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) plus nivolumab in ovarian cancer. The goal is to activate the most relevant immune population—the immune cells and the lymphatics in the peritoneal cavity—while decreasing toxicity.

H&O How do you see immunotherapy being used in ovarian cancer in the future?

AJ Nobody is certain at this point, but immunotherapy is in its infancy in ovarian cancer compared with melanoma and many other cancers. I think the next 5 years will be key to finding out what does and does not work, and to identifying more-specific targets in ovarian cancer. I predict that 2 years from now, we will know far more about rational combinations of immunotherapy approaches

in ovarian cancer. My guess is that a combination of T cells and immune-modulating drugs may be necessary to provide widespread benefit.

Disclosure

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Suggested Readings

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