BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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The Dawn of Immunotherapy for Breast Cancer

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H&O Why have most of the efforts regarding immunotherapy in breast cancer been focused on triple-negative breast cancer?

LE Triple-negative breast cancer (TNBC) is a good target for immunotherapy for several reasons. First, these patients have a major unmet medical need because TNBC does not express the estrogen receptor, the progesterone receptor, or human epidermal growth factor receptor 2 (HER2)—the standard therapeutic targets in breast cancer. Because of this, in most circumstances no targeted therapies are available and we are left with only chemotherapy to treat these patients. Second, triple-negative tumors are more likely than other types of breast cancer to be infiltrated with immune cells, in particular T cells. Third, these tumors are more likely to be positive for programmed death ligand 1 (PD-L1). Fourth, the T cells in TNBCs are more likely to express the programmed death 1 (PD-1) receptor on their surface. The most successful immunotherapies to date target the PD-1 receptor or its ligand, PD-L1. The interaction between PD-1 and PD-L1 sends a negative signal to T cells within the tumor, shutting them down. Disrupting the PD-1/PD-L1 interaction with drugs that target this pathway takes the brakes off intratumoral T cells, unleashing their ability to attack and destroy the tumor.

Poly(ADP-ribose) polymerase (PARP) inhibitors are approved for use if a patient with metastatic TNBC has a germline mutation in *BRCA*, but in the majority of cases we are left with only chemotherapy to treat these patients. That is why the opportunity to use the anti–PD-L1 antibody atezolizumab (Tecentriq, Genentech) plus nab-paclitaxel (Abraxane, Celgene) in these patients represents a significant clinical advance. This immunotherapy combination received accelerated approval on March 8, 2019 from the US Food and Drug Administration (FDA) as a treatment for patients with unresectable locally advanced or metastatic TNBC that expresses PD-L1 in tumor-infiltrating immune cells.

H&O Is there any role for immunotherapy in other breast cancer subtypes?

LE Breast cancers overall tend to contain fewer T cells, and are thus "colder"—or less inflamed—than other tumors in which immunotherapy is widely used, such as melanoma, lung cancer, and bladder cancer. Within the breast cancer subtypes, the most inflamed tumors are triple-negative, the next most-inflamed tumors are HER2-positive, and the coldest tumors are those that are positive for the estrogen and/or progesterone receptor (luminal).

Researchers have been investigating the use of immunotherapy in patients with HER2-positive breast cancer. Although numerous therapies are available to treat these patients, immunotherapy has the potential to work in at least some cases because these patients are more likely than those with luminal breast cancer to have immune cells in their tumors. Even if immunotherapy does not work well on its own in HER2-positive breast cancer, the potential exists for synergy between HER2-directed therapies and immunotherapy.

Luminal breast cancer tumors, which are less inflamed and tend to contain far fewer T cells, are the least likely to respond to immunotherapy. As a result,

fewer studies of immunotherapy have been conducted in this breast cancer subtype. Researchers will need to take a different approach to immunotherapy in the vast majority of patients with luminal breast cancer. A combination immunotherapy strategy that either provides or induces T cells, thereby setting the stage for response to immunotherapy with drugs that target PD-1 and/or PD-L1, is a rational strategy for immunotherapy in these luminal cancers. These strategies might include adoptive T-cell transfer or vaccine administration.

PD-1/PD-L1 inhibitors are being tested in combination with many other treatments, including chemotherapy agents, radiation therapy, PARP inhibitors, and immunotherapy agents.

H&O Could you discuss the results of the IMpassion130 study that you were part of?

LE The IMpassion130 study (A Study of Atezolizumab in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Participants With Previously Untreated Metastatic Triple-Negative Breast Cancer) served as the basis for the FDA's approval of atezolizumab and nab-paclitaxel. This study was a global, randomized, double-blind, placebo-controlled phase 3 study that was published in the *New England Journal of Medicine* in the fall of 2018. A total of 902 patients were randomly assigned in a 1:1 ratio to nab-paclitaxel plus either atezolizumab or a placebo as first-line treatment for locally advanced unresectable or metastatic TNBC. Patients were not required to express PD-L1 in their tumors, but they were required to provide a tumor sample so this biomarker could be measured as part of the study, to assess its potential relationship with clinical benefit.

After a median follow-up of 12.9 months, we found that the median progression-free survival (PFS) was 7.2 months in the immunotherapy group and 5.5 months in the placebo group (hazard ratio [HR] for progression or death, 0.80; 95% CI, 0.69-0.92; *P*=.002) in the intention-to-treat patient population. The difference in median PFS was more pronounced among the 41% of patients whose tumors were positive for PD-L1 expression on tumor-infiltrating immune cells, with a median PFS of 7.5 months in the immunotherapy group and 5.0 months in the placebo group (HR, 0.62; 95% CI, 0.49-0.78; *P*<.0001). Median overall survival (OS) was also longer in the immunotherapy group than in the placebo group among patients with PD-L1–positive tumors, at 25.0 vs 15.5 months, respectively (HR, 0.62; 95% CI, 0.45-0.86)—almost a 10-month improvement. This is a clinically significant finding in this group of patients. Notably, among the PD-L1–negative patients, the addition of immunotherapy to nab-paclitaxel failed to extend PFS or overall survival. The combination of atezolizumab and nab-paclitaxel is therefore not indicated for PD-L1–negative patients with advanced TNBC.

H&O Which patients with breast cancer should be tested for PD-L1 expression?

LE The standard of care for a patient who is suspected of having metastatic breast cancer is to obtain a biopsy to confirm the diagnosis, and also to test the tumor for expression of HER2, the estrogen receptor, and the progesterone receptor. Patients with locally advanced unresectable or metastatic TNBC also should be evaluated for PD-L1 expression in tumor-infiltrating immune cells prior to first-line treatment for advanced TNBC to determine whether they could benefit from atezolizumab combined with nab-paclitaxel.

H&O What additional treatment combinations are being examined in an effort to boost the response to PD-1/PD-L1 inhibitors?

LE PD-1/PD-L1 inhibitors are being tested in combination with many other treatments, including chemotherapy agents, radiation therapy, PARP inhibitors, and immunotherapy agents. They are being combined with such agents as trastuzumab (Herceptin, Genentech) and trastuzumab emtansine (T-DM1; Kadcyla, Genentech) in HER2-positive breast cancer, and with endocrine therapy and cyclin-dependent kinase (CDK) 4/6 inhibitors in estrogen receptor–positive tumors. Multiple combination strategies also exist that integrate PD-1/PD-L1 inhibitors with other immuno-oncology agents such as vaccines; immune checkpoint antagonists of lymphocyte activation gene 3 (LAG-3), T-cell immunoglobulin and mucin protein 3 (TIM-3), cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and others; immune checkpoint agonists such as those that target the OX40 or 41BB pathways; innate immune agonists that target the Toll-like receptor (TLR) or stimulator of interferon genes (STING)

pathways; and metabolic pathways such as the indoleamine 2,3-dioxygenase (IDO) and adenosine pathways.

H&O What are some of the more notable studies of combination treatment with PD-1/PD-L1 inhibitors?

LE The combination of eribulin (Halaven, Eisai) and the anti–PD-1 agent pembrolizumab (Keytruda, Merck) has been tested in 104 patients with advanced TNBC who were not selected for PD-L1 expression. In the results that Dr Sara Tolaney presented at the 2018 San Antonio Breast Cancer Symposium, greater clinical benefit was observed with the combination than was seen in other studies with either eribulin or pembrolizumab alone, and clinical benefit occurred regardless of PD-L1 expression. I presented the results of KATE2 (A Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine in Combination With Atezolizumab or Atezolizumab-Placebo in Participants With Human Epidermal Growth Factor-2 Positive Locally Advanced or Metastatic Breast Cancer Who Received Prior Trastuzumab and Taxane Based Therapy) at the same meeting. KATE2 was a phase 2 global trial evaluating the addition of atezolizumab to T-DM1 in patients with metastatic HER2-positive breast cancer who had previously been treated with trastuzumab and a taxane. A total of 202 patients were randomly assigned in a 2:1 ratio to T-DM1 plus either atezolizumab or a placebo. After approximately 8 months, no difference in PFS was seen between the groups. However, an exploratory analysis revealed that among the patients who were PD-L1–positive, median PFS appeared to be longer with atezolizumab than with placebo, at 8.5 vs 4.1 months, respectively, although the difference was not statistically significant (HR, 0.60; 95% CI, 0.32-1.11). The combination of the PARP inhibitor niraparib (Zejula, Tesaro) and the PD-1 inhibitor pembrolizumab is being tested in both TNBC and ovarian cancer in the TOPACIO/KEYNOTE-162 study (Niraparib in Combination With Pembrolizumab in Patients With Triple-Negative Breast Cancer or Ovarian Cancer). Preliminary data in TNBC have revealed evidence of durable responses in some patients regardless of *BRCA* mutation status, PD-L1 expression status, or prior platinum exposure; the response rate was higher in patients with *BRCA* mutations.

H&O What other studies are being planned?

LE PD-1/PD-L1 agents are currently being added to single-agent and combination chemotherapies, particularly for the treatment of TNBC in the metastatic and neoadjuvant settings. Multiple trials are also looking at combinations of immunotherapy plus endocrine therapy, novel immune agents, new targeted agents, or radiation for patients with breast cancer, particularly TNBC or luminal breast cancer. There is also great interest in personalized immunotherapy, in which an individualized vaccine or cell-based immunotherapy that targets the genomic mutations unique to a patient's tumor is produced and then given with immune checkpoint blockade.

H&O What other immunotherapy approaches besides checkpoint inhibitors are being studied for use in breast cancer?

LE In addition to the strategies described earlier combining multiple immuno-oncology agents to further improve clinical benefit with immune checkpoint blockade, there is great interest in cell-based immunotherapies. Some of these are tumor infiltrating lymphocyte–based therapies, in which T cells are removed from the patient's tumor, expanded, and then reinfused; and chimeric antigen receptor (CAR) T-cell therapies, in which T cells are genetically engineered to express a protein that contains a binding domain that can recognize tumor antigens on the surface of the tumor cell and a signaling domain that can turn the T cell on. CAR T-cell–based therapies are approved for some hematologic malignancies, but so far they have not shown much success in solid tumors. There is great interest in developing these cell-based therapies in solid tumors, including breast cancer.

H&O How do the side effects of immunotherapy compare with those of other agents for breast cancer?

LE What immunotherapy does—at least the immune checkpoint agents that are most commonly used in the clinic today—is target a pathway that the body normally uses to prevent the immune system from getting out of control and causing autoimmune disease. When we disrupt that regulatory pathway, we increase the likelihood that patients will develop an immune response against their own tissues. That is why the side effect profile of immunotherapy includes autoimmune-type side effects. The combination we tested in IMpassion130 was pretty well-tolerated; the primary immune-related side effect was hypothyroidism, which tended to be mild and simple to treat with thyroid replacement. It is important to keep in mind that both patients who are on immunotherapy and their treating physicians need to be on the alert for the emergence of symptoms that could reflect an immune-related side effect. Early diagnosis is essential for the effective treatment of immune-related side effects associated with immune checkpoint blockade

with immunosuppressive agents such as corticosteroids and antagonists of cytokine signaling pathways.

H&O What do you see changing in the next few years?

LE In the next few years, we will see data from phase 3 trials testing the addition of PD-1/PD-L1 blockade to standard neoadjuvant and adjuvant therapies for TNBC, where preliminary data in the neoadjuvant setting has revealed a significant improvement in response rates. Studies adding PD-1/PD-L1 blockade to novel HER2-targeted agents are also likely to be launched. Greater numbers of trials testing a variety of immunotherapy strategies for luminal breast cancers will also be launched, and there should be some positive clinical data for combinations that harness the unique biology of luminal tumors. Studies exploring the use of immunotherapies using CAR T cells in solid tumors will increase, including in patients with breast cancer. Immunotherapy is an exciting and rapidly growing area of cancer research and treatment. I would encourage breast cancer patients for whom immunotherapy is not approved as a standard treatment option to participate in clinical trials whenever possible, because that will most quickly and effectively advance the area of breast cancer immunotherapy.

Disclosure

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Suggested Readings

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