Immunotherapy for the Treatment of Triple-Negative Breast Cancer

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Abstract

At JADPRO Live Virtual 2021, Sara M. Tolaney, MD, MPH, and Lindsay Shaw, ANP-BC, AOCNP®, presented on recent clinical trial data for approved immune checkpoint inhibitors and antibody-drug conjugates, and their implications in the current treatment landscape, for metastatic triple-negative breast cancer. Dr. Tolaney and Ms. Shaw also discussed principles of monitoring and managing adverse events associated with immunotherapies.

Checkpoint inhibitors as monotherapy have demonstrated limited activity in metastatic triple-negative breast cancer, but when given in combination with chemotherapy, significant improvements in disease control and survival have been made. During JADPRO Live Virtual 2021, Sara M. Tolaney, MD, MPH, and Lindsay Shaw, ANP-BC, AOCNP®, of the Dana-Farber Cancer Institute, evaluated recent clinical trial data for approved immune checkpoint inhibitors and antibody-drug conjugates in metastatic triple-negative breast cancer and discussed the management of adverse events associated with immunotherapies.

IMMUNE CHECKPOINT INHIBITION IN TNBC

Of the three different subtypes of breast cancer (hormone receptor-positive, HER2-positive, and triple negative), triple negative is considered more immunogenic given the increased presence of tumor infiltrating lymphocytes found in the microenvironment and the higher levels of expression of PD-L1. Triple-negative breast cancer is also associated with increased tumor mutational burden.

As Dr. Tolaney explained, however, response rates to checkpoint inhibitor monotherapy have been very low, especially among patients who have received prior therapies. Thus, the field is moving towards more novel combinations, she said, not just for triple-negative disease but also for other subtypes of breast cancer.

IMMUNOTHERAPY AND CHEMOTHERAPY COMBINATION

IMpassion130 was the first pivotal trial to use standard chemotherapy in combination with immunothera-
In the study, patients with untreated metastatic triple-negative breast cancer were randomized to receive the PD-L1 inhibitor atezolizumab (Tecentriq) plus nab-paclitaxel or placebo plus nab-paclitaxel (Schmid et al., 2018).

The addition of atezolizumab to nab-paclitaxel prolonged progression-free survival, said Dr. Tolaney, but only in patients whose tumors expressed PD-L1. Patients whose tumors were PD-L1 negative had no benefit in progression-free survival.

The same was true for overall survival. While there was no benefit in overall survival in PD-L1-negative patients, a positive trend was observed for PD-L1-positive patients, with a difference in survival of about 7 months.

IMMUNE-RELATED TOXICITIES
Despite the improvements in survival and disease control, advanced practitioners should be mindful of immune-related toxicities associated with immunotherapies.

“When you take the brakes off T cells, they can get overstimulated and start to attack the body’s organs,” said Ms. Shaw. “One of the challenges with immunotherapy is the adverse events caused by inflammation. These drugs can cause an autoimmune response in any organ.”

Endocrinopathy is one of the most common subsets of adverse events associated with immunotherapies. Thyroid toxicity tends to occur within the first 12 to 16 weeks of therapy, and patients who are already on thyroid replacement often need dose adjustments.

“The data suggest checking thyroid function every 8 to 12 weeks, but we tend to check it more frequently because we’ve seen a fair amount of people with this toxicity,” said Ms. Shaw.

Although less commonly observed, type 1 diabetes is another endocrine toxicity associated with immunotherapy. Most people who develop type 1 diabetes present with diabetic ketoacidosis and can require admission, an endocrine consult, and immediate insulin therapy.

Adrenal insufficiency is another rare but potentially significant endocrine toxicity.

“If people present with asthenia, severe fatigue, low sodium, decreased appetite, weight loss, or are feeling generally unwell, we check AM cortisol levels and may need to do an adrenocorticotropic hormone test,” said Ms. Shaw. “Patients with AM cortisol less than 1 need an endocrine referral quickly and are treated with hydrocortisone and fludrocortisone.”

Skin toxicity is another common side effect. Mild rashes will often respond to topical steroids, but more diffuse rashes may require dermatology, said Ms. Shaw, who noted that several patients have also developed vitiligo.

Lung toxicity is also a concern. Patients who are short of breath or have a dry cough should receive a CT scan to assess for pneumonitis. Patients with severe symptoms require admission or pulmonary referral and should be started on a steroid taper (e.g., prednisone) that lasts 8 to 12 weeks.

Diarrhea can be indicative of colitis. Although rare, severe colitis requires endoscopy, colonoscopy, and oral steroids. Other complications included pancreatitis and hepatitis.

“Even though severe side effects are rare, it’s important to warn patients about potential toxicities,” said Ms. Shaw. “We counsel patients extensively about these and tell them to give us a call if anything is amiss.”

“It’s also important to have a low threshold for evaluation of immune-related toxicities because they can lead to serious complications if not caught and properly addressed,” Dr. Tolaney added.

ATEZOLIZUMAB: FDA WITHDRAWS ACCELERATED APPROVAL
The FDA recently withdrew the accelerated approval for atezolizumab based on data from the confirmatory IMpassion131 trial (Miles et al., 2021).

“Accelerated approval was granted by the FDA based on the improvement in progression-free survival reported in the IMpassion130 trial, but a confirmatory study was required to prove survival benefit,” said Dr. Tolaney. “Unfortunately, no benefit was seen with the addition of atezolizumab to paclitaxel.”

Dr. Tolaney noted that paclitaxel, which requires steroid premedication, was used in the IMpassion131 study, whereas nab-paclitaxel, which does not, was used in the original pivotal trial.

“Patients can continue atezolizumab if they are receiving it already and benefitting, but atezolizumab is no longer an option for patients in the US,” said Dr. Tolaney.
PEMBROLIZUMAB
Pembrolizumab (Keytruda), a checkpoint inhibitor targeting PD-1, is now the only immunotherapeutic option for patients with triple-negative breast cancer. Results from the KEYNOTE-355 study of pembrolizumab plus chemotherapy vs. placebo plus chemotherapy showed a 4-month improvement in progression-free survival in patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer that was PD-L1 positive (Cortes et al., 2020). No benefit was seen in PD-L1-negative tumors.

Unlike the IMpassion131 study, physicians were given a choice of chemotherapy to administer with pembrolizumab: paclitaxel, nab-paclitaxel, or a combination of carboplatin and gemcitabine. Benefit was seen regardless of chemotherapy backbone.

“Even with paclitaxel, which requires steroid premedication, a very nice benefit was observed, so physicians are free to choose the chemotherapy that they use in combination with pembrolizumab,” Dr. Tolaney said.

A test using the 22C3 antibody and a combined positive score (CPS) greater than or equal to 10 to confirm PD-L1–positivity is required to receive pembrolizumab.

“Immunotherapy is standard with pembrolizumab in combination with chemotherapy if your tumor is PD-L1 positive but only in the first-line setting for metastatic triple-negative disease,” said Dr. Tolaney.

IMMUNOTHERAPY FOR EARLY-STAGE TNBC
Immunotherapy is also effective for early-stage breast cancer. Recent data from the pivotal phase III KEYNOTE-522 trial showed a positive-event free survival in patients with high-risk, early-stage, triple-negative breast cancer who received pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab vs. neoadjuvant chemotherapy followed by adjuvant placebo (Schmid et al., 2021).

“The addition of one year’s worth of pembrolizumab to chemotherapy improved both pathologic complete response rates and event-free survival, so in essence, it was preventing recurrence of breast cancer,” said Dr. Tolaney, who called the 40% reduction in recurrence in the experimental arm “very impressive.”

“These data show that we can improve long-term outcomes for these patients,” she added.

Data from the KEYNOTE-522 trial led to the FDA approval of pembrolizumab for early-stage patients. The benefit for early-stage patients was seen regardless of PD-L1 status, so there is no need to test for the 22C3 antibody.

PARP INHIBITION
For patients who have germline BRCA mutations, recent data also suggest that adjuvant PARP inhibitors can improve outcomes. Results of the OlympiA study showed a 40% reduction in recurrence events with 1 year of olaparib following completion of systemic therapy (Tutt et al., 2021).

“This signifies that we need to be testing all high-risk, early-stage patients for genetic mutations,” said Dr. Tolaney. “BRCA mutation status can now impact systemic treatment recommendations in the early-stage setting, so it’s really important to get that information.”

PARP inhibitors are also approved in the metastatic setting for germline BRCA-mutant patients based on data comparing PARP inhibitors to chemotherapy.

“The results of both the EMBRACA and OLYMPIA trials suggest that PARP inhibition not only controls disease longer but is also associated with better quality of life compared with chemotherapy,” said Dr. Tolaney, who reported a 3-month improvement in progression-free survival with PARP inhibitors.

ANTIBODY-DRUG CONJUGATES: SACITUZUMAB GOVITECAN
Antibody-drug conjugates are another treatment option for patients with metastatic triple-negative breast cancer. Results of the phase III ASCENT trial, which compared sacituzumab govitecan (Trodelvy) to standard chemotherapy in patients with refractory/relapsed metastatic triple-negative breast cancer who had received at least two prior lines of chemotherapy, showed a significant improvement in progression-free survival (Bardia et al., 2021). Patients who received the antibody-drug conjugate had a progression-free survival of 5.6 months compared with just 1.7 months with standard chemotherapy.
“Sacituzumab did much better than standard chemotherapy in this study, but these data also show, unfortunately, that chemotherapy isn’t doing what it needs to do in this pretreated group of patients,” said Dr. Tolaney. “Sacituzumab also dramatically improved overall survival, nearly doubling the time that these patients are alive.”

The toxicity profile of sacituzumab includes neutropenia, diarrhea, and alopecia.

“The hair loss occurs quickly and is fairly complete,” said Ms. Shaw. “Patients also experience fatigue, low-grade diarrhea, and low-grade nausea, and there is at least a 50% chance of neutropenia, which could result in dose delays.”

Neutropenia is treated with growth factor (filgrastim and/or pegfilgrastim). Ms. Shaw recommended using filgrastim for 3 to 4 days after day 1 and pegfilgrastim after day 8. Ondansetron or chlorpromazine is used for nausea, and loperamide is recommended for diarrhea.

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