BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Managing Adverse Events of Immunotherapy in Breast Cancer

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H&O Which immunotherapy agents have been approved for use in breast cancer?

HS The first immunotherapy agent to receive accelerated approval for breast cancer in the United States was the programmed death ligand 1 (PD-L1) inhibitor atezolizumab (Tecentriq, Genentech). Atezolizumab, in combination with nab-paclitaxel (Abraxane, Bristol Myers Squibb), was approved for use in metastatic triple-negative breast cancer (TNBC). The approval was based on results of the IMpassion130 trial, which appeared in the *New England Journal of Medicine* in 2018. However, these results were not confirmed by IMpassion131, in which solvent-based paclitaxel was used instead of nab-paclitaxel. Following discussions with the US Food and Drug Administration, the sponsor elected to withdraw its accelerated approval of atezolizumab within the United States.

The programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck) is approved for 3 breast cancer indications in the United States. The first indication is for the first-line treatment of metastatic TNBC with a combined positive score of 10 or higher; pembrolizumab is administered in combination with paclitaxel/nab-paclitaxel or carboplatin/gemcitabine. This approval is based on the results of KEYNOTE-355. The second indication is for the treatment of any metastatic cancer—including breast cancer—that is microsatellite instability–high or that has a tumor mutation burden greater than 10 mutations per megabase. The third indication is for the treatment of stage II or III TNBC in combination with carboplatin/paclitaxel, followed by doxorubicin/cyclophosphamide in the preoperative setting and then by up to 9 cycles of pembrolizumab in the postoperative setting. This approval is based on the results of KEYNOTE-522.

H&O What adverse events (AEs) are most common with immunotherapy?

HS AEs that are commonly seen with immunotherapy drugs such as pembrolizumab are fatigue, rash, muscle/joint aches, diarrhea, fever, cough, shortness of breath, and laboratory abnormalities in blood counts, liver enzymes, blood sugar levels, and the thyroid gland. The majority of these AEs are mild, but in some rare cases they can be life-threatening.

H&O Which AEs are most concerning?

HS Autoimmune AEs can rarely cause life-threatening complications that must be treated promptly, such as severe diarrhea, pneumonitis with breathing difficulty, myocarditis, and severe skin reactions. Another concern is adrenal insufficiency, which may require life-long corticosteroid replacement therapy following treatment.

H&O How are these AEs addressed?

HS Mild asymptomatic abnormalities or limited skin reactions can be treated conservatively with observation or topical agents while therapy continues. For most symptomatic or severe systemic immune AEs, the checkpoint agent is withheld and a systemic corticosteroid (prednisone at 1 mg/kg per day or its equivalent) is initiated, with a slow taper that is started when the side

effect has resolved. If endocrine dysfunction is present, then appropriate replacement therapy for the deficiency is initiated. Other immune suppressant drugs are used in cases, such as infliximab for severe autoimmune colitis or mycophenolate mofetil for hepatitis that are refractory to corticosteroids. Published guidelines from Emens and colleagues for the Society for Immunotherapy of Cancer and from the National Comprehensive Cancer Network are available to guide oncology providers on how to manage autoimmune adverse events, but appropriate specialists should be consulted for more severe cases.

H&O What are the risks of long-term corticosteroid use?

HS The long-term use of supraphysiologic doses of corticosteroids can result in symptoms of Cushing syndrome, such as hypertension, hyperglycemia, weight gain, immune dysfunction, and osteoporosis.

H&O Are certain patients more likely to experience AEs?

HS Younger age, the use of combination immunotherapy treatments such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) blockade plus PD-1 blockade, and a diagnosis of lung cancer are associated with an elevated risk for the development of a severe immune-related AE, as detailed by Kalinich and colleagues in the *Journal for ImmunoTherapy of Cancer* in 2021. A variety of exploratory biomarker studies have been done to identify additional predictors of AEs, but none to date are considered to be actionable or standard of care, as discussed in a systematic review by Hommes and colleagues in *Frontiers in Oncology* in 2021.

H&O Should immunotherapy be used for patients with a pre-existing autoimmune condition?

HS Decisions about immunotherapy in patients with a pre-existing autoimmune condition are complicated. The provider must conduct an individualized risk/benefit assessment based on the specific condition, its severity, requirements regarding the use of systemic immunosuppressive agents, the risk from the malignancy, and the potential for clinical benefit—whether the treatment would be curative or palliative. We have limited data from Menzies and colleagues, published in the *Annals of Oncology* in 2017, suggesting that selected patients with certain well-controlled autoimmune conditions that do not affect critical organ systems—such as mild vitiligo and thyroiditis—can safely undergo checkpoint therapy with close monitoring.

H&O Can immunotherapy be used in transplant recipients?

HS The data on using immunotherapy in transplant patients are limited, but there does appear to be an elevated risk for graft rejection and mortality when it is used. In a retrospective study by Abdel-Wahab and colleagues, published in the *Journal for ImmunoTherapy of Cancer* in 2019, organ rejection occurred in 41% of patients who received checkpoint inhibition at a median of 9 years after solid organ transplant. Of these, organ loss occurred in 81%, and 46% died. As a result, the routine use of immunotherapy is discouraged in this population outside a clinical trial or specialized referral center.

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H&O Does the occurrence of immune-related AEs predict response to treatment?

HS Some information suggests that the occurrence of certain dermatologic, endocrine, and gastrointestinal immune-related AEs may be associated with a higher likelihood of improved overall survival (OS) in patients with lung, melanoma, or genitourinary cancer. We believe that the development of these AEs may indicate an ability of the checkpoint inhibitor to overcome the body's immune tolerance of self-antigens.

For example, a retrospective study by Martini and colleagues, published in *The Oncologist* in 2021, found significantly longer OS, longer progression-free survival, and a higher chance of clinical benefit among patients treated for metastatic renal cell carcinoma with checkpoint inhibitors if they experienced endocrine immune-related AEs, particularly if those events were related to the thyroid.

A meta-analysis by Wang and colleagues, which appeared in *Frontiers in Oncology* in 2021, found that OS was improved in patients treated with checkpoint inhibitors for lung cancer who experienced dermatologic, endocrine, or gastrointestinal immune-related AEs. In contrast, OS was not improved in patients who experienced hepatobiliary,

pulmonary, or high-grade immune-related AEs. These findings suggest that when autoimmunity is severe, it negates the clinical benefits of immunotherapy. On the other hand, a retrospective study by Suo and colleagues, which appeared in *The Oncologist* in 2020, found an association between grade 3 or higher immune-related AEs and improved OS among patients with advanced melanoma.

The association between immune-related AEs and breast cancer is not well defined and requires further follow-up as more patients receive immunotherapy.

Disclosures

Dr Soliman has done consulting for Eisai, AstraZeneca, Seagen, Novartis, and Daiichi Sankyo.

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