BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Novel Therapies for Triple-Negative Breast Cancer

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H&O How common is triple-negative breast cancer?

RN Triple-negative breast cancer (TNBC) is less common than other forms of breast cancer, accounting for approximately 15% of all breast cancers. Nonetheless, because breast cancer is so common, TNBC affects a large number of people. It is especially prevalent in individuals of African or Hispanic ancestry, as well as in younger women and those with a *BRCA1* germline mutation.

H&O What is the standard treatment approach for individuals with TNBC?

RN The treatment for TNBC has historically been chemotherapy because no targeted therapies had received US Food and Drug Administration (FDA) approval until relatively recently. Although chemotherapy remains the mainstay of treatment, poly(ADP-ribose) polymerase (PARP) inhibitors are an option in the advanced setting for patients who have TNBC with a germline *BRCA1* or *BRCA2* mutation. PARP inhibitors also are being investigated in carriers of a *BRCA* mutation with early-stage disease. In addition, for individuals with advanced TNBC whose tumors express programmed death ligand 1 (PD-L1), we have 2 FDA-approved immunotherapy options. Some 20% to 40% of patients with recurrent, metastatic TNBC have PD-L1–positive disease; in these patients, atezolizumab (Tecentriq, Genentech) and pembrolizumab (Keytruda, Merck) have both demonstrated the ability to improve progression-free survival (PFS) when added to chemotherapy. For the majority of patients with TNBC, however, chemotherapy remains the primary option.

H&O Which new treatment approaches are currently being investigated?

RN A number of trials—both ongoing and completed—are evaluating the effectiveness of PARP inhibitors, immunotherapy, or both in patients with early-stage TNBC; these include a phase 2 study of talazoparib (Talzenna, Pfizer; NCT03499353) and the ongoing phase 2 I-SPY2 trial, results of which were published earlier this year in *JAMA Oncology*. PARP inhibitors have been evaluated as monotherapy in individuals with germline *BRCA1/2* mutations and in combination with chemotherapy and immunotherapy in patients who do not carry a mutation. In patients with metastatic disease, immunotherapy is approved for those who have PD-L1–positive TNBC. In the early-stage setting, immunotherapy appears to benefit patients regardless of PD-L1 status (in data from I-SPY2, KEYNOTE-522, and IMpassion031), and those with high-risk disease seem to benefit the most from the addition of immunotherapy to standard neoadjuvant chemotherapy.

Furthermore, phase 3 trials are studying the efficacy of mitogen-activated protein kinase 1 (MEK) inhibitors, AKT serine/threonine kinase 1 (AKT1) inhibitors, or phosphoinositide 3-kinase (PI3K) inhibitors in combination with chemotherapy—and immunotherapy as well—in patients who have advanced TNBC.

In another approach, the use of androgen receptor (AR) antagonists is being investigated in patients with TNBC that expresses the AR. The Translational Breast Cancer Research Consortium (TBCRC) will soon be opening a trial to evaluate physician's choice of chemotherapy vs enzalutamide (Xtandi, Astellas) vs enzalutamide plus a glucocorticoid receptor antagonist (mifepristone) in patients with advanced AR-positive TNBC.

Finally, the antibody-drug conjugate sacituzumab govitecan-hziy (Trodelvy, Immunomedics) received FDA approval earlier this year for use in patients with metastatic TNBC who have received at least 2 lines of therapy for advanced disease. Trials are ongoing evaluating the role of sacituzumab in the (neo)adjuvant setting.

Researchers are also looking at combination immunotherapy in advanced-stage and even early-stage disease. These immunotherapy agents include novel drugs that target such proteins as lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin- and mucin-domain-containing-3 (TIM3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and Toll-like receptors (TLRs).

H&O Are any trials looking at endocrine therapy for TNBC?

RN Estrogen receptor beta (ERβ) expression in early TNBC is associated with a high risk for recurrence and poor overall survival. ERβ is expressed in up to 30% of TNBCs, and in vivo studies have shown that treatment of ERβ-positive tumors with estradiol has led to tumor regression. The phase 2 TBCRC 051 trial is examining the efficacy of estradiol therapy in patients with advanced TNBC that expresses ERβ (NCT03941730).

> I suspect that immunotherapy will eventually receive FDA approval for use in early-stage TNBC.

H&O What approaches can potentially be used in the neoadjuvant setting?

RN In the neoadjuvant setting, multiple trials have shown an improvement in the pathologic complete response (pCR) rate with the addition of immunotherapy to standard neoadjuvant chemotherapy, including I-SPY2, KEYNOTE-522, and IMpassion031. In I-SPY2, we found that the addition of pembrolizumab to standard neoadjuvant chemotherapy more than doubled the estimated pCR rates in both patients with hormone receptor–positive/human epidermal growth factor receptor 2 (HER2)–negative breast cancer and those with TNBC. KEYNOTE-522, a randomized phase 3 trial published earlier this year in the *New England Journal of Medicine*, confirmed that the addition of pembrolizumab to neoadjuvant chemotherapy significantly improved the pCR rate among patients with early-stage TNBC. IMpassion031, which was presented at the European Society for Medical Oncology (ESMO) 2020 annual meeting and simultaneously published in the *Lancet*, showed that the addition of atezolizumab to standard neoadjuvant chemotherapy also significantly improved pCR in comparison with chemotherapy alone. I suspect that immunotherapy will eventually receive FDA approval for use in early-stage TNBC, but more work to identify biomarkers predictive of response to immunotherapy is needed.

H&O Do researchers understand why immunotherapy was shown to be effective in PD-L1–positive metastatic TNBC in IMpassion130 but not in IMpassion131?

RN In IMpassion130, the addition of atezolizumab to nab-paclitaxel (Abraxane, Celgene) significantly improved PFS and overall survival. In IMpassion131, by contrast, the addition of atezolizumab to paclitaxel did not significantly improve PFS or overall survival in either the PD-L1–positive population or the intent-to-treat population. Although it remains unclear why IMpassion130 and IMpassion131 had differing results, a number of explanations are possible. First, we know that PD-L1 is not a robust predictive biomarker. In the setting of early breast cancer, PD-L1 status does not correlate with benefit from the addition of an immune checkpoint inhibitor to chemotherapy. Secondly, it is possible that the difference between the outcomes of these 2 trials occurred by chance; the confidence intervals for the paclitaxel and paclitaxel-plus-atezolizumab arms overlapped. Although some believe that the corticosteroid premedication used with paclitaxel may have suppressed the efficacy of the immune checkpoint inhibitor, I believe this explanation is less likely given the significant efficacy signals observed in the neoadjuvant setting when checkpoint inhibitors were added to paclitaxel-based chemotherapy.

H&O What does the future hold for research on TNBC?

RN A number of advances in the treatment of TNBC have been made over the last 2 years, including the approvals of PARP inhibitors for disease associated with a *BRCA1/2* mutation, immunotherapy for PD-L1–positive disease, and sacituzumab govitecan-hziy for pretreated metastatic TNBC. With the identification of these effective agents for metastatic TNBC, future trials will focus on investigating their role in early breast cancer.

What has become increasingly apparent is the need for biomarkers predictive of response. We know that mutations in *BRCA1* and *BRCA2* can help predict who will benefit from PARP inhibitors, and ongoing trials are evaluating other biomarkers predictive of a PARP inhibitor response. Dr Nadine Tung recently published data demonstrating that PARP inhibition also benefits patients with metastatic breast cancer who have germline *PALB2* mutations. Additionally, those with somatic *BRCA1/2* mutations derived benefit from the PARP inhibitor olaparib (Lynparza, AstraZeneca).

Although PD-L1 positivity is predictive of an immunotherapy benefit in metastatic TNBC, it is far from perfect as a biomarker. Research focused on identifying more robust markers predictive of benefit is ongoing.

Disclosure

Dr Nanda has served on the advisory boards of Aduro Biotech, Athenex Oncology, Clovis, Daiichi Sankyo, Genentech, Immunomedics, MacroGenics, Merck, Pfizer, and Seattle Genetics; has served on the data and safety monitoring board of G1 Therapeutics; and has received research funding from AstraZeneca, Celgene, Corcept Therapeutics, Genentech/Roche, Immunomedics, Merck, OBI Pharma, Odonate Therapeutics, Pfizer, and Seattle Genetics.

Suggested Readings

Emens LA, Adams S, Barrios CH et al. IMpassion130: final overall survival analysis from the pivotal phase III study of atezolizumab plus nab-paclitaxel vs placebo plus nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. [ESMO abstract LBA16]. *Ann Oncol*. 2020;30(5)(suppl).

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