Advances in the Treatment of HER2-Positive Breast Cancer

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Although targeted therapies have improved outcomes, including survival, for many women with human epidermal growth factor receptor 2 (HER2)–positive breast cancer, the risk of recurrence remains an issue for many. At JADPRO Live 2018, Reshma Mahtani, DO, of Sylvester Comprehensive Cancer Center and Lisa Hineman, MS, AOCN®, PHN, ANP-C, of the Los Angeles Cancer Network, reviewed the landmark clinical trials of adjuvant therapies for these women, explored the decision points along the way regarding adjuvant systemic therapies, addressed which patients may be candidates for extended adjuvant therapy, and highlighted newer agents being evaluated for brain metastases. They also focused on the key role played by advanced practitioners in managing the adverse effects of adjuvant therapies, particularly diarrhea, and helping these women remain on treatment to reap the long-term benefits.

ESTABLISHED AND NEWER AGENTS

A greater understanding of the molecular mechanisms underlying the pathogenesis of this type of breast cancer has led to increased therapeutic options targeting the HER2 molecular pathway for patients with HER2-positive breast cancer. Among the targeted therapies, some such as trastuzumab (Herceptin), pertuzumab (Perjeta), and ado-trastuzumab emtansine (Kadcyla; also known as T-DM1) are larger molecules that work on the outside of the cell, explained Dr. Mahtani. Others, including lapatinib (Tykerb) and neratinib (Nerlynx), work intracellularly "to decrease downstream signaling and ultimately decrease cellular proliferation," she said.

Landmark Adjuvant Trials

Dr. Mahtani briefly reviewed the four landmark trials in support of adjuvant trastuzumab: HERA (Cameron et al., 2017; Goldhirsch et al., 2013; Romond et al., 2005), the NSABP B-31 and NCCTG N9831 joint analysis (Perez et al., 2014), and BCIRG 006 (Slamon et al., 2011, 2015; Table 1). All studies showed a "consistent benefit" to adding trastuzumb for 1 year over chemotherapy alone—reducing the risk of relapse, improving disease-free survival, and overall survival.

To answer the question of whether patients with smaller, node-negative, HER2-positive tumors could be spared more toxic

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Table 1. Disease-Free Survival Adjuvant Studies

Trial	Chemotherapy alone	Chemotherapy + trastuzumab
NCCTG N9831/ NSABP B-31 N = 3551 10-year 20% crossover	62%	73%
HERA N = 5,090 8-year 52% crossover	66%	72%
BCIRG-006 Abs PD5-01 N = 3,222 10-year 3% crossover	68%	74%[a]

Note. Information from Goldhirsch et al. (2013); Romond et al. (2005); Slamon et al. (2011).
[a]73% docetaxel, carboplatin, and trastuzumab [TCH]; 75% doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab [ACTH].

chemotherapy regimens, investigators at Dana-Farber Cancer Institute conducted the APT trial (Tolaney et al., 2015). The APT trial was a single-arm, phase II study. The patient population included those with HER2-positive, node-negative, estrogen receptor–positive or –negative disease with small tumors (≤ 3 cm). In lieu of aggressive chemotherapy, patients received weekly paclitaxel along with trastuzumab and then completed 1 year of trastuzumab in the adjuvant setting.

The updated 7-year disease-free survival rate was 93.3% (Tolaney et al., 2017). According to Dr. Mahtani, this finding suggests that the field is "making headway" for women with smaller, node-negative tumors; however, for patients with more advanced disease, relapse remains a problem. Adjuvant trastuzumab has improved—but not eliminated—the risk of recurrence for many patients with HER2-positive disease, she said. In fact, the disease-free survival rate 10 years out in the NCCTG N9831, BCIRG 006, and NSABP B-31 trials is between 73% and 74%. "This is clearly not as high as we would like to see," Dr. Mahtani stated.

Thus, relapse after adjuvant trastuzumab-containing therapy represents a therapeutic challenge, with between 15% and 20% of patients experiencing a recurrence of invasive breast cancer at a median follow-up of 10 years (Goldhirsch et al., 2013; Perez et al., 2014; Piccart-Gebhart et al., 2016). In addition, HER2-positive breast cancer also often metastasizes to the liver, brain, and lungs.

RECOMMENDATIONS FOR *HER2* TESTING

Dr. Mahtani briefly mentioned the struggle for many clinicians on how best to incorporate some of the new guidelines for HER2 testing into clinical practice. She focused on the recommendations for HER2 testing from the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP; Wolff et al., 2013) and the National Comprehensive Cancer Network (NCCN, 2018a). In brief, they state that all patients with invasive breast cancer should be tested by an accredited laboratory, and when results are equivocal, reflex testing with alternative assay is warranted, with testing repeated if results are discordant.

"Many patients are referred to my institution to help resolve confusion surrounding HER2 test results," Dr. Mahtani said, "Physicians are struggling to understand how to interpret HER2 test results, and hopefully the ASCO/CAP 2018 update will help resolve some of this confusion."

To refine some of the more controversial criteria, the 2018 iteration of the ASCO/CAP guidelines focused on several clinical questions (Wolff et al., 2018): (1) the appropriate definition of immunohistochemistry (IHC) 2+ results (equivocal for HER2 protein expression [nonuniform or weak membrane staining but has circumferential distribution in at least 10% of cells]); (2) the need to repeat testing on the biopsy and on the definitive specimen; and (3) unusual patterns of in situ hybridization (ISH) testing. Although two of the categories clearly define HER2-positive and HER2-negative disease, the other groups, which center on ISH-positive but a discordant ratio and copy number, require more clarity. These other groups represent "less than 5% of the cases but 100% of the confusion," noted Dr. Mahtani. These updated guidelines should help clinicians employ HER2 testing more accurately.

SYSTEMIC THERAPY DECISION POINTS

Neoadjuvant Therapy

Who is a candidate for neoadjuvant systemic therapy for early breast cancer? Patients with a high

tumor-volume-to-breast ratio; lymph node–positive disease; and high-risk features (high-grade, hormone receptor–negative, HER2-positive, triple-negative disease), according to Dr. Mahtani. She recommended that women with HER2-positive, T2, and/or node-positive disease receive neoadjuvant chemotherapy with trastuzumab/pertuzumab (Burstein et al., 2016). "It has been shown to increase pathologic complete response rates; it is my standard practice and what the guidelines support," she said.

According to the NCCN Clinical Practice Guidelines in Oncology for breast cancer (NCCN, 2018a), the preferred regimen for neoadjuvant therapy for HER2-positive breast cancer is doxorubicin and cyclophosphamide followed by paclitaxel plus trastuzumab with or without pertuzumab, or docetaxel, carboplatin, and trastuzumab with or without pertuzumab. The NCCN Guidelines also list a host of other combination regimens.

Adjuvant Therapy

Who is a candidate for adjuvant chemotherapy? "We know that the biology of HER2-positive disease is aggressive, so many of these patients are going to require adjuvant chemotherapy and trastuzumab," Dr. Mahtani pointed out. Generally, these are patients with clinical stage I, IIA, IIB, or T3N1M0 breast cancer. Studies have shown that patients who have hormone receptor–negative, HER2-positive disease should receive chemotherapy plus HER2-targeted therapy, and those with hormone receptor–positive, HER2-positive disease need the same, plus endocrine therapy (Burstein et al., 2016). The possible exception in both cases is T1a disease, "which represents an area of debate," she added.

The decision regarding adjuvant chemotherapy should be based on the patient's predicted sensitivity to treatment, potential benefit, the risk of relapse, as well as patient preferences and comorbidities, she sumarized.

Duration of Adjuvant Trastuzumab

Many studies have questioned whether a shorter duration of trastuzumab would be noninferior to the standard 1 year of treatment, and whether a longer duration may be more effective. The French PHARE trial failed to show noninferiority for 6 months vs. 12 months of adjuvant trastuzumab (Pivot et al., 2013), and in the HERA trial (Cameron et al., 2017; Goldhirsch et al., 2013), extending the duration of adjuvant trastuzumab beyond 1 year did not improve disease-free survival. On the other hand, the PERSEPHONE trial actually did show that 6 months was noninferior to 12 months after 5.4 years of follow-up (Earl et al., 2018), but Dr. Mahtani urged caution in applying these findings to clinical practice: "Not many of our patients receive only anthracycline-based or only taxane-based therapy, but in this trial, some did," she explained. Although noninferiority with the shorter duration of therapy was reported, Dr. Mahtani maintained that 1 year of adjuvant trastuzumab remains the standard of care for now, although the PERSEPHONE data are "reassuring," she said.

BUILDING ON TRASTUZUMAB: ADDITIONAL TARGETED THERAPIES

Trastuzumab Plus Pertuzumab

For women with HER2-positive early breast cancer who are at high risk of recurrence, additional HER2-targeted therapy may be indicated. For instance, the combination of trastuzumab and pertuzumab may offer a benefit for patients who have hormone receptor–negative or node-positive disease, based on the findings of the phase III APHINITY trial (von Minckwitz et al., 2017), which led to the regimen's approval by the US Food and Drug Administration (FDA) in the adjuvant setting. For the APHINITY trial patients, all of whom had surgery upfront, the 4-year invasive disease-free survival was 92.3% vs. 90.6% with placebo (von Minckwitz et al., 2017).

Dr. Mahtani considered the 1.7% benefit to be "quite small but still present" in reducing the risk of recurrence. "We were a bit underwhelmed, as we expected to see a little bit more of a benefit," she acknowledged. The benefit was greatest in patients with node-positive and hormone receptor–negative disease (hazard ratio = 0.81). No new safety signals were observed, and cardiac events were infrequent.

Neratinib

Neratinib is the only approved therapy for extended adjuvant treatment after adjuvant trastuzumab-

based therapy. In the 5-year update of the ExteNET trial, Martin and colleagues reported a 2.5% benefit in terms of invasive disease–free survival with the addition of neratinib (Martin et al., 2017). In fact, the rate was 4% among patients with hormone receptor–positive disease, which Dr. Mahtani called a "striking difference," but patients with hormone receptor–negative disease experienced no benefit from the extended adjuvant treatment. Overall survival data are expected to mature in 2019.

"In the extended adjuvant setting, I'd encourage you to consider the use of neratinib in patients who have already completed 1 year of HER2-directed therapy," she suggested, especially for patients considered at high risk for recurrence, such as those who initially presented with node-positive disease or had residual disease after neoadjuvant chemotherapy.

Following JADPRO Live 2018, at the San Antonio Breast Cancer Symposium, practice-changing data were presented from the KATHERINE trial. The trial showed that for patients with residual invasive disease following neoadjuvant therapy, T-DM1 reduced the risk of developing an invasive recurrence or death by 50% (von Minckwitz et al., 2019).

MANAGING ADVERSE EVENTS OF ADJUVANT THERAPIES: FOCUS ON DIARRHEA

Ms. Hineman then discussed the management of adverse events associated with adjuvant therapies, an area in which advanced practitioners play a role. She noted that managing one such toxicity—diarrhea—is the key to assuring that patients remain on anti-HER2 agents and thus derive optimal benefit. "Knowing how well adjuvant therapies work, it's our job to learn how to treat patients and get them through their therapies," she said.

Among the adverse events of interest with the combination of trastuzumab and pertuzumab are diarrhea and neutropenia (Genentech, 2012). Rare side effects include cardiac toxicity (which requires baseline assessment of left ventricular ejection fraction) and infusion reactions. Gastrointestinal toxicities, especially diarrhea, are also common with neratinib, with liver toxicity (rare) and drug interactions noted as well (Puma Biotechnology, Inc., 2017). Diarrhea requires attention, as it can lead both to dose modification and discontinuation if not managed aggressively.

In the APHINITY trial (von Minckwitz et al., 2017), the occurrence of diarrhea was most common during cycle 1 of pertuzumab-based treatment and did not generally require dose delay or discontinuation. Any-grade diarrhea was noted in 71.2% of patients who received trastuzumab plus pertuzumab compared with 45.2% of those who received trastuzumab plus placebo (von Minckwitz et al., 2017). It also occurred predominantly during chemotherapy and with a nonanthracycline regimen, noted Ms. Hineman.

In the ExteNET trial, diarrhea was the main adverse event reported, with grade 3 diarrhea noted in 40% of patients treated with neratinib. The median duration was 5 days, and most patients had recovered by 30 days. According to patient-reported outcomes (Delaloge et al., 2017), there was a transient reduction in quality of life, especially during the first month. The speakers emphasized the need to manage diarrhea promptly so that symptoms do not escalate.

Educating Patients About Treatment-Induced Diarrhea

Both Dr. Mahtani and Ms. Hineman stated that communication with patients about diarrhea with these adjuvant therapies is essential. "I don't tell patients they 'could have' [diarrhea with neratinib]," Ms. Hineman said. "I say there is a high likelihood they will have some diarrhea, but that we have a plan to manage it."

"I have seen a potassium level go from 4.0 to 2.8 mEq/L in one day's time in a patient I suspected might have a harder time [with neratinib]," she commented. "This is a patient who can get into trouble fast, if we aren't on top of managing it."

The management plan centers on dose modifications, diet, and antidiarrheal prophylaxis and agents. Hydration—8 to 10 glasses of water per day and electrolytes—is also important. Preferred foods are those that are low in fiber, high in protein, and high in potassium. Items to avoid include dairy, alcohol, caffeine, and greasy, fatty, or spicy food.

Antidiarrheal medications (loperamide alone or with budesonide and colestipol) may be used before and/or after each episode until symptoms

subside. Ms. Hineman has found that the best time to consider these drugs is at the start of adjuvant treatment—not after symptoms develop. How best to use loperamide and when to modify the dose of neratinib in the prevention of diarrhea are illustrated in Figure 1. In short, if grade 2 diarrhea lasts more than 5 days or grade 3 diarrhea lasts more than 2 days, the dose of neratinib should be held. If the diarrhea resolves to grade 1 or lower in fewer than 7 days, the same dose of neratinib should be resumed, but if resolution of the diarrhea takes 8 to 21 days, neratinib should be resumed at a lower dose.

AGENTS UNDER INVESTIGATION AND THE UNMET NEED OF TREATING BRAIN METASTASES

Dr. Mahtani briefly highlighted new molecular targets and novel therapies in the treatment of metastatic disease, particularly brain metastases. Margetuximab is an anti-HER2 antibody that has been studied in the phase III SOPHIA trial in combination with chemotherapy (Rugo et al., 2016). Margetuximab has improved binding to immune cells and has been reported to enhance antibody-dependent cellular cytotoxicity. "We'll see if these properties translate into improvements in outcomes over trastuzumab," she commented.

The small-molecule inhibitor of HER2, tucatinib (also known as ONT-380), was combined with capecitabine plus trastuzumab in a phase 1B study, in which it showed antitumor activity in a heavily pretreated population, including patients with brain metastases (Hamilton et al., 2016). The objective response rate was 61% and median progression-free survival was 7.8 months. The FDA granted tucatinib orphan drug designation for treating brain metastases resulting from breast cancer.

Finally, the HER2-targeting antibody-drug conjugate trastuzumab deruxtecan (DS-8201) is under study. "It has a potent bystander effect due to a highly membrane-permeable payload and is another agent to watch," she said.

One agent that may already be useful in treating brain metastases is neratinib, which appears in the updated NCCN Clinical Practice Guidelines in Oncology for central nervous system cancers (NCCN, 2018b). In fact, the combination of neratinib and capecitabine carries a category 2A ranking for treating HER2-positive patients with brain metastases. (A category 2A recommendation means that based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.) In addition, the combination of neratinib and paclitaxel has a category 2B ranking in the guidelines for this indication. (A category 2B recommendation means that based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.) Other regimens for treating brain metastases in this patient population featured in the NCCN Guidelines include high-dose methotrexate, capecitabine with or

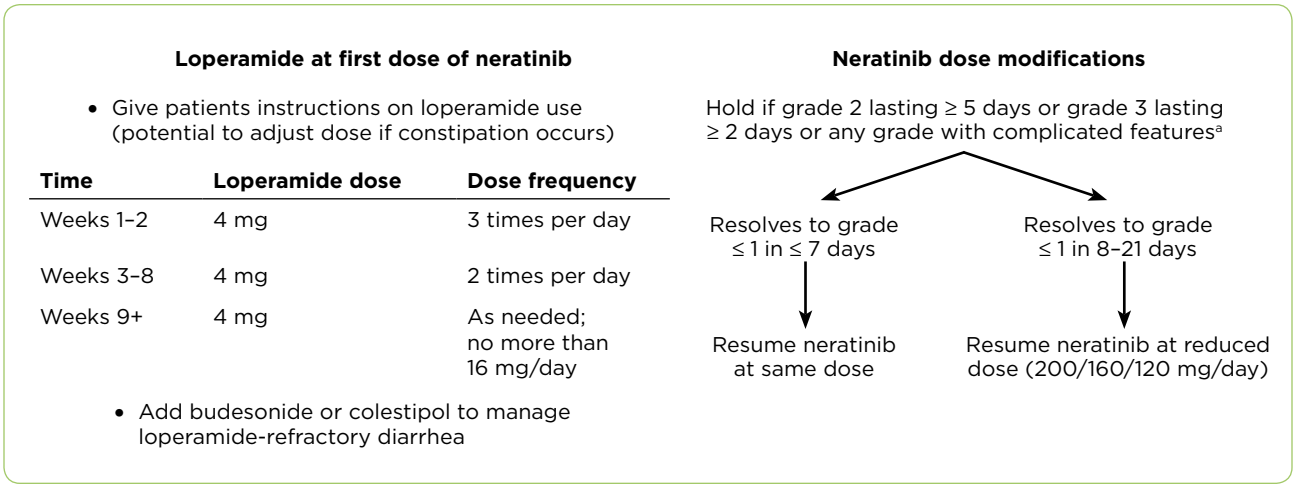

Figure 1. Prophylactic considerations for the management of neratinib-induced diarrhea. Information from Puma Biotechnology, Inc (2017).
[a]Includes dehydration, fever, hypotension, renal failure, or grade 3 to 4 neutropenia.

without lapatinib, cisplatin, etoposide, and trastuzumab (NCCN, 2018b).

Disclosure

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