Improving Outcomes in HER2-Positive Breast Cancer: Analysis and Application of Evolving Data and Best Practices

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Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2020.11.3.11

Abstract

Through expert, case-based discussion, Jame Abraham, MD, and Kelley Mayden, MSN, FNP, AOCNP®, presented existing and emerging data for current and investigational therapies for HER2-positive breast cancer and their associated adverse events, in addition to best practices for managing central nervous system metastases.

Historical standards of care for HER2-positive breast cancer have been impacted by emerging evidence over the past several years, leading to a significant decrease in breast cancer mortality. Nevertheless, approximately 268,000 women will be diagnosed this year, and more than 20,000 patients will die from the disease. At JADPRO Live 2019, Jame Abraham, MD, Taussig Cancer Institute, Cleveland Clinic, and Kelley D. Mayden, MSN, FNP, AOCNP®, Legacy Wellmont Cancer Institute, Ballad Health, discussed the clinical significance of data for current and investigational therapies for HER2-positive breast cancer.

"Women are living longer, and we have done better, but we still can't say that this is a completely curable disease," said Ms. Mayden, an oncology nurse practitioner. "As advanced practitioners, we need to come to the table knowing all of our options, understanding the data, and being able to put together a care plan for our patients from the very beginning of their therapy" (Figure 1).

NEOADJUVANT THERAPY

Dr. Abraham, Chairman of Hematology/Oncology Department and Director of Breast Cancer Program and Professor of Medicine, Taussig Cancer Institute, Cleveland Clinic, emphasized that HER2-positive breast cancer is an aggressive phenotype that needs to be treated aggressively because recurrent malignant HER2-positive disease is incurable and associated with shortened progression-free survival and overall survival. In the neoadjuvant setting, said Dr. Abraham, the current standard of care is trastuzumab plus chemotherapy, or trastuzumab plus

J Adv Pract Oncol 2020;11(3):271–274

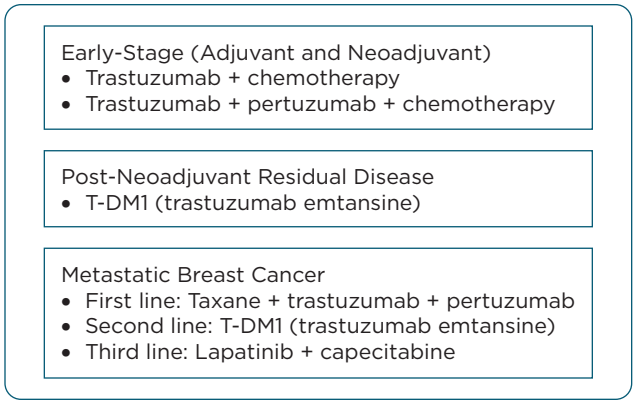

Figure 1. Current standards of care for HER2+ breast cancer.

pertuzumab and chemotherapy, and this is driven by data from the TRYPHAENA and NeoSphere phase II trials.

In the NeoSphere study, the addition of pertuzumab to trastuzumab/docetaxel significantly improved pathological complete response vs. trastuzumab/docetaxel alone (45.8% vs. 29.0%). Furthermore, 5-year follow-up data confirmed the benefit of neoadjuvant pertuzumab plus trastuzumab, which was supported by longer progression-free survival (86% vs. 81%) and disease-free survival (84% vs. 81%; Gianni et al., 2016).

These data resulted in pertuzumab/trastuzumab-based therapy becoming a standard treatment option for early-stage HER2-positive breast cancer, said Dr. Abraham, who noted that total pathological complete response may also be an early indicator of long-term outcome in this patient population.

"For high-risk patients in the neoadjuvant setting, I tend to use both trastuzumab and pertuzumab," said Dr. Abraham. "For hormone receptor–positive, HER2-postive disease, there's a 50% chance of complete pathological response, which is pretty amazing."

Based on data from the TRYPHAENA study, docetaxel, carboplatin, and trastuzumab plus pertuzumab (TCHP) has become the preferred regimen, Dr. Abraham reported (Schneeweiss et al., 2018).

ADJUVANT THERAPY

As Dr. Abraham explained, the adjuvant setting is about optimizing therapy because not every patient needs the most aggressive form of treatment. In the APT trial, more than 400 patients with tumors less than three centimeters received adjuvant paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab monotherapy for 9 months. Three-year disease-free survival was nearly 99%, and a recent update showed 94% disease-free survival at 7 years (Tolaney et al., 2019).

"These are very good results," said Dr. Abraham, who noted that trastuzumab is playing the most important role but is aided by chemotherapy. "It's important to make sure that we don't expose our patients to unnecessary toxicity by giving more aggressive treatment when we can treat them with this regimen."

Another option in the adjuvant setting is docetaxel plus carboplatin with trastuzumab. In a three-arm study, women with HER2-positive early-stage breast cancer were randomly assigned to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-TH), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). As Dr. Abraham reported, the addition of anthracycline conferred no survival advantage for AC-TH vs. TCH, but there was a five times higher rate of congestive heart failure with AC-TH (Slamon et al., 2011).

There is also a role for pertuzumab in the adjuvant setting, said Dr. Abraham. A phase III randomized trial showed improvement in invasive disease-free survival with pertuzumab across various patients subgroups, including those with hormone receptor–positive and hormone receptor–negative breast cancer (von Minckwitz et al., 2017). As Dr. Abraham reported, survival benefit was mainly in patients with node-positive disease.

"Based on these studies, paclitaxel/trastuzumab and TCH are both appropriate regimens in the adjuvant setting, and in high-risk patients, we can use TCHP," said Dr. Abraham.

Finally, in a separate study, extended adjuvant treatment with neratinib vs. placebo demonstrated a 30% improvement in disease-free survival, with hormone receptor–positive patients receiving the maximum benefit (Singh et al., 2018).

POST-NEOADJUVANT THERAPY

As Dr. Abraham explained, patients who have residual invasive breast cancer after receiving

neoadjuvant chemotherapy plus HER2-targeted therapy have a worse prognosis than those who have no residual cancer, but clinicians were initially reluctant to treat patients with an alternative to trastuzumab given its effectiveness. In the KATHERINE trial, however, patients randomized to trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine, had a nearly 50% reduction in invasive disease-free survival (von Minckwitz et al., 2019).

"We knew the data would be decent, but we didn't expect it would be this remarkable," said Dr. Abraham. "Impressively, all subsets of patients benefited by adding T-DM1."

HER2-POSITIVE METASTATIC BREAST CANCER

First-line treatment for HER2-positive metastatic breast cancer often involves combining HER2-targeted agents with standard chemotherapy. As Dr. Abraham explained, data from the CLEOPATRA trial showed that the addition of pertuzumab led to a statistical and clinically meaningful increase in survival compared with trastuzumab plus docetaxel alone (Swain et al., 2015).

Pertuzumab plus trastuzumab plus docetaxel has now replaced trastuzumab and taxane combination as the first-line treatment of choice for HER2-positive metastatic breast cancer, but the optimal duration of the regimen has yet to be determined. What's more, said Dr. Abraham, biomarkers are needed to better predict responders. If patients are unsuitable for the previously mentioned regimen or if fast progression on trastuzumab and pertuzumab is observed, clinicians should consider T-DM1, Dr. Abraham added.

In the second-line setting, the preferred treatment is T-DM1 based on randomized data that showed significantly prolonged survival with less toxicity vs. lapatinib plus capecitabine (Larionov et al., 2018).

The addition of neratinib to T-DM1 is being tested in clinical trials but is not yet standard of care, Dr. Abraham noted.

CLINICAL PEARLS: MANAGEMENT OF CENTRAL NERVOUS SYSTEM METASTASES

Finally, Dr. Abraham discussed the management of metastases in the central nervous system (CNS), which is a major problem for patients with breast cancer, with approximately 30% to 55% of patients developing metastases.

"Management of brain metastases is increasingly important given recent improvements in the survival of patients with HER2-positive breast cancer," said Dr. Abraham, who noted that young age, HER2-positive disease, high-grade tumor, and large tumor size are all predictors of CNS metastases.

As Dr. Abraham reported, recent clinical trial data support the use of chemotherapy to enhance HER2-directed therapy for brain metastases, and the National Comprehensive Cancer Network (NCCN) Guidelines now recommend neratinib plus capecitabine as a treatment option for CNS disease in HER2-positive metastatic breast cancer.

MANAGEMENT OF COMMON ADVERSE EVENTS

Ms. Mayden discussed several common toxicities associated with HER2-targeted therapies, including fatigue, headache, rash, alopecia, gastrointestinal toxicities, hematologic toxicities, peripheral neuropathy, and cardiotoxicity (Figure 2).

Cardiotoxicity is the most frequent adverse event with trastuzumab treatment, said Ms. Mayden, who noted that this typically manifests as an asymptomatic decline in left ventricular ejection fraction (LVEF), especially when used

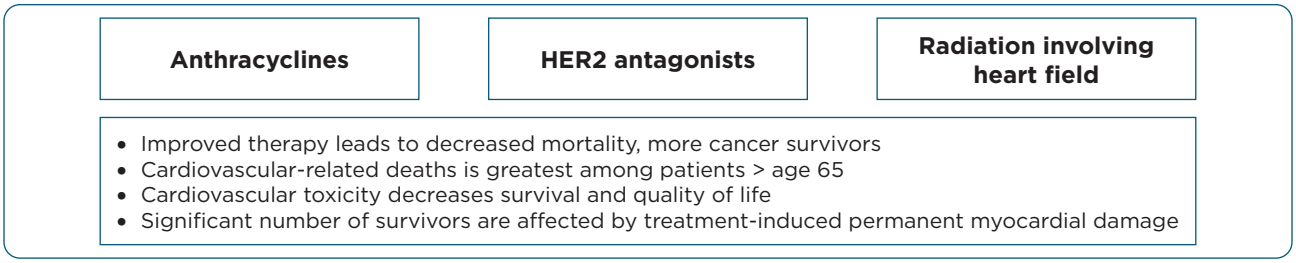

Figure 2. Treatment-associated cardiotoxicity.

with anthracyclines or in high-risk patients with preexisting cardiac conditions. LVEF is recommended after treatment in high-risk patients or when using high doses of anthracyclines. Secondary cardiac events are reported in 7% of patients with trastuzumab monotherapy and up to 19% with trastuzumab plus chemotherapy, Ms. Mayden reported.

"Clinicians should avoid concomitant use of trastuzumab and anthracyclines," she cautioned, "but cardiotoxicity is usually reversible and patients can be rechallenged after recovery."

DIARRHEA WITH NERATINIB

Another adverse effect with HER2-targeted therapy is diarrhea, which can result in dose reductions or delays, reduced quality of life, higher costs, and reduced treatment adherence. It can also be life threatening, said Ms. Mayden, who noted that diarrhea is the most commonly observed adverse event with neratinib.

Diarrhea occurs in up to two thirds of all treated patients (all grades) and was reported in 95% of patients in ExteNET trial (93% within first month), with 40% of patients experiencing grade 3 severity (Chan, Buyse, & Yao, 2016).

To manage diarrhea with neratinib, said Ms. Mayden, providers should initiate antidiarrheal prophylaxis with loperamide, plus budesonide or colestipol with initial neratinib dose, and continue during the first two cycles. For severe and/or persistent diarrhea, neratinib should be withheld and subsequent doses should be reduced, and in the case of grade 4 diarrhea, neratinib should be permanently discontinued.

Finally, said Ms. Mayden, it's essential for advanced practitioners to have knowledge of treatment options and patient selection and to obtain baseline characteristics, especially in terms of cardiac function. Patient education is also critical.

"Patients on HER2-targeted therapies need to be proactive regarding self-management of potential toxicities, and report any unexpected or serious side effects immediately," Ms. Mayden concluded. ●

Disclosure

Dr. Abraham has no conflicts of interest to disclose. Ms. Mayden has consulted with Amgen, Pfizer, and Puma Biotechnology. This symposium was supported by educational grants from Daiichi Sankyo, Inc., Puma Biotechnology, Inc., and Seattle Genetics.

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