Extended Adjuvant Therapy for HER2+ Breast Cancer: A Case Study

From the Guest Editor

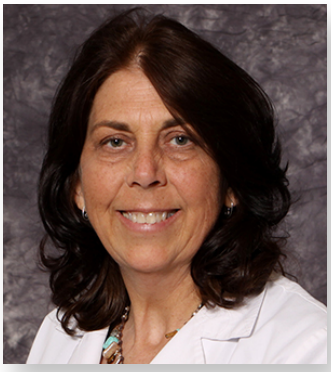
As advanced practice providers (APPs), we play a unique and important role in the care of our patients with breast cancer. We help them understand their disease and prognosis, educate them on their treatment options, prepare them for and help manage treatment-related side effects, and provide guidance and resources along the way.

But breast cancer care doesn't stop when adjuvant treatment with trastuzumab ends. Women with early-stage HER2-positive breast cancer can reduce their risk of recurrence by more than 25% with extended adjuvant treatment with Nerlynx® (neratinib). As APPs, it's our job to educate patients about this important benefit.

In the article you'll find on the following pages, you'll read about Abbey, a 38-year-old woman with two children, who was diagnosed with early-stage HER2-amplified breast cancer, and learn how she and our team worked together throughout her time on therapy. You'll also find data on important clinical trials involving neratinib, as well as resources to help you and your patients. You can also access two online components: a video interview in which I highlight the important aspects of extended adjuvant therapy with neratinib, and a patient handout including tips and resources to encourage adherence to oral cancer medications.

I hope you find this article, video, and resource guide insightful and empowering as you help breast cancer patients navigate their diagnosis, treatment, and beyond.

—Lori B. Ranallo, RN, MSN, ARNP-BC, CBCN



Guest Editor

Lori B. Ranallo, RN, MSN, ARNP-BC, CBCN, is a breast oncology nurse practitioner at the University of Kansas Cancer Center, in Kansas City, Kansas. In her 27 years of practice, Ms. Ranallo has worked with patients who have recently been diagnosed with breast cancer, those who have completed treatment, and individuals at risk for developing the disease. She also has expertise and experience in managing lymphedema and tobacco cessation.

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Case Study: Abbey's Story

Meet Abbey, a 38-year-old active working mother with two young children, who presented with cancer of the left breast. Ultrasound-guided core needle biopsy revealed invasive ductal carcinoma, grade 2, ER 80%, PR 70%, and HER2/*neu* amplified with a FISH of 3.9. Her tumor measured 2.6 cm, and biopsy confirmed a positive axillary lymph node. Abbey's breast cancer was a clinical stage IIB.

Data show that about 20% of breast cancers will be HER2 amplified.[1] Although HER2-positive disease is more likely to be aggressive and has a greater chance of recurrence, several effective HER2-targeted therapies are available.[1]

Abbey received six cycles of neoadjuvant docetaxel, carboplatin, pertuzumab, and trastuzumab, and then proceeded to lumpectomy. She achieved a pathologic complete response, ypT0N0. Abbey completed adjuvant radiation and continued adjuvant trastuzumab for 1 year. As she was ER positive, she was also taking tamoxifen. As she neared the end of her treatment, the nurse practitioner on Abbey's care team discussed next steps, including the risk of recurrence.

Even with the advent of HER2-targeted therapies, a significant proportion of patients do experience disease recurrence.[2,3] Further, 93% of patients with HER2-positive breast cancer say they fear recurrence, with 78% citing it as their greatest concern.[4]

Extended Adjuvant Treatment

Abbey's advanced practice provider (APP) explained that taking extended adjuvant neratinib for 1 year could reduce her risk of recurrence.[5] She walked Abbey through the data from the ExteNET trial, which showed that among patients with early-stage HER2-positive breast cancer who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab, those who received 1 year of oral neratinib (240 mg/day) experienced 90.2% invasive disease-free survival, vs. 87.7% among those who received placebo (HR 0.73 [95% CI: 0.57–0.92]; $p = .0083$).[5,6] Further, patients with hormone receptor–positive disease, like Abbey, who received neratinib experienced 90.8% invasive disease-free survival, compared with 85.7% for those receiving placebo (HR 0.58 [95% CI: 0.41–0.82]; 2-sided $p = .002$).[6]

Abbey's APP also educated her about the potential side effects from neratinib therapy. In ExteNET, without diarrhea prophylaxis, 95% of patients experienced diarrhea (40% grade 3 and <1% grade 4 with neratinib vs. 2% grade 3 with placebo).[5] Treatment-emergent serious adverse events were seen among 7% of patients who received neratinib (vs. 6% with placebo). And the study did not demonstrate an increased risk of long-term toxicity with neratinib or long-term adverse effects of neratinib-associated diarrhea vs. placebo.

However, because diarrhea prophylaxis was not mandated in ExteNET, the subsequent CONTROL trial aimed to determine the most effective antidiarrheal prophylaxis and neratinib dose escalation to prevent and manage neratinib-associated diarrhea. In this open-label, sequential-cohort phase II study, patients with HER2-positive early-stage breast cancer receiving extended adjuvant neratinib were given loperamide alone or in combination with budesonide or colestipol, or neratinib dose escalation, for 1-2 cycles (28 days).[7]

CONTROL showed that adding prophylactic loperamide for 1-2 cycles reduces the incidence, severity, and duration of neratinib-associated diarrhea (vs. ExteNET), and budesonide or colestipol may further decrease the duration and incidence of diarrhea.[7] Analysis of the neratinib dose-escalation cohort

KEY POINTS

- **Extended adjuvant treatment is an important part of breast cancer survivorship care, and APPs play a vital role in educating patients on their options and guiding them through therapy.**
- **APPs need to be educated about the risk of diarrhea with Nerlynx and the recommended antidiarrheal prophylaxis and dose-escalation strategies to help patients manage side effects to successfully complete therapy.**
- **It's important for APPs to make patients aware of the available resources and support to help them stay on therapy, afford treatment, and adhere to their 1-year dosing cycle.**

is ongoing; early data, including the rate of grade 3 diarrhea and neratinib discontinuation due to diarrhea, are promising.

After discussing these data with her APP, Abbey—a working mother with young, very active children—voiced concern that she would not be able to continue her busy pace and enjoy any quality of life while taking neratinib, due to the diarrhea. Her APP listened to Abbey's concerns and walked her through the antidiarrheal prophylaxis regimen, based on CONTROL,[7] which helped Abbey feel confident in her decision to start neratinib.

Abbey started on neratinib 240 mg. Her APP explained that she should take each dose with food. She also received loperamide 4 mg three times daily for 2 weeks, and then 4 mg twice daily for 6 weeks. As of day 56, she was told to use 4 mg as needed after each loose stool (maximum dose of 32 mg daily). Based on data from the CONTROL trial, APPs can also employ a neratinib dose-escalation strategy for their patients to help prevent treatment-related diarrhea.[7]

The team also suggested dietary modifications that could impact the incidence of Abbey's diarrhea: smaller, more frequent meals; no dairy (except yogurt); low-fiber foods; and plenty of fluids.

Oral Therapy Adherence

Because neratinib is taken orally once daily with food, continuously for 1 year, along with the antidiarrheal prophylaxis, Abbey and her APP also discussed the importance of adhering to the dosing schedules. Considering Abbey's busy family and working life, her APP suggested that she use a family calendar to record her children's activities, sporting events, and other daily tasks, along with her daily neratinib dose and antidiarrheal regimen. She also referred Abbey to several support resources, including a Nerlynx patient-to-patient mentor program, a 24/7 nurse call center, and information on financial assistance.

93% of patients with HER2+ breast cancer say they fear recurrence

Conclusion

Abbey tolerated her neratinib treatment well without interruption. The loperamide, in combination with the dietary modifications, helped control her diarrhea, and she did not require the addition of other antidiarrheal medications or a neratinib dose modification. With the help of her health-care team, family, and resources, she has completed 6 months of neratinib thus far, continues to do well, and expects to complete the year-long course of treatment.

References

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4. Jenkins M, et al. Patient perspectives on HER2+ breast cancer recurrence: Results from an online patient survey. Poster presented at 2018 San Antonio Breast Cancer Symposium; December 4-8, 2018; San Antonio, TX.
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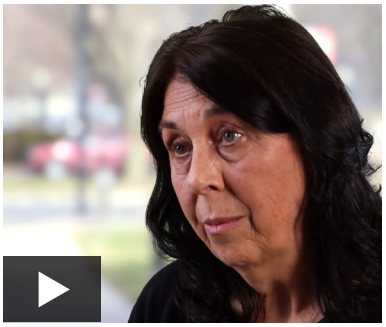

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"You have to know the data. Only then can a meaningful relationship and conversation occur—not only among you and the other members of the healthcare team, but most importantly, between you and your patient."

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Important Clinical Trials

Trial	ExteNET 5-Year Data[a]	CONTROL[c]
Phase/Type	Randomized, double-blind, placebo-controlled, phase III	Open-label, sequential-cohort, phase II
Patients	Stage 1–3c operable breast cancer, previously completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastasis	Patients with HER2+ early-stage breast cancer receiving extended adjuvant neratinib
Design	**Arm A:** 1 year oral neratinib 240 mg/day **Arm B:** 1 year matching placebo	Given for 1-2 cycles (28 days): **Cohort 1:** loperamide **Cohort 2:** loperamide + budesonide **Cohort 3:** loperamide + colestipol **Cohort 4:** loperamide prn + colestipol **Cohort 5:** loperamide prn + neratinib dose escalation with no mandatory prophylaxis (two cohorts)
n	**Arm A:** 1420 **Arm B:** 1420	**Cohort 1:** 137 **Cohort 2:** 64 **Cohort 3:** 136 **Cohort 4:** 104 **Cohort 5:** 60
Endpoint	Invasive disease-free survival (IDFS), analyzed by intention to treat	Incidence of grade ≥ 3 diarrhea
Major Findings	5-year IDFS: **Arm A:** 90.2% **Arm B:** 87.7% HR 0.73 (95% CI: 0.57–0.92); *p* = .0083 5-year HR+ subgroup IDFS: **Arm A:** HR+ (n = 816): 90.8% **Arm B:** HR+ (n = 815): 85.7% HR 0.58 (95% CI: 0.41–0.82); 2-sided *p* = .002[b] Grade 3 diarrhea: **Arm A:** 561 (40%) **Arm B:** 23 (2%)*	• All prophylactic regimens and dose escalation reduced incidence of grade 3 diarrhea and drug discontinuation (vs. ExteNET trial). • Median cumulative duration of ≥ grade 3 diarrhea: 2.0 to 3.5 days across regimens for entire treatment period • No grade 4 diarrhea reported.

[a]See Reference 5. [b]See Reference 6. [c]See Reference 7.
* Patients receiving neratinib on the ExteNET trial did not receive diarrhea prophylaxis.

RESOURCES

Puma Patient Lynx Support Program—Puma Biotechnology provides financial assistance programs for Nerlynx, a free voucher program for antidiarrheal prophylaxis, a patient-to-patient mentor program, and a 24/7 nurse call center. https://nerlynx.com

NCCN Clinical Practice Guidelines in Oncology: Breast Cancer—Keep up to date with the definitive source for treatment guidelines for patients diagnosed with HER2-positive breast cancer. https://www.nccn.org/professionals/physician_gls/default.aspx

Oral Cancer Therapy: The Importance of Adherence—This downloadable patient education handout features some useful tips for encouraging better adherence to oral cancer medications. https://www.advancedpractitioner.com/ce/2017/oral-oncolytics.aspx

Advances in HER2-Positive Breast Cancer: Novel Therapies and Adverse Event Management—Read this JADPRO article to learn more about the APP's role in managing patients receiving HER2-directed therapies. advancedpractitioner.com/her2

Improving Outcomes in HER2+ Breast Cancer: Analysis and Application of Evolving Data and Best Practices—Access this dynamic presentation direct from JADPRO Live 2019. jadproce.com/2019/her2-bc