BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

Section Editor: Hope S. Rugo, MD

Treatment of Early-Stage Hormone Receptor–Positive Breast Cancer

Hope S. Rugo, MD
Professor of Medicine
Director of Breast Oncology and Clinical Trials Education
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

H&O What are the most important questions for oncologists treating patients with early-stage hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer after surgery?

HR The main questions for oncologists treating patients with early-stage hormone receptor (HR)-positive, human epidermal growth factor receptor 2–negative breast cancer after surgery are who needs chemotherapy, what treatment is best, and, for premenopausal patients, what is the optimal duration of endocrine therapy.

Regarding the question of who needs chemotherapy, the key trial is TAILORx (Trial Assigning Individualized Options for Treatment). In TAILORx, which was originally published in 2018, more than 10,000 women were categorized as being at low, intermediate, or high risk for recurrence based on their score on the Oncotype DX assay: 0 to 10, 11 to 25, or 26 and higher, respectively. Women at intermediate risk were randomly assigned to chemotherapy plus endocrine therapy or endocrine therapy alone and followed for 9 years. The researchers found that although intermediate-risk women younger than 50 years and those with a recurrence score in the higher range of intermediate (16-25) benefitted from chemotherapy, the majority of women in the intermediate group could skip it.

More recently, the TAILORx investigators drilled down on some of the details regarding which patients benefit from chemotherapy. In an analysis that was published in the *New England Journal of Medicine* in 2019 and presented by Dr Joseph Sparano at the most recent annual meeting of the American Society of Clinical Oncology (ASCO), the investigators applied criteria from the MINDACT trial (Microarray in Node-Negative Disease May Avoid Chemotherapy) to the TAILORx patients. MINDACT divided patients into high or low clinical risk scores based on tumor size and histologic grade. The TAILORx analysis found that clinical risk scores affected prognosis but did not predict response to chemotherapy. This finding contradicted the long-held belief that benefit from chemotherapy is proportionately related to the risk of recurrence based on clinicopathologic factors, including burden of disease.

The new analysis also showed that within the premenopausal group, the benefit of chemotherapy in patients at intermediate risk for recurrence was clear for the women who were close to the age of menopause but not for the younger women. One hypothesis to explain this finding is that the chemotherapy is more effective at inducing permanent menopause in older vs younger premenopausal women.

Clinical risk had no effect on the low-risk patients, who had an extremely good outcome regardless and did not need chemotherapy. And of course, the high-risk patients were not randomized, and received chemotherapy regardless of clinical risk.

H&O Could you address the role of ovarian suppression and endocrine therapy in premenopausal women?

HR Two trials have examined the role of ovarian suppression and endocrine therapy in premenopausal women:

TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial). The most recent results from these clinical trials have continued to show benefit from ovarian suppression plus endocrine therapy. An analysis that was published by Pagani and colleagues in 2019 found that absolute improvement in 8-year freedom from distant recurrence was 5.1 percentage points higher in the exemestane/ovarian suppression group than in the tamoxifen/ovarian suppression group. This improvement was even more pronounced among women at the highest risk for recurrence, in which the absolute improvement was more than 15 percentage points higher with exemestane/ovarian suppression. Of course, this impact must be balanced against risk and toxicity. Grade 3 or higher adverse events were reported in 32.3% of the exemestane/ovarian suppression group, 31.0% of the tamoxifen/ovarian suppression group, and 24.6% of the tamoxifen-alone group, according to a 2018 analysis by Francis and colleagues.

The greatest benefit from ovarian suppression plus endocrine therapy was seen in women younger than 35 years, although this represented a small subset within the trials.

The greatest benefit from ovarian suppression plus endocrine therapy was seen in women younger than 35 years, although this represented a small subset within the trials. The hypothesis is that these patients both have higher estrogen production and also are unlikely to be placed into permanent menopause by current chemotherapy for early-stage disease. Lastly, breast cancer in young women may be relatively more endocrine-resistant, which is why the combination of ovarian suppression and endocrine therapy may have greater efficacy. Women who did not receive chemotherapy because of low-risk disease did not seem to benefit from the addition of ovarian suppression to endocrine therapy, and had an excellent outcome with tamoxifen alone.

An important question that TAILORx was not designed to answer is whether patients who have a high-intermediate score can receive ovarian suppression and endocrine therapy without chemotherapy. If the main benefit of chemotherapy in these patients is ovarian suppression, these patients might benefit just as much from ovarian suppression plus endocrine therapy as from chemotherapy. Ovarian suppression may cause less acute toxicity than chemotherapy, but ovarian suppression plus endocrine therapy generally is administered for at least 5 years, whereas chemotherapy is administered for just a few months. We are still struggling with how to best manage the toxicities of ovarian suppression, particularly those that arise when ovarian suppression is combined with aromatase inhibition in younger women. This is a tough treatment to tolerate, and we have seen this play out in a lower-than-expected adherence over time. Some endocrine therapy is clearly better than none, and developing and implementing strategies to boost adherence is an important area for investigation.

H&O How long should endocrine therapy last in early-stage breast cancer?

HR The optimal duration of endocrine therapy in early-stage breast cancer continues to be a challenging area. Reasons include tumor heterogeneity, studies that include relatively lower-risk disease, and the long duration of follow-up that is clearly required to see an impact on distant recurrence. However, in a 2017 analysis by Pan and colleagues from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the 20-year risk of recurrence after 5 years of tamoxifen ranged from 13% in patients with T1N0 disease to 41% in patients with T2N4-9 disease. Although this group of patients was treated with tamoxifen in the distant past, rather than more contemporary therapies, this finding has led to a great deal of interest in the question of whether prolonging endocrine therapy will improve outcome. The data on this question have been highly variable. The MA.17 trial (Letrozole in Treating Women With Primary Breast Cancer Who Have Received 5 Years of Aromatase Inhibitor Therapy), which was published by Goss and colleagues in 2016, found that extending aromatase inhibitor treatment to 10 years improved disease-free survival but not overall survival, with a greater benefit in women with node-positive disease and those who were premenopausal at diagnosis. A meta-analysis presented at the San Antonio Breast Cancer Symposium (SABCS) in 2018 by the EBCTCG suggested that only patients at high clinicopathologic risk benefited from this approach. In another study presented at the 2018 SABCS, the Japanese AERAS trial (Arimidex Extended Adjuvant Randomized Study), everybody benefited from extended-duration endocrine therapy, even the patients with very low-risk disease.

The aTTom trial (Adjuvant Tamoxifen-To Offer More?) evaluated the duration of therapy with tamoxifen, and a retrospective substudy called Trans-aTTom was recently published by Bartlett and colleagues in the *Annals of Oncology* in 2019. The aTTom trial randomly assigned nearly 7000 women with HR-positive disease or unknown HR status to either 5 or 10 years of tamoxifen, and found that recurrence rates were lower with the longer duration of therapy. The improvement in recurrence rates was a little bit greater in patients with node-positive disease—who were at elevated risk for late recurrence—than in those with node-negative disease.

Although these data are intriguing and bring us a step closer to determining which patients could possibly benefit from extended adjuvant endocrine therapy, it is important to keep in mind the limitations of these studies.

For this retrospective subset analysis, investigators looked only at patients who had node-positive disease and available formalin-fixed paraffin-embedded primary tumor blocks to confirm HR positivity. This group ended up being a small subset of the overall population, just 583 patients, albeit with clinical characteristics that were reasonably similar to those of the original group. Using a measure called the Breast Cancer Index, or H/I ratio, they divided patients into H/I-high and H/I-low groups. They found that in the H/I-high group, the recurrence rate was significantly lower with 10 years of tamoxifen vs 5 years, with a hazard ratio of 0.35 (P=.027), and the absolute risk reduction for recurrence was 10.2 percentage points. In contrast, the recurrence rate was not significantly different between 10 years and 5 years in the H/I-low group.

This finding was consistent with that seen in a retrospective 2013 study by Sgroi and colleagues that looked at a subset of 249 patients from the MA.17 study with the same assay. The researchers found that extending hormone therapy with 5 years of letrozole after 5 years of tamoxifen seemed to benefit only patients who had a high H/I score.

Although these data are intriguing and bring us a step closer to determining which patients could possibly benefit from extended adjuvant endocrine therapy, it is important to keep in mind the limitations of these studies. Trans-aTTom was a subset analysis of patients with node-positive disease, the MA.17 analysis included a very small subset of patients, and both studies began with tamoxifen rather than with an aromatase inhibitor. Trans-aTTOM used 10 years of tamoxifen, and the primary study data have not been published. For patients considering extending tamoxifen therapy for node-positive, early-stage hormone receptor–positive breast cancer, or for those switching from tamoxifen to aromatase inhibition, this test may provide additional information useful for decision making, keeping in mind the retrospective subset nature of these trials. It is not yet known how these data apply to patients who use extended adjuvant aromatase inhibition.

H&O What other studies are ongoing regarding duration of endocrine therapy?

HR Several trials are ongoing that are randomly assigning patients to receive 10 vs 5 years of an aromatase inhibitor, or 8 vs 7 years. We will see updated data with longer follow-up from the NSABP B-42 trial (Letrozole in Treating Postmenopausal Women Who Have Received Hormone Therapy for Hormone Receptor-Positive Breast Cancer) at the 2019 SABCS, along with an analysis of late relapse with a more contemporary group of patients from the EBCTCG. In addition, further genomic analyses are critical. The National Surgical Adjuvant Breast and Bowel Project (NSABP) trials collect tumor samples up front from all their patients. The ability to analyze differences in the ways genomic assays predict benefit from extended adjuvant hormone therapy with aromatase inhibitors in prospective trials will help determine which patients are more likely to benefit from extended adjuvant endocrine therapy.

Disclosure

Dr Rugo has received research support for clinical trials at the University of California from Pfizer, Merck, Novartis, Lilly, Genentech/Roche, OBI, Odonate, Daiichi Sankyo, Eisai, Seattle Genetics, MacroGenics, and Immunomedics. She has received travel support for educational meetings from Daiichi Sankyo, Mylan, Pfizer, Novartis, Amgen, Merck, AstraZeneca, MacroGenics, and Puma.

Suggested Readings

Hurvitz Bartlett J, Sgroi D, Treuner K, et al. Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence (DR) in patients with HR+ breast cancer treated in the adjuvant tamoxifen—to offer more? (aTTom) trial [ASCO abstract 505]. *J Clin Oncol*. 2019;37(15)(suppl).

Bartlett JMS, Sgroi DC, Treuner K, et al. Breast cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the adjuvant tamoxifen - to offer more? (aTTom) trial [published online August 28, 2019]. *Ann Oncol*. doi:10.1093/annonc/mdz289.

Francis PA, Pagani O, Fleming GF; SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379(2):122-137.

Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med*. 2016;375(3):209-219.

Gray R; Early Breast Cancer Trialists' Collaborative Group. Effects of prolonging adjuvant aromatase inhibitor therapy beyond five years on recurrence and cause-specific mortality: an EBCTCG meta-analysis of individual patient data from 12 randomised trials including 24,912 women [SABCS abstract GS3-03]. *Cancer Res*. 2019;79(4)(suppl).

Ohtani S, Iijima K, Higaki K, et al. A prospective randomized multi-center open-label phase III trial of extending aromatase-inhibitor adjuvant therapy to 10 years - results from 1697 postmenopausal women in the N-SAS BC 05 trial: Arimidex extended adjuvant randomized study (AERAS) [SABCS abstract GS3-04]. *Cancer Res*. 2019;79(4)(suppl).

Pagani O, Francis PA, Fleming GF, et al; SOFT and TEXT Investigators and International Breast Cancer Study Group. Absolute improvements in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: results from TEXT and SOFT [published online October 16, 2019]. *J Clin Oncol*. doi:10.1200/JCO.18.01967.

Pan H, Gray R, Braybrooke J, et al; EBCTCG. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836-1846.

Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst*. 2013;105(14):1036-1042.

Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121.

Sparano JA, Gray RJ, Makower DF, et al. Clinical outcomes in early breast cancer with a high 21-gene recurrence score of 26 to 100 assigned to adjuvant chemotherapy plus endocrine therapy: a secondary analysis of the TAILORx randomized clinical trial [published online September 30, 2019]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.4794.

Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. *N Engl J Med*. 2019;380(25):2395-2405.

Viale G, Slaets L, Bogaerts J, et al; TRANSBIG Consortium & the MINDACT Investigators. High concordance of protein (by IHC), gene (by FISH; HER2 only), and microarray readout (by TargetPrint) of ER, PgR, and HER2: results from the EORTC 10041/BIG 03-04 MINDACT trial. *Ann Oncol*. 2014;25(4):816-823.

This is part 3 of a 3-part series on the treatment of HR-positive breast cancer.