BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Balancing the Risks and Benefits of Extended Adjuvant Endocrine Therapy

Komal L. Jhaveri, MD
Attending, Breast Medicine Service and Early Drug Development Service
Memorial Sloan Kettering Cancer Center
Attending, Weil Cornell Medical College
New York, New York

H&O What is the standard duration of adjuvant endocrine therapy in patients with hormone receptor–positive breast cancer?

KJ Historically, it has been at least 5 years of adjuvant endocrine therapy. This recommendation was based on the meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), published in the *Lancet*, which found that treatment with 5 years of tamoxifen-based endocrine therapy resulted in both increases in disease-free survival and reductions in breast cancer mortality that lasted up to 15 years after the completion of endocrine therapy. As a result, that regimen has remained the standard for a long time.

What we have learned since then is that certain patients are at an elevated risk for recurrence, and disease can recur as late as 20 years out. Another meta-analysis by the EBCTCG, published in the *New England Journal of Medicine* in 2017, looked at the 20-year risk for recurrence in patients with estrogen receptor–positive disease. The study found that after 5 years of endocrine therapy—in this case tamoxifen—even patients with the lowest-risk (stage I) disease had a 21% risk for recurrence (nearly 1%/year) at 20 years, of which 14% was a risk for distant recurrence. The risk for recurrence increased with the degree of nodal involvement—up to 52% for patients with disease in 4 or more nodes.

Clearly, patients who have high-risk disease (specifically, those who have nodal involvement), are younger and require chemotherapy, have high-grade cancer, or have a Breast Recurrence Score above 31 on the Oncotype DX test, can benefit from a longer duration of therapy. Data from several trials now support the use of extended adjuvant therapy.

H&O What are the main studies that are evaluating extended adjuvant endocrine therapy?

KJ With tamoxifen, the ATLAS trial (Adjuvant Tamoxifen: Longer Against Shorter), published in 2013, and the British aTTom trial (Adjuvant Tamoxifen—To Offer More?), presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2013, support the use of 10 rather than 5 years of treatment. Treatment with 10 years of tamoxifen reduced the risk for recurrence by 3.7% and the risk for breast cancer mortality by 2.8%; both of these were absolute reductions.

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Regarding aromatase inhibitors (AIs), trials can

be divided into 3 groups according to the approach to treatment. In the first group, women completed 5 years of tamoxifen therapy and then began taking an AI. The 3 main trials that have looked at this approach are the MA.17 trial from the Cancer Institute of Canada Clinical Trials Group, which appeared in the *New England Journal of Medicine* in 2016; the NSABP B-33 trial from the National Surgical Adjuvant Breast and Bowel Project, which appeared in the *Journal of Clinical Oncology* in 2008; and the ABCSG-6a trial from the Austrian Breast and Colorectal Cancer Study Group, which appeared in the *British Journal of Cancer* in 2013. MA.17 found that patients who received 5 years of tamoxifen up front, followed by 5 years of letrozole, had a statistically significant reduction in both risk for recurrence and risk for mortality at a longer follow-up of 64 months.

In the second group, women had up-front sequencing of tamoxifen to an AI and were then treated with additional AI. This approach was studied in many trials, including NSABP B-42, which appeared in *Lancet Oncology* in early 2019, and the IDEAL trial (BOOG 2006-05), which appeared in the *Journal of the National Cancer Institute* in 2018.

In the third group, patients received an AI alone up front and then continued with the AI. One of the studies presented at the 2018 San Antonio Breast Cancer Symposium (SABCS) that delved into this approach was the AERAS trial (Arimidex Extended Adjuvant Randomized Study), which is also called N-SAS BC 05. In AERAS, a Japanese trial, nearly 1700 postmenopausal women received 5 years of AI therapy with anastrozole and then were randomly assigned either to stop anastrozole or to continue it for another 5 years. After a median of 4.9 years, the 5-year disease-free survival rate was significantly higher in the group that continued anastrozole than in the group that did not continue anastrozole: 91.9% vs 84.4%, respectively. The 5-year distant disease–free survival rate also was higher in the group that continued anastrozole than in the group that did not continue anastrozole: 97.2% vs 94.3%, respectively. A difference in overall survival was not seen between the 2 groups. It is interesting that unlike all prior studies, AERAS found no difference between the rates of contralateral breast cancer recurrence in the 2 groups. Another unusual finding was that the development of a second, non-breast primary tumor was up to 3 times less likely in patients in the longer-duration group. We do not have an explanation for why AI therapy for a longer time might prevent colorectal cancer, for example, but that is what this trial reported.

H&O Did AERAS have any other unusual findings?

KJ This is the only trial in which treatment with an AI followed by more treatment with the AI achieved a statistically significant, large, clinically meaningful improvement in disease-free survival. Why would that be? We are unclear on the reasons. The one factor that caught my eye as a possible explanation was that the adherence rate in this trial was slightly higher than the rates in the other trials, approximately 70% to 75% rather than 50% to 60%, so that might have played a role. Another possibility might be differences between Japanese women and women in the United States and Europe, where the other trials were conducted, in regard to pharmacogenomics, diet, and rates of obesity. At this point, it is unclear why the results of AERAS turned out to be more positive than those of the other trials.

> We need to discuss with our patients the risk-to-benefit ratio of extended therapy.

An important point about the sum of the data from all these trials (except the AERAS trial) is that the benefit in disease-free survival with AIs is rather small, occurs in a small population, and is derived mainly from the prevention of contralateral breast cancers.

H&O Could you talk about the most recent EBCTCG meta-analysis?

KJ The EBCTCG study presented at the 2018 SABCS was a meta-analysis of more than 22,000 women in 11 randomized trials; it did not include the AERAS trial. Women were placed in the same 3 treatment groups that were discussed earlier: tamoxifen alone for 5 years followed by an AI, tamoxifen for 5 to 10 years sequenced to an AI followed by additional extended AI, and 5 years of an AI alone up front followed by additional extended AI.

The meta-analysis found a 35% proportional reduction in recurrence among women who received tamoxifen alone for 5 years and a 20% proportional reduction in recurrence among women in the 2 groups in which treatment included an extended AI. The reductions in recurrence were apparent in the first 2 years following tamoxifen but did not occur until the third year after an AI had been started. The absolute benefit of extended therapy was greater in patients with more extensive involvement of lymph nodes, increasing from 1% in women with node-negative disease to 7.7% in women who had disease in 4 or more nodes.

H&O What adverse events are seen with an extended duration of therapy?

KJ With any therapy, extension leads to an increase in adverse events or toxicity. The EBCTCG meta-analysis found a 25% increase in bone fracture risk, for example. In the ATLAS and aTTom trials, the risk for pulmonary embolism and endometrial cancer nearly doubled with a longer duration of tamoxifen. AIs increase the risk for cardiovascular events, myalgias, and arthralgias.

Because of these toxicities, we need to figure out a better way to determine which women are most likely to benefit from an extended duration of therapy. The benefits are real, but they are small and easily offset by toxicities. We need to discuss with our patients the risk-to-benefit ratio of extended therapy.

H&O What steps should be taken to monitor for risks and mitigate toxicities?

KJ We need to be good listeners and talk to our patients so that we can recognize side effects early on. Patients may need emotional support or management of their physical symptoms. We know that tamoxifen can cause or worsen hot flashes, for example, especially if it is used in combination with ovarian suppression. Fortunately, we now have data to support the use of selective serotonin reuptake inhibitors and gabapentin. We also heard exciting data at the 2018 SABCS on oxybutynin, which can also help relieve that symptom. In addition, the phase 3 Southwest Oncology Group (SWOG) S1200 trial, presented by Dr Dawn Hershman at the SABCS in 2017, found that acupuncture could mitigate the myalgias and arthralgias caused by AIs. We can recommend vaginal lubricants for patients with vaginal dryness and refer those who require further assistance to a sexual health clinic. We also need to keep an eye on bone density and use bone-modifying agents as and when appropriate.

H&O According to the most recent data, which subsets of patients are more likely to benefit from extended adjuvant endocrine therapy?

KJ Patients who are at high risk for recurrence are the ones most likely to benefit—those who are younger than 35 or 40 years and require chemotherapy, those who have larger tumors or high-grade tumors with increased nodal involvement, and those with a genomic test score, such as the Oncotype DX assay Breast Recurrence Score, indicating a high risk for recurrence.

Additional tools can help us identify high-risk patients. An evaluation of the Clinical Treatment Score post-5 years (CTS5), which is an online tool that factors in tumor size, tumor grade, patient age, and number of affected nodes in postmenopausal women, appeared in the *Journal of Clinical Oncology* in 2018. This tool, which was studied in the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination) and then validated in the Breast International Group (BIG) 1-98 trial, generates a score indicating high, intermediate, or low risk for late recurrence.

Ongoing work is looking at molecular signatures and profiles, such as the EPclin Risk Score (generated with the EndoPredict test), in an effort to improve selection of the right patients to receive extended therapy. Neither of these tools are ready for routine use in all patients in the clinic, and they certainly are not validated in premenopausal women, but they are definitely a step forward in helping us identify women at higher risk for late recurrences.

H&O What other advances are being made in adjuvant endocrine therapy?

KJ Ovarian function suppression has become the standard of care in premenopausal women who are at high risk for recurrence, on the basis of the results of 2 trials: SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial). The other big change in the landscape of estrogen receptor–positive metastatic breast cancer has been the introduction and approval of CDK 4/6 inhibitors, which have become our first- and second-line choice in the metastatic setting. The big burning question that ongoing phase 3 trials are currently working to answer is whether we can delay recurrent or metastatic disease by using these agents in the early-stage setting in patients at high risk for recurrence. We are eagerly awaiting results from many of these trials. One example is PALLAS (Palbociclib Collaborative Adjuvant Study; NCT02513394), which is a phase 3 trial looking at the addition of 2 years of palbociclib (Ibrance, Pfizer) to standard adjuvant endocrine therapy for patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative early breast cancer. We hope that this trial will help us adjust the standard of care for women with early-stage breast cancer, especially those at high risk for recurrence.

Disclosure

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Suggested Readings

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