The Optimal Duration of Endocrine Therapy in Hormone Receptor–Positive Breast Cancer

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**H&O** Which patients are eligible for endocrine therapy alone vs endocrine therapy plus chemotherapy?

**GS** Historically, we based this decision on the TNM (tumor, node, metastasis) staging system classification. More recently, we have begun to use genomic assays that not only allow us to determine the aggressiveness of the cancer but also give us a sense of how likely patients are to benefit from chemotherapy. The 2 assays for which level 1 evidence for use in early-stage breast cancer is available are the MammaPrint Breast Cancer Recurrence Assay, a 70-gene signature test, and the Oncotype DX Breast Recurrence Score Test, a 21-gene assay. Our evidence for MammaPrint comes from the MINDACT trial. Our evidence for the Oncotype DX 21-gene assay in the setting of lymph node negativity comes from the TAILORx trial, which was published in the *New England Journal of Medicine* in 2018; in the setting of positivity in 1 to 3 lymph nodes evidence comes from the RxPONDER trial, which Kalinsky presented at the most recent meeting of the San Antonio Breast Cancer Symposium.

Data from TAILORx showed that adjuvant chemotherapy does not provide additional benefit beyond endocrine therapy in postmenopausal women with a recurrence score of 25 or less. This finding applies both to women who are lymph node–negative and to those who have 1 to 3 positive nodes. Postmenopausal women with a high recurrence score, defined as 26 or higher, should receive adjuvant chemotherapy in addition to adjuvant endocrine therapy. These are very solid findings.

The TAILORx trial also suggested that some premenopausal women—particularly those who have an intermediate or high-intermediate recurrence score—may benefit from adjuvant chemotherapy. Finally, data from RxPONDER suggested that premenopausal women with 1 to 3 positive nodes can benefit from adjuvant chemotherapy regardless of their Oncotype DX score, in terms of invasive disease–free survival. Why do these women benefit from chemotherapy? The RxPONDER trial did not answer this question because it was not designed to, but one possibility is that adjuvant chemotherapy may benefit women by rendering them postmenopausal. In other words, the chemotherapy may be providing an endocrine therapy benefit. Although we do not have any studies that can establish this as fact, many of us feel that giving chemotherapy to a 45-year-old woman, for example, will lead to ovarian failure. In other words, the chemotherapy may be the equivalent of giving a luteinizing hormone–releasing hormone (LHRH) agonist to shut down the ovaries, which we know can provide additional benefit to these women. That is a real possibility, and one that I discuss when I speak to premenopausal patients—does the chemotherapy work in the standard way, by killing dividing cells, or is the benefit related predominantly to its endocrine effect?

**H&O** What is the recommended duration of endocrine therapy?

**GS** Tamoxifen was the standard-of-care endocrine therapy for decades, although that began to shift around 2004 or 2005. We have data from randomized controlled trials showing that 10 years of therapy is superior to 5 years of therapy. Of special interest, we have seen that the benefit is greatest at approximately year 15. If a woman...
has been on tamoxifen for 5 years, it is realistic to tell her that continuing tamoxifen for another 5 years will add significant further benefit. I think that tamoxifen for an extended duration is very reasonable.

We also have evidence from randomized controlled trials showing that if someone has been on tamoxifen for 5 years—let us say in a premenopausal setting—and then switches to an aromatase inhibitor because she is now postmenopausal, those 5 years of aromatase inhibitor therapy can provide additional benefit.

Aromatase inhibitors have been shown to provide a somewhat higher disease-free survival rate than tamoxifen, so these are typically our initial go-to drugs in postmenopausal women. One of the tougher decisions to make right now is what to recommend for a postmenopausal woman who has been on an aromatase inhibitor for 5 years. Does this woman need further endocrine therapy? A number of randomized trials have compared 5 years with 10 years. In general, these trials have shown no additional benefit from further endocrine therapy in the lymph node–negative population. The results in lymph node–positive patients have been mixed, with one trial showing some benefit and the other trials showing little or no benefit. I would add the qualifier that in the original trials comparing 5 vs 10 years of tamoxifen, such as aTTom and ATLAS, the greatest benefit did not occur until year 15, as I mentioned earlier. The current trials comparing 5 vs 10 years of aromatase inhibitor therapy have not yet reported 15-year data, so the advice may change over the next few years if we have stronger data in favor of a longer duration.

**H&O What additional considerations exist for premenopausal women?**

**GS** Premenopausal women may not need any endocrine therapy if they have very small, low-grade, well-differentiated tumors. Such women are likely to benefit from tamoxifen, whereas those with larger tumors or positive lymph nodes can benefit from the use of an LHRH agonist plus an aromatase inhibitor. In the SOFT and TEXT trials, which enrolled premenopausal women, all participants received an LHRH agonist plus an aromatase inhibitor for a set period. These trials established that the best disease-free survival rates could be achieved in premenopausal women with this combination.

If a woman begins treatment at age 48 years and is premenopausal, she is likely to be postmenopausal after 5 years of LHRH agonist use. On the other hand, I had a patient in whom breast cancer had been diagnosed at the age of 18 and who finished her 5 years of adjuvant endocrine therapy at the age of 23 years, so she likely was left with 2½ decades of ovarian estrogen production. What is the appropriate duration of endocrine therapy in such a patient? We do not know the answer. The suppression of ovarian function in a young woman, whether with an LHRH agonist or oophorectomy, is certainly not without toxicity. Premature menopause carries with it real physical and emotional issues. These may include infertility, menopausal symptoms, and increased risk for fractures. Patients pay a high price for a reduced risk for recurrence, and we need to be very open and honest with our patients about the potential toxicities of this therapy.

**H&O What factors can help in decisions regarding the duration of therapy?**

**GS** When patients are at higher risk, whether because their tumor is large or because they have 1 or more positive lymph nodes, we discuss the value of continuing aromatase inhibitor therapy beyond 5 years. Part of that discussion, of course, addresses the risks of therapy. Aromatase inhibitors have the potential to cause chronic joint pain that limits mobility, which makes some patients miserable. These agents can also cause significant osteoporosis. The risks continue into the second 5 years for women on aromatase inhibitors, so I usually sit down with the patient and have that discussion at the 5-year point. The decision to continue the aromatase inhibitor is easy for a patient who initially had a 5-cm tumor and 3 positive lymph nodes, has had no significant bone loss, and is experiencing no symptoms from the aromatase inhibitor. Another patient may tell me that her medication is making her feel like a 90-year-old woman and that she is having homicidal thoughts about her medical oncologist. In that case, I graciously suggest that we call it quits at 5 years.

**H&O What additional toxicities must be considered in choosing between tamoxifen and aromatase inhibitors?**

**GS** Tamoxifen causes a small increase in the risk for uterine cancer, which is in the range of 4 or 5 additional cases per 1000 women over 5 years. The increase in risk probably continues if women receive an additional 5 years of tamoxifen. Tamoxifen also causes a small increase in the risk for blood clots of approximately 1 per 100 women. I sometimes recommend one agent over another according to a particular patient’s underlying symptomatology. For example, I had a patient who was already experiencing severe pain and loss of mobility from rheumatoid arthritis, and I did not wish to exacerbate these problems. Avoiding tamoxifen may be more important for a woman who is already at increased risk for blood clots. In most cases, though, we can learn about which side effects will occur, and which will be most bothersome, by trying out the agents. I always explain to women up front that if they experience a significant toxicity on a particular
endocrine therapy, we have the option of switching to a different one down the road.

As important as it is to be honest with patients about both common and rare toxicities, these should always be discussed in context. The agents have risks, but we prescribe them because they significantly reduce the risk of dying of breast cancer.

H&O Do you still use 10 years of tamoxifen in some patients?

GS Every breast cancer doctor I know finds that some patients are simply unable to tolerate aromatase inhibitors. Although tamoxifen is not quite as good as aromatase inhibitors from the standpoint of disease-free survival, it is still quite good. I would rather have a patient on adjuvant tamoxifen than on adjuvant nothing because tamoxifen certainly does lower the risk for a distant recurrence. I usually try a second aromatase inhibitor when a patient is having problems with the first one she tries, but if someone continues to object to the use of aromatase inhibitors, I will use tamoxifen.

H&O Can genomic assays help in decisions regarding the duration of therapy?

GS The data from assays such as MammaPrint and Oncotype DX are less useful when you are looking at long-term outcomes, by which I mean the risk for recurrence after 5 years. Level 2 evidence looking back at prospective randomized trials of extended adjuvant therapy suggests that the Breast Cancer Index may predict benefit from extended adjuvant endocrine therapy in patients with early-stage breast cancer. My sense is that there has not been huge pickup for that, but it certainly is an option for physicians.

Other technologies are emerging that may transform this issue over the next few years. For example, Sparano was the first author of a paper we published in *JAMA Oncology* in 2018, in which we found that the presence of circulating tumor cells 5 years after a diagnosis of hormone receptor–positive breast cancer predicted a greatly heightened risk for a late recurrence of cancer. We also have emerging data suggesting that the presence of circulating tumor DNA can predict recurrence in the relatively near future. These findings undoubtedly will be studied in large randomized studies in the not-too-distant future. The use of genomic assays to determine the optimal duration of endocrine therapy is not supported by anything approaching level 1 evidence, but my patients are certainly interested in the answer to this question.

What is exciting is that genomic assays may someday give you a clue as to which drugs might or might not work. For example, if someone has a mutation in the estrogen receptor (ER) gene *ESR1*, aromatase inhibitors probably will not work. Emerging evidence also suggests that patients with the *PIK3CA* mutation are more likely to respond to the phosphoinositide 3-kinase inhibitor alpelisib (Piqray, Novartis). Although we may have anecdotal reports regarding the use of these assays in that manner, we do not have anything approaching randomized controlled trial data, and their use is far from the standard of care at this time.

H&O Do you expect the gene expression studies currently being conducted on tumor samples from the duration studies to help clarify who is more or less likely to benefit from extended endocrine therapy?

GS I hope that next-generation sequencing will be able to define a population that is at higher risk for late recurrence. A number of different approaches are being examined. Here at Stanford, we are examining data from the METABRIC studies of Curtis and colleagues. This research suggested that “integrative clusters” exist within the ER-positive population that are characterized by distinct genomic signatures and point to an increased risk for late recurrence, a finding that has led to a new study in development at our institution whose purpose is to look at novel therapeutics for patients in these subgroups. We hope that studies such as this one will point both to who is at highest risk for late recurrence and to therapies that might help to prevent late recurrence.

H&O Which women should receive bisphosphonates?

GS Many physicians wrestle with the question of when to use bisphosphonates. A large number of randomized controlled trials of bisphosphonates have been carried out. A meta-analysis of these trials, published in the *Lancet* in 2015, suggested that bisphosphonates lowered the risk for bone metastasis in patients, most of whom were postmenopausal women with ER-positive cancers. The meta-analysis also found a modest reduction in mortality.

My recommendation regarding bisphosphonates is based on risk. For example, a postmenopausal woman who has a small, lymph node–negative, ER-positive tumor with a low Oncotype DX recurrence score is probably at low risk for the development of a bone metastasis, so the likelihood of benefit is very small. In contrast, a woman with a large, lymph node–positive tumor is at higher risk for distant metastasis and therefore bone metastasis. I would certainly consider the use of bisphosphonates in a high-risk patient.

Something I frequently discuss with my endocrinology colleagues is the fact that aromatase inhibitors increase the use of bisphosphonates.
the risk for fractures. Although oncologists tend to think of bisphosphonate use to reduce the risk for bone metastasis, endocrinologists are more likely to think about using bisphosphonates to reduce the risk for fractures. I order regular bone density testing for patients who take aromatase inhibitors, and the fracture-reducing properties of bisphosphonates factor into my discussions with patients regarding the risks and benefits of therapy.

H&O What is your opinion regarding the use of CDK4/6 inhibitors in early-stage breast cancer?

GS The data regarding CDK4/6 inhibitors in early-stage disease are emerging. We know that all 3 of the CDK4/6 inhibitors provide real benefit for patients with metastatic disease, but from phase 3 trials in the adjuvant setting we have data on only 2 of the agents. The PALLAS and PENELOPE-B trials looked at palbociclib (Ibrance, Pfizer), and the ongoing monarchE trial is looking at abemaciclib (Verzenio, Lilly). PALLAS was a classic adjuvant trial in which half the patients were randomly assigned to receive palbociclib plus an aromatase inhibitor. In PENELOPE-B, patients who had received neoadjuvant chemotherapy were randomly assigned to palbociclib or placebo if they had residual disease when they went into surgery. Both trials failed to show any significant benefit in terms of overall disease-free survival or the prevention of distant relapse.

In contrast, the monarchE trial—which enrolled relatively high-risk patients who had either at least 4 positive lymph nodes or 1 to 3 positive nodes plus an additional risk factor—showed a significant improvement in invasive disease-free survival with abemaciclib. The caution here is that the median follow-up was only 19 months at the most recent follow-up, which is very short for a trial of adjuvant therapy. The PENELOPE-B trial showed an early split in the curves, and then the curves came back together once we got out to 4 years. That adds to our skepticism regarding the abemaciclib data. I still discuss the possibility of the off-label use of abemaciclib in certain patients who are at high risk for recurrence, but that is just based on a hunch. We need to see how the data play out over the next few years before we can know what the standard of care should be.

H&O What do you make of the potential risk for cognitive impairment seen in your TAILORx sub-study?

GS The TAILORx sub-study looked at 552 patients who had been randomly assigned to receive either endocrine therapy alone or endocrine therapy plus chemotherapy as part of the larger TAILORx trial. The endocrine therapy could be either tamoxifen or an aromatase inhibitor. The study showed a cognitive decline in both groups at 3, 6, 12, 24, and 36 months, and it showed a worse cognitive decline in the chemotherapy group at 3 and 6 months, but not at 12, 24, and 36 months. This decline was modest in most patients, and many of them did not experience cognitive decline, but this risk is certainly something I discuss with patients when they begin adjuvant chemotherapy.

Disclosure Dr Sledge has served on the board of directors for Tessa Therapeutics and has served on the scientific advisory boards of G1 Therapeutics, Syndax Pharmaceuticals, and Synaffix. He has received stock options from Syndax Pharmaceuticals and Tessa Therapeutics.

Suggested Readings


Kalinowsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+)/negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder) [SABCS abstract GS3-00]. Cancer Res. 2020;80(40).


