Extending Endocrine Therapy in Women With Hormone Receptor–Positive Breast Cancer

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H&O What are the most recent recommendations on the duration of endocrine therapy for women with hormone receptor–positive breast cancer?

PG The current recommendations from the American Society of Clinical Oncology (ASCO), which came out in May 2014, state that women who are premenopausal at diagnosis of breast cancer or are going through menopause when they are diagnosed should begin with 5 years of adjuvant tamoxifen treatment. After completing this initial 5 years of tamoxifen, women can either continue tamoxifen for an additional 5 years of treatment, or be switched to an aromatase inhibitor (AI) for 5 years if they have gone through menopause.

Women who are postmenopausal at diagnosis can choose among 5 options: (1) tamoxifen for 10 years, (2) an AI for 5 years, (3) tamoxifen for 5 years followed by an AI for up to 5 years, or (4) tamoxifen for 2 to 3 years followed by an AI for up to 5 years.

H&O Will these recommendations change soon?

PG These recommendations are likely to change for premenopausal women in response to new data from the SOFT (Suppression of Ovarian Function Trial) trial that were presented at the 2014 San Antonio Breast Cancer Symposium and simultaneously published online in the New England Journal of Medicine. In this 3-arm clinical trial, more than 3000 women who were premenopausal at breast cancer diagnosis were randomly assigned to receive 5 years of either tamoxifen alone, tamoxifen plus ovarian function suppression (OFS), or exemestane plus OFS. After a median follow-up of 67 months, those treated with exemestane plus OFS and those treated with tamoxifen plus OFS were less likely to experience disease recurrence than those who received tamoxifen alone. Women who were chemotherapy-naive did equally well whether they received tamoxifen alone, tamoxifen plus OFS, or exemestane plus OFS. These results will lead to a change in up-front therapy for young women, which going forward should include OFS coupled with an AI. That in turn will change options for extended endocrine therapy depending on whether a woman is postmenopausal or continues to be premenopausal at completion of the first 5 years of therapy. For those who have become postmenopausal either naturally or from adjuvant chemotherapy, 2 ongoing clinical trials of extended AI therapy, MA.17R (NCT00754845) and NSABP B-42 (NCT00382070), are examining the use of extended therapy in women receiving up-front AIs as initial adjuvant therapy.

At the same time, many women worldwide, both premenopausal and postmenopausal, will continue to receive initial tamoxifen. In the immediate future, the need for extended adjuvant therapy will continue to be decided within the boundaries of this up-front use of tamoxifen.

H&O Do you have any other concerns about the ASCO recommendations?

PG Regarding women who are premenopausal at diagnosis, there are long-standing data supporting the initial 5 years of tamoxifen. Beyond that, the current recommendation...
option of extending tamoxifen for an additional 5 years is based on the aTTom (Adjuvant Tamoxifen—To Offer More?) and ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) studies, which focused almost exclusively on postmenopausal, not premenopausal, women. By way of illustration, none of the women in the aTTom study were reported as premenopausal and a small minority of those in the ATLAS study were—which taken together was not sufficiently representative of premenopausal women. This calls into question the ASCO recommendation that a further 5 years of extended tamoxifen should be recommended to these patients as it is not sufficiently evidence-based.

SOFT is not the only trial to have looked at the combination of OFS and endocrine therapy as up-front adjuvant therapy for premenopausal women; TEXT (Tamoxifen and Exemestane Trial) also has looked at this question. These trials support the superiority of OFS plus an AI over OFS plus tamoxifen, as well as the use of tamoxifen alone for certain patients.

H&O What course of action will you now recommend for premenopausal women?

PG Based on current evidence, my recommendations for up-front treatment of premenopausal women include OFS plus an AI, OFS plus tamoxifen, or tamoxifen alone, depending on the risk of disease. The need for extended therapy in higher-risk patients is unclear, as is the choice of therapy if extended therapy is desired. These questions are impossible to resolve in the absence of more clinical trial evidence. Until we have such data for those considered at the highest risk for recurrence, extending OFS plus an AI beyond the initial 5 years is likely the most reasonable choice. Further trial data will be needed to confirm this.

H&O What do you think of the ASCO recommendations for postmenopausal women?

PG I have doubts about the current ASCO guidelines for postmenopausal women. Staying on tamoxifen for 10 years may be a reasonable choice for women living in countries where AIs are unavailable or unattainable, but switching to an AI after the initial 5 years of tamoxifen has been shown to be markedly more beneficial than remaining on tamoxifen for 10 years. The other 2 options from the ASCO guidelines are reasonable options based on published data. Despite the absence of data to support the option of providing up to 7 or 8 years of endocrine treatment, this is nevertheless one of the most common endocrine therapeutic approaches in many countries. This treatment strategy is based on extrapolation from other data showing the advantage of switching to an AI after 2 to 3 years of tamoxifen, in conjunction with the data showing the advantage of switching to 5 years of an AI after 5 years of tamoxifen.

As mentioned, what we need next are data regarding remaining on an AI for longer than 5 years, when the AI is given either up-front or as a second agent. We are likely to have these results by 2016 at the earliest.

H&O What is the basis for prescribing extended endocrine therapy to women with hormone receptor–positive breast cancer?

PG Paradoxically, a woman with an estrogen receptor (ER)-positive tumor—although she has a lower risk of recurrent disease in the first 5 years of follow-up—will have a greater risk thereafter than a woman with an ER-negative tumor. This chronic relapsing nature of ER-positive disease has led to consideration of extended endocrine therapy.

This paradoxical natural history and paradoxical relapse pattern of these 2 important subtypes of breast cancer (ER-positive vs ER-negative) is reminiscent of the childhood story of the tortoise and the hare. The disease type with the lower initial risk of recurrence—ER-positive—“catches up” after a long period of follow-up.

In the MA.17 trial of 5187 postmenopausal women with breast cancer, published in the New England Journal of Medicine in 2003, it was shown that 5 years of tamoxifen followed by 5 years of an AI improved the estimated 4-year disease-free survival from 87% to 93%.

H&O Do women without side effects benefit as much from the drug?

PG The answer is probably yes. Some controversy exists around this important question, because of the publication of contradictory findings from 3 large clinical trials. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) and BIG (Breast International Group) 1-98 trials found that women with more treatment-related symptoms have better breast cancer outcomes than those with fewer symptoms. In contrast, we found the opposite in our analysis of 7576 patients from the MA.27 trial that was published in the Journal of Clinical Oncology in 2013.

H&O Is there a benefit to restarting endocrine therapy after having discontinued it?

PG Yes. We published a paper in the Journal of Clinical Oncology in 2008 regarding the effects of interrupting therapy. We examined patients in the MA.17 clinical trial with a gap of 1 to 6 years between their up-front
tamoxifen and their extended therapy, and found that giving delayed or interrupted AI therapy was both effective and worthwhile. Similar findings were published previously showing that giving tamoxifen after a long delay remained highly efficacious. Although the absolute risk of recurrence goes down over time, the proportional benefit from endocrine therapy in our study appeared to increase with longer follow-up. This seemingly counterintuitive result might be explained by earlier relapse of disease that is less endocrine sensitive, which in turn would leave much of the remaining risk of disease recurrence to be caused by disease that is highly endocrine sensitive.

**H&O Could you talk more about the side effects of endocrine therapy?**

**PG** The side effects of tamoxifen and AIs can be divided into: (1) symptoms that are not dangerous but affect quality of life, and (2) more serious toxicities that are potentially dangerous but do not necessarily cause symptoms. Anecdotally, the women who experience the most vasomotor symptoms from endocrine therapy tend to be those who were already having these symptoms before therapy began. When Whelan and coauthors examined postmenopausal women receiving prolonged (>5 years) therapy with the AI letrozole (Femara, Novartis) after an initial 5 years of tamoxifen, patients reported minimal effects on physical functioning and no impact on overall self-reported quality of life. Apart from mild bone loss, which generally is very easy to manage in patients on an AI, we see no serious long-term side effects with the AIs. In contrast, tamoxifen can cause serious unexpected toxicities, including venous thromboembolism and endometrial cancer.

**H&O Are molecular assays available that potentially could help decide which patients need longer treatment?**

**PG** Yes. We and others have identified biomarkers, tested using the Breast Cancer Index (BCI), in the patient’s primary tumors that is able to divide patients with lymph node–negative disease into 2 groups: low-risk and high-risk. This can guide therapeutic choices, although it is rarely used in the clinic. The same is true for studies of other markers, such as the PAM50 biomarker test.

**H&O What studies are ongoing that will help oncologists in making recommendations about endocrine therapy?**

**PG** Results from our ongoing MA.17R trial are awaited, as are results from the NSABP B-42 trial. These trials are evaluating the role of longer (10 years or longer) vs shorter (2 to 5 years) durations of AI therapy without tamoxifen. These studies will answer one of the most common questions remaining in the clinic today: for how long should AI endocrine therapy be recommended?

**Suggested Readings**


