

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

IN FOCUS: Breast Cancer

The Optimal Duration of Adjuvant Hormonal Therapy for Early-stage Breast Cancer

Eric Winer, MD
Associate Professor
Department of Medicine
Harvard Medical School
Director, Breast Oncology Center
Dana-Farber Cancer Institute
Boston, Mass.

H&O What is the purpose of adjuvant hormonal therapy in women with breast cancer?

EW Simply put, adjuvant hormonal therapy is administered to decrease a woman's chance of experiencing a recurrence of breast cancer and to prolong her survival. Any woman who has hormone receptor–positive disease, whether she is premenopausal or postmenopausal, is a candidate for receiving hormonal therapy. In a postmenopausal woman, an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor are the two standard treatment options. In a premenopausal woman, tamoxifen is standard, and it is sometimes administered in conjunction with ovarian suppression.

H&O What is the standard recommendation for the duration of hormonal therapy in the adjuvant setting?

EW In premenopausal women, the standard duration of adjuvant hormonal therapy is 5 years. The benefit of this therapy in terms of reducing the risk of death extends beyond 5 years, but there is no clear evidence that tamoxifen should be administered for longer than 5 years. In postmenopausal women, the optimal total duration of hormonal therapy remains less clear.

H&O What is the controversy regarding the optimal duration of therapy?

EW For those women who become menopausal while taking tamoxifen, benefit from 5 years of aromatase-inhibitor therapy has been demonstrated. However, for a hypothetical 42-year-old woman who was diagnosed with breast cancer at age 37, who has been receiving tamoxifen for 5 years, and is still experiencing regular menstrual cycles, there is no standard treatment beyond 5 years of tamoxifen. Recent data suggest that continuing tamoxifen may be of value in some women, but I do not believe the data are ready for clinical application. It is likely that clinical trials will be developed to address this specific clinical situation. Currently, in the absence of clinical-trial data, the recommendation for such a patient would be to discontinue therapy after 5 full years.

H&O In the postmenopausal setting, what is the recommended duration of therapy with aromatase inhibitors?

EW Aromatase inhibitors are safe and effective when given for 5 years. This period can occur upfront as the initial therapy, or it can occur after 5 years of therapy with tamoxifen. Although there is no study that has specifically looked at 5 years of therapy with an aromatase inhibitor after 2–3 years of therapy with tamoxifen, there is no reason to believe that such therapy would be any less effective or safe than if given after the full 5-year tamoxifen therapeutic period.

H&O Do the pharmacogenetic tests under development for assessing which patients are candidates to receive tamoxifen have any effect on treatment duration?

EW No. The pharmacogenetic tests would not affect treatment duration because they are intended to discern whether a patient metabolizes tamoxifen and, hence, whether the agent would be efficacious. Most clinicians likely agree that these assays are not yet far enough along in development for clinical application.

H&O What are the potential drawbacks to administering hormonal therapy for longer than 5 years?

EW It is unknown whether administration of hormonal therapy for longer than 5 years is safe. Clinical trials are currently addressing the question of the safety of treatment durations over 5 years for an aromatase inhibitor. These trials will define the overall safety profile and toxicity experiences of women receiving more prolonged therapy. The safety concerns relate to these agents' long-term effect on bone health. Although there are encouraging data that the bisphosphonates are able to prevent bone loss, the community is awaiting long-term fracture data. In general, when a medication is used for a long period of time, it is possible that toxicities will arise that were not anticipated. Therefore, it will be important to evaluate large groups of patients over time.

Hormonal therapy results in a modest improvement in patient outcomes. It is theoretically a real improvement but there are not sufficient data to determine whether these agents continue to be efficacious for longer than 5 years. For some or for many women, extending therapy

past 5 years may not confer benefit beyond this recommended duration. Assuming hypothetically that these agents do remain effective for longer than 5 years, it will still be necessary to ascertain whether they lead to any significant harm.

H&O What research questions remain to be answered in this setting?

EW In postmenopausal women, the main questions to be answered in terms of adjuvant hormonal therapy will be: 1) what is the better approach, tamoxifen followed by an aromatase inhibitor or an aromatase inhibitor upfront? 2) is there a single best approach for all women or does therapy need to be individualized based on characteristics of the tumor and potentially the patient (ie, CYP2D6 status)? 3) what is the optimal duration of total therapy for all women and can this duration be individualized so that only those who need treatment receive it? 4) are there ways that hormonal therapy can be "supercharged" so to speak, meaning can this therapy be given in conjunction with other treatments that will allow it to be more efficacious and prevent the occurrence of resistance?

Suggested Readings

Buzdar AU, Coombes RC, Goss PE, Winer EP. Summary of aromatase inhibitor clinical trials in postmenopausal women with early breast cancer. *Cancer*. 2008;112(3 suppl):700-709.

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Punglia RS, Burstein HJ, Winer EP, Weeks JC. Pharmacogenomic variation of CYP2D6 and the choice of optimal adjuvant endocrine therapy for postmenopausal breast cancer: a modeling analysis. *J Natl Cancer Inst*. 2008;100:642-648.

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