Research To Practice: Adjuvant Endocrine Therapy

27TH ANNUAL San Antonio Breast Cancer Symposium 10

While extensive resources have been allocated to evaluate new breast cancer treatment interventions, relatively minimal investment has been made to determine how these advances are implemented in practice. Continuing medical education has the potential to be a useful component in the clinical research continuum, not only by informing clinicians about available trials and emerging research findings, but by implementing outcomes assessments to evaluate how research advances are being implemented in clinical practice. The data presented here from the *Breast Cancer Update* Patterns of Care Study is from a national telephone survey of 150 randomly selected United States-based medical oncologists initiated in May 2004.

One of the key aspects of this initiative was the use of hormonal therapy. The most important databases currently affecting nonprocotol use of adjuvant endocrine therapy were derived from trials of aromatase inhibitors in postmenopausal patients, both as initial therapy and after two to three, or five years of tamoxifen. In premenopausal women, controversy continues on the use of ovarian ablation/suppression, particularly in women who continue to menstruate after receiving adjuvant chemotherapy.

CHOICE OF ADJUVANT ENDOCRINE THERAPY BASED ON TUMOR SIZE, NODAL AND HER2 STATUS

Which endocrine therapy would you likely recommend to a 65-year-old woman with an ER-positive tumor?

Therapy	2.2-cm, N2+ HER2-neg	2.2-cm, N- HER2-neg	0.8-cm, N- HER2-neg	2.2-cm, N10+ HER2-pos
Tamoxifen	34%	33%	43%	23%
Anastrozole	59%	61%	45%	75%
Letrozole	7%	6%	2%	2%
Exemestane	0%	0%	0%	0%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

USE OF ADJUVANT AROMATASE INHIBITORS FOR INITIAL THERAPY

When you use an aromatase inhibitor as initial adjuvant therapy, what percentage of this use is with each of the following agents?

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SWITCHING ADJUVANT THERAPY AFTER 2-3 YEARS OF TAMOXIFEN

The patient is a 65-year-old woman in average health with a 1.2-cm, ER-positive, HER2-negative, Grade II tumor and 3 positive lymph nodes on tamoxifen for 2 years. How would you manage this patient's endocrine therapy?

	No side effects with tamoxifen	Complains of 20 lb weight gain	Complains of moderate hot flashes
Continue tamoxifen	45%	17%	16%
Stop tamoxifen	—	—	—
Stop tamoxifen and switch to anastrozole	12%	35%	36%
Stop tamoxifen and switch to letrozole	11%	16%	12%
Stop tamoxifen and switch to exemestane	32%	32%	36%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SEQUENCING ADJUVANT THERAPY AFTER 5 YEARS OF TAMOXIFEN

The patient is a 65-year-old woman in average health with a 1.2-cm, ER-positive, HER2-negative, Grade II tumor and 3 positive lymph nodes who has completed 5 years of tamoxifen therapy. How would you manage this patient's endocrine therapy?

	Has just completed 5 years of tamoxifen	Is 1 year post-5 years of tamoxifen	Is 3 years post-5 years of tamoxifen
Continue tamoxifen	—	—	—
Start anastrozole	16%	14%	4%
Start letrozole	77%	58%	19%
Start exemestane	1%	—	—
Use no further hormonal therapy	6%	28%	77%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

Which endocrine therapy would you recommend for a woman in average health with a 1.2-cm, ER-positive, HER2-negative Grade II tumor and negative lymph nodes?

	Age 35	Age 45
Tamoxifen	73%	76%
Aromatase inhibitor + LHRH agonist or ovarian ablation	4%	4%
Tamoxifen + LHRH agonist or ovarian ablation	14%	9%
LHRH agonist or ovarian ablation	2%	2%
Other	5%	7%
Would not recommend endocrine therapy	2%	2%

SOURCE: *Breast Cancer Update* Patterns of Care Study, 2004.

SELECT PUBLICATIONS

Baum M et al; The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10.

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;Abstract 3.

Boccardo F et al. **Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study.** *J Clin Oncol* 2001;19(22):4209-15.

Castiglione-Gertsch M et al. **Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: A randomized trial.** *J Natl Cancer Inst* 2003;95(24):1833-46.

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Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;Abstract 770.

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002;Abstract 12.

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802.

AROMATASE INHIBITORS AS INITIAL ADJUVANT THERAPY IN POSTMENOPAUSAL WOMEN

The results of the ATAC trial are quite compelling. Even if you assume, for the sake of argument, that the curves will come together with further follow-up, the safety profile of anastrozole is still clearly better than that of tamoxifen. I cannot prevent endometrial cancer short of removing the uterus, but I can prevent or treat osteoporosis and fractures. Because the safety profile of anastrozole is better than that of tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my postmenopausal patients — not as a neutral choice, but as a better choice. I discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but I would certainly recommend anastrozole as opposed to tamoxifen.

— Gabriel N Hortobagyi, MD

"Many more years will be required to fine-tune the risk-benefit assessment of adjuvant aromatase inhibitors, but the use of these agents should be discussed with patients who are suitable candidates, and they should be informed about the limitations of the current data. In my opinion, women whose risk of recurrence is high are reasonable candidates for the inclusion of an aromatase inhibitor in plans for adjuvant treatment, whereas women with a low risk of recurrence might give more weight to long-term safety and be better served by tamoxifen therapy."

— Martine J Piccart-Gebhart, MD, PhD
N Engl J Med 2004;350:1140-1142

SEQUENCING AROMATASE INHIBITORS AFTER ADJUVANT TAMOXIFEN

It may be reasonable to offer an aromatase inhibitor to patients who completed a five-year course of adjuvant tamoxifen for as long as five or 10 years previously. However, with every year that passes, the absolute risk of recurrence decreases; therefore, the risk-to-benefit ratio changes. Every year the risks become more important relative to the benefit.

— I Craig Henderson, MD

Over the past couple of decades, tamoxifen has had a huge impact on the management of breast cancer, but its use in the adjuvant setting may be declining. Several studies have demonstrated the superiority of aromatase inhibitors over tamoxifen, including the ATAC trial, the NCIC-CAN-MA17 trial in which women received letrozole after five years of tamoxifen and two trials in which women were switched to an aromatase inhibitor after two or three years of tamoxifen. The Intergroup study utilizing exemestane, and Boccardo's trial utilizing anastrozole in node-positive breast cancer demonstrated an advantage to switching early from tamoxifen to the aromatase inhibitor. When I use endocrine therapy in newly diagnosed patients, I select anastrozole. If I'm going to switch therapy after two or three years of tamoxifen, I use exemestane, but after five years of tamoxifen, I choose letrozole.

— Nicholas J Robert, MD

Off protocol in a postmenopausal woman, I generally use adjuvant anastrozole up front or, if the patient has been on tamoxifen for two or three years, I switch her to exemestane. After five years of tamoxifen therapy, I offer patients letrozole. The issue here is that because patients generally do well after five years of tamoxifen, we have to carefully weigh the potential benefit and side effects of further adjuvant therapy. A patient with a small tumor may not need it; however, in a patient with multiple positive nodes, it probably is indicated.

— Adam M Brufsky, MD, PhD

AROMATASE INHIBITORS AND OVARIAN SUPPRESSION

I'm very enthusiastic about the research strategy of evaluating LHRH agonists with aromatase inhibitors. Extrapolating from the data in postmenopausal breast cancer, which suggest that anastrozole may have superior efficacy compared to tamoxifen, this seems like a rational strategy to transfer to premenopausal women. The two issues are whether or not it is actually going to be efficacious, and what the cost is in terms of side effects. I wouldn't utilize this strategy outside the context of a clinical trial.

— Nancy Davidson, MD