Research To Practice: Adjuvant Endocrine Therapy

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8

Extensive resources are allocated for the evaluation of breast cancer treatments. In contrast, minimal investments are made to determine how these therapeutic strategies are implemented in clinical practice. Continuing medical education not only informs clinicians about ongoing clinical trials and emerging research results, but it can also evaluate the implementation of research results by physicians in clinical practice. Data from the *Breast Cancer Update* Patterns of Care Study, a telephone survey conducted in September 2005 of randomly selected medical oncologists in the United States, are presented here. One of the key facets of this initiative was the use of adjuvant hormonal therapy. In postmenopausal women, the adjuvant trials evaluating the aromatase inhibitors as initial therapy and following two to three or five years of adjuvant tamoxifen have had a dramatic impact on the clinical use of adjuvant endocrine therapy. In premenopausal women, controversy continues with regard to the use of ovarian ablation/suppression.

CHOICE OF AROMATASE INHIBITORS AS ADJUVANT THERAPY

When you use an aromatase inhibitor in each of the following settings, what percentage of this use is with each of the following agents?

	Anastrozole	Letrozole	Exemestane
Initial adjuvant therapy	86%	11%	3%
After 2 to 3 years of adjuvant tamoxifen	37%	18%	45%
After 5 years of adjuvant tamoxifen	19%	73%	8%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

CHOICE OF ADJUVANT ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN

Which endocrine therapy would you be most likely to recommend to a 55-year-old postmenopausal woman with each of the following tumors?

	1.2-cm, ER+/PR+, HER2-, N-	1.2-cm, ER+/PR+, HER2-, 3N+	1.2-cm, ER+/PR-, HER2-, 3N+
Anastrozole	72%	80%	83%
Letrozole	—	—	—
Exemestane	2%	—	2%
Tam x 5y	4%	4%	4%
Tam x 2-3y → AI	16%	8%	9%
Tam x 5y → AI	6%	8%	2%

Tam = tamoxifen; AI = aromatase inhibitor; N = node

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SEQUENCING ADJUVANT THERAPY AFTER FIVE YEARS OF TAMOXIFEN

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

	Has just completed 5 years of tamoxifen	Completed 5 years of tamoxifen 1 year ago	Completed 5 years of tamoxifen 3 years ago
Continue tamoxifen	2%	—	—
Start anastrozole	16%	12%	6%
Start letrozole	78%	62%	18%
Start exemestane	2%	2%	2%
Use no further hormonal therapy	2%	24%	74%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SWITCHING ADJUVANT THERAPY AFTER TWO TO THREE YEARS OF TAMOXIFEN

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

	Tolerability of tamoxifen		
	No side effects with tamoxifen	Complains of 20-pound weight gain	Complains of moderate hot flashes
Continue tamoxifen	24%	4%	8%
Stop tamoxifen	—	2%	—
Stop tamoxifen and switch to exemestane	38%	40%	36%
Stop tamoxifen and switch to anastrozole	26%	40%	44%
Stop tamoxifen and switch to letrozole	12%	14%	12%

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

Which endocrine therapy would you be most likely to recommend to a 35-year-old premenopausal woman with each of the following tumors?

	1.2-cm, ER+/PR+, HER2-, 3N+	1.2-cm, ER+/PR-, HER2-, 3N+	1.2-cm, ER+/PR+, HER2+, 3N+
Tam x 5y	52%	50%	46%
Tam x 5y → AI	10%	10%	12%
Tam x 2-3y → AI	4%	4%	4%
Tam + LHRH or OA	20%	20%	26%
AI + LHRH or OA	6%	6%	6%
Other	6%	4%	4%
None	2%	6%	2%

Tam = tamoxifen; AI = aromatase inhibitor; LHRH = LHRH agonist
OA = ovarian ablation; N = node

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005. (n = 50)

SELECT PUBLICATIONS

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial.** *J Clin Oncol* 2005;23(22):5138-47.

Coombes RC et al; Intergroup Exemestane Study. **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.

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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.

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2.

Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62.

Jakesz R, on behalf of the ABCSG. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005;Abstract 527.

Punglia RS et al. **Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: A decision analysis.** *J Clin Oncol* 2005;23(22):5178-87.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 511.

THE ROLE OF ADJUVANT AROMATASE INHIBITORS IN POSTMENOPAUSAL WOMEN

Based on data from various adjuvant endocrine therapy trials, I believe it is unreasonable to withhold aromatase inhibitors from postmenopausal women with hormone receptor-positive disease. ATAC is still the definitive adjuvant trial in terms of comparing tamoxifen to an aromatase inhibitor, and the data are very compelling. An aromatase inhibitor is now my drug of choice, and that changed in just the past years.

As for switching patients from tamoxifen to an aromatase inhibitor, I discuss this with every postmenopausal patient on tamoxifen. My tendency, which is based on my intuition rather than data, is to advise patients on tamoxifen to complete two or three years and then switch. We don't know the optimal time to switch, and we don't know the optimal duration of various endocrine therapies. While we know that five years of tamoxifen is as good as or better than 10 years, the optimal duration of aromatase inhibitors is unknown at this time.

— I Craig Henderson, MD.* Breast Cancer Update *2005 (2)

If you start with tamoxifen, after two and a half, three or five years, more patients will have relapsed than on an aromatase inhibitor. A substantial number of those patients will be irretrievable — they have incurable disease — and so you're banking on the fact that you'll be able to capture more patients later, but we don't have any data for that. That's just speculation. While I believe sequencing therapy may be better, ultimately, I still don't see any reason not to start with the most effective therapy. An aromatase inhibitor followed by tamoxifen or a nonsteroidal aromatase inhibitor makes more sense to me. We have to wait to see the data from the BIG FEMTA trial, which includes an arm with letrozole as initial treatment followed by tamoxifen.

— Rowan T Chlebowski, MD, PhD.* Breast Cancer Update *2005 (7)

I believe a clear, consistent story is emerging without a lot of conflicts and conundrums: Adjuvant aromatase inhibitors are better than tamoxifen. Whether the aromatase inhibitors are used at the time of initial diagnosis, after two to three years or five years of tamoxifen, there is a favorable impact on local, distant and even contralateral breast cancer recurrences.

The unresolved questions are: Should you use a little tamoxifen, maybe two years and then cross over? Should you only use an aromatase inhibitor right off the bat and maybe even think of continuing beyond five years? The trial that will provide the most information in this regard is the BIG FEMTA/BIG 1-98 trial.

— Debu Tripathy, MD.* Breast Cancer Update *2005 (5)

I sit on the NCCN guidelines committee. If you evaluate the next rendition of the guidelines, you'll find we have not dismissed the use of tamoxifen but rather moved the use of aromatase inhibitors up front. Within the NCCN guidelines, we're trying to select the aromatase inhibitor to be used based on the design of the study. For first-line therapy, we would use anastrozole. If a patient has been on tamoxifen for a period of time, exemestane is now a legitimate choice, and after five years of tamoxifen, letrozole is an option. We view all of these agents as active and well tolerated.

— William J Gradishar, MD.* Breast Cancer Update *2005 (4)

ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

I have combined an LHRH agonist with an aromatase inhibitor in premenopausal women, but it's rare because for women who are at high enough risk for that therapy — multiple positive nodes or even node-positive, HER2-positive breast cancer — I generally recommend oophorectomy, and then I'm comfortable with an aromatase inhibitor.

— Joyce O'Shaughnessy, MD.* Patterns of Care *2004 (2)