



**Evidence-based Series #1-18**

**The Role of Aromatase Inhibitors in Adjuvant Therapy for  
Postmenopausal Women with Hormone Receptor-positive Breast Cancer**

*A. Eisen, M. Trudeau, W. Shelley, S. Sinclair, and the Breast Cancer Disease Site Group*

**Report Date: October 25, 2005**

**Evidence-based Series #13-1 is comprised of 3 sections:**

- Section 1: A Clinical Practice Guideline
- Section 2: A Systematic Review
- Section 3: Guideline Development and External Review: Methods and Results

A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)  
Developed by the Breast Cancer Disease Site Group

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## Evidence-based Series #1-18: Section 1

# The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: A Clinical Practice Guideline

*A. Eisen, M. Trudeau, W. Shelley, S. Sinclair, and the Breast Cancer Disease Site Group*

A Quality Initiative of the  
Program in Evidence-Based Care, Cancer Care Ontario,  
Developed by the Provincial Breast Cancer Disease Site Group

**Report Date: October 25, 2005**

### Questions

In postmenopausal women with early-stage, hormone receptor-positive breast cancer:

1. Compared with adjuvant tamoxifen alone for five years, do adjuvant aromatase inhibitors (anastrozole, letrozole, or exemestane) alone for five years improve clinically meaningful outcomes (disease-free or overall survival)?
2. Compared with adjuvant tamoxifen alone for five years, do adjuvant aromatase inhibitors in sequence with tamoxifen for a total of five years improve clinically meaningful outcomes?
3. Compared with placebo, do aromatase inhibitors after five years of adjuvant tamoxifen therapy improve clinically meaningful outcomes?
4. Compared with tamoxifen or placebo, what are the harms associated with aromatase inhibitors?
5. Compared with tamoxifen, does the efficacy of aromatase inhibitors depend on p185<sup>HER2/neu</sup> glycoprotein expression?

### Target Population

These recommendations apply to postmenopausal women with early-stage, hormone receptor-positive breast cancer.

### Recommendations and Key Evidence

#### Question 1

**Adjuvant tamoxifen (20mg daily for five years) remains a recommended standard of care for women with hormone receptor-positive breast cancer.**

**Adjuvant anastrozole (1mg daily for five years) is also a recommended standard of care for women with hormone receptor-positive breast cancer. Additionally, anastrozole is the preferred hormone treatment for postmenopausal women with hormone receptor-positive breast cancer who are thought to have a relative or absolute contraindication to tamoxifen or who have significant adverse effects with tamoxifen therapy.**

- The Arimidex (anastrozole) or Tamoxifen Alone or in Combination study (n=9,366) compared tamoxifen versus anastrozole versus tamoxifen plus anastrozole. At 68 months (5.7 years), disease recurrence was improved in the anastrozole group versus the tamoxifen

group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; p=0.03). The absolute difference in the four-year, disease-free survival estimates was 2.4% (86.9% with anastrozole versus 84.5% with tamoxifen). Overall survival was not significantly different.

*Qualifying Statements*

- Tamoxifen remains a recommended standard of care for two reasons. First, to date there has been no overall survival benefit detected for anastrozole over tamoxifen. Second, the evidence indicates that patients treated with aromatase inhibitors experience greater loss of bone mineral density. Third, based on the excess incidence of myocardial infarction in the IES trial, and the non-statistically significant two-fold increase in cardiac deaths in the BIG 1-98 trial, it is the expert opinion of the Breast Cancer Disease Site Group (DSG) that concerns regarding cardiac toxicity with aromatase inhibitors are justified. Therefore, especially for women at a low risk of recurrence or high risk of known complications, or both, tamoxifen may still be the preferred therapy option.
- Letrozole may be an alternative to anastrozole. The Breast International Group 1-98 trial compared letrozole versus tamoxifen in 8,028 women. After a median follow-up of 35.5 months, patients treated with letrozole had significantly better disease-free survival versus those treated with tamoxifen (HR, 0.81; 95% CI, 0.70 to 0.93). However, that trial has to date only been published in abstract form, and the results have not been widely disseminated. No specific recommendation can be made until the final results are published.

**Question 2**

**Adjuvant tamoxifen (20mg daily for five years) remains a recommended standard of care for women with hormone receptor-positive breast cancer.**

**Adjuvant exemestane therapy (25mg daily, to a total of five years of hormone therapy) is also a recommended standard of care for postmenopausal women with hormone receptor-positive breast cancer who have completed two to three years of tamoxifen treatment.**

- The Intergroup Exemestane Study (n=4,742) compared two to three years of tamoxifen followed by exemestane with two to three years of tamoxifen followed by further tamoxifen, each to a total of five years of adjuvant hormone therapy. Three-year, disease-free survival estimates at 30.6 months median follow-up were 91.5% (95% CI, 90.0% to 92.7%) in the exemestane group and 86.8% (95% CI, 85.1% to 88.3%) in the tamoxifen group (4.7% absolute difference). At 37.4 months, recurrence rates favoured exemestane after tamoxifen (HR, 0.73; 95% CI, 0.62 to 0.86; p=0.0001). Overall survival was not different at the time of this analysis (HR, 0.83; 95% CI, 0.67 to 1.02; p=0.08).

*Qualifying Statements*

- Tamoxifen remains a recommended standard of care for the reasons described in the qualifying statement for Question 1.
- Although more definitive results from larger trials are required, early results from the Italian Tamoxifen Arimidex trial suggest that, for women who need to discontinue tamoxifen after two to three years, anastrozole may be a reasonable alternative to exemestane. The Italian Tamoxifen Arimidex (anastrozole) trial (n=426) compared tamoxifen (20mg daily) for two or more years followed by further tamoxifen or anastrozole (1mg daily) to a total of five years of adjuvant hormone therapy. At 24 months (two years), recurrence was improved in women who switched to anastrozole (HR, 0.36; 95% CI, 0.17 to 0.75; p=0.006). The absolute difference in the percentage of women who experienced a recurrence was 5.4% (9.1% with tamoxifen and 3.7% with anastrozole). Overall survival was not significantly different at the time of the analysis (HR, 0.18; 95% CI, 0.02 to 1.57; p=0.07).
- Women in the Intergroup Exemestane Study and the Italian Tamoxifen Arimidex (anastrozole) trial

received tamoxifen for at least two years. Decisions regarding initiating aromatase inhibitors in those who have taken tamoxifen for less than two years will have to be individualized.

**Question 3**

**Postmenopausal women with hormone receptor-positive tumours who have completed five years of adjuvant tamoxifen therapy (20mg daily) should be considered for letrozole treatment (2.5mg daily for five years).**

- The MA-17 study (n=5,187) compared letrozole to placebo following 4.5 to six years of tamoxifen. In an interim analysis at 2.4 years, there was an improvement in disease-free survival favouring letrozole over placebo (HR, 0.57; 95% CI, 0.43 to 0.75; p=0.00008). The estimated four-year, disease-free survival rates were 93% with letrozole versus 87% with placebo (6% absolute difference). The final analysis at 2.5 years continues to show improved rates of recurrence (42% reduction in risk, p=0.0004). In the whole sample, overall survival was not significantly different at either analysis. In the final analysis, overall survival was significantly improved with letrozole in node-positive women (HR, 0.61; 95% CI, 0.38 to 0.98; p=0.04) but not in node-negative women (HR, 1.52; 95% CI, 0.76 to 3.06; p=0.24).

*Qualifying Statements*

- To date, there are only data for the first 2.5 years of letrozole treatment after five years of adjuvant tamoxifen therapy. Clinicians and patients should expect to review the question of letrozole treatment duration as more data on efficacy and toxicity become available over the next several years.
- Patients in the MA-17 trial were treated within three months of stopping tamoxifen and had received tamoxifen for 4.5 to 6 years. Decisions regarding the initiation of letrozole therapy in women who have been off tamoxifen for more than three months will have to be individualized, based on the time since tamoxifen was discontinued, the prognosis of the patient, and the toxicity of treatment. Similarly, decisions regarding the initiation of letrozole in those who have taken tamoxifen for three to 4.5 years will have to be individualized.

**Question 4**

**Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.**

- Compared with tamoxifen, preliminary evidence exists to suggest that aromatase inhibitors reduce the occurrence of venous thromboembolic and gynecologic events. Compared with tamoxifen or placebo, aromatase inhibitors likely increase the occurrence of bone events, including fractures and osteoporosis. Early data on clinical cardiac outcomes and lipid profile changes are mixed.
- Compared with placebo, letrozole may adversely affect quality of life and increase the occurrence of arthritis and/or arthralgia.

*Qualifying Statements*

- Due to theoretical concerns and the lack of long-term data, clinical cardiac outcomes and lipid profile changes, as well as other harms associated with aromatase inhibitors, should be monitored.
- Aromatase inhibitors are contraindicated for premenopausal women.

**Question 5**

**Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on HER2/neu status could be made.**

- No eligible trials on the efficacy of aromatase inhibitors according to HER2/neu status in the

adjuvant setting were identified.

- A randomized trial comparing four months of neoadjuvant tamoxifen with letrozole in postmenopausal women with breast cancer ineligible for conservation surgery reported superior overall response rates in the letrozole group (60% versus 41%;  $p=0.004$ ). In HER2/*neu*-overexpressing women, response rates were 88% and 21%, respectively ( $p=0.0004$ ). Conversely, in HER/*neu*-normal women, respective response rates were 54% and 42% ( $p=0.078$ ).
- In two trials where the primary outcome was the proliferation marker Ki67, HER2/*neu*-overexpressing women with operable breast cancer experienced greater reductions in Ki67 compared with HER2/*neu*-normal women; however, the difference was statistically significant in only one trial.

#### *Qualifying Statements*

- Based on the neoadjuvant trial evidence, it is the opinion of the Breast Cancer Disease Site Group that aromatase inhibitors may be the preferred treatment in women with HER2/*neu*-overexpressing breast cancer.

#### **Related Guidelines**

The following Program in Evidence Based Care (PEBC) guideline is related and may be of interest:

- Practice Guideline Report #1-5: *The Role of Aromatase Inhibitors in the Treatment of Postmenopausal Women with Metastatic Breast Cancer (4)*.

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