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Evidence-based Series 1-18 EDUCATION AND INFORMATION 2011

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

Members of the Breast Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

A review conducted in 2011 put Evidence-based Series (EBS) 1-18 in the Education and Information Section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

The reviewed report consists of:

1. **Guideline Report Overview**
2. **Section 1: Guideline Recommendations**
3. **Section 2: Evidentiary Base**
4. **Section 3: EBS Development Methods and External Review Process**

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Breast Cancer Disease Site Group page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/

Release Date: May 15, 2012

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

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version October 2005	1966 to 2005	Full Report	Web publication	Not applicable (NA)
Updated Version February 2008	2005 to 2007	Full Report	Peer review publication[1] Web publication	No change in guideline recommendations
Reviewed Version May 2012	N/A	N/A	Updated Web publication	Guideline ARCHIVED

[1] Eisen A, Trudeau M, Shelley W, Messersmith H, Pritchard KI. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review. Cancer Treat Rev. 2008;34(2):157-74. doi:10.1016/j.ctrv.2007.11.001.

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Evidence-based Series 1-18 ARCHIVED 2011

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

Guideline Review Summary

Review Date: September 2011

The 2008 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2005 and was updated in 2008. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Summary and Full Report in this version are the same as February 2008 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is completed with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore no update search was conducted. A new guideline that will incorporate questions from this guideline is being produced. Thus, the 2008 guideline and its recommendations on the role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer have been ARCHIVED.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and **each page is watermarked** with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool in the document.

4. **UPDATE –** An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.

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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: Guideline Recommendations

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 (PEBC), Cancer Care Ontario.
Developed by the PEBC Breast Cancer Disease Site Group

Current Report Date: February 26, 2008
Original 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 $p185^{HER2/neu}$ glycoprotein expression?

TARGET POPULATION

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

RECOMM ENDATIONS AND KEY EVIDENCE

Recommended treatment options for postmenopausal women with hormone receptor-positive early breast cancer:

Available trial evidence supports six adjuvant hormonal therapy options, summarized across four recommendations directly below, for the treatment of the target population. At

present, there are no data available to compare between the various adjuvant aromatase inhibitor strategies. Rather, the use of adjuvant aromatase inhibitors has been compared to the standard of five years of adjuvant tamoxifen. Therefore, the decision about which therapy option to consider for patients beginning hormonal therapy should be made on an individual patient basis. Key evidence and qualifying statements in support of the recommendations will follow the recommendations and proceed in a similar order.

Recommendations

1. Adjuvant tamoxifen (20 mg daily for five years) remains an acceptable option for the treatment of women with hormone receptor-positive, early-stage breast cancer.
2. Adjuvant anastrozole (1.0 mg daily for five years) or letrozole (2.5 mg daily for five years) is an acceptable alternative to five years of adjuvant tamoxifen therapy.
3. Adjuvant tamoxifen (20 mg for two to three years) followed by switching to either adjuvant exemestane (25 mg daily, to a total of five years of hormone therapy) or adjuvant anastrozole (1mg daily, to a total of five years) therapy is also an acceptable alternative to five years of tamoxifen.
4. Adjuvant letrozole (2.5 mg daily for five years) should be considered for women who have completed five years of adjuvant tamoxifen therapy.

Key Evidence

- The Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) study (n=9,366) compared tamoxifen versus anastrozole versus tamoxifen plus anastrozole. At 68 months (5.7 years), disease-free survival was significantly 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 four-year disease-free survival estimates was 2.4% (86.9% with anastrozole versus [vs.] 84.5% with tamoxifen). Additional benefit was seen for time to recurrence (TTR) and time to distant recurrence (TDR) with anastrozole. Overall survival was not significantly different.
- The Breast International Group (BIG) 1-98 trial compared letrozole versus tamoxifen in 8,028 women. After a median follow-up of 51 months, patients treated with letrozole had significantly better disease-free survival (primary endpoint) versus those treated with tamoxifen (HR, 0.82; 95% CI, 0.71 to 0.95). There was also significant benefit for TTR and TDR with letrozole. Overall survival was not significantly different.
- The Intergroup Exemestane Study (IES) (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. At 55.7 months median follow-up, the exemestane arm showed significantly improved disease-free survival (HR, 0.76; 95% CI, 0.6 to 0.88) but showed no significant benefit for overall survival. Time to contralateral breast cancer, TTR, and TDR were also significantly improved in women who switched to exemestane. Overall survival was significantly improved only during a subgroup analysis that excluded patients with estrogen receptor-negative disease (HR 0.83, 95% CI 0.69 to1.00 in favour of switching to exemestane).
- The Italian Tamoxifen Arimidex (anastrozole) (ITA) trial (n=426) compared tamoxifen (20 mg daily) for two or more years followed by further tamoxifen or anastrozole (1.0 mg daily) to a total of five years of adjuvant hormone therapy. At 64 months follow-up, disease-free survival (primary endpoint) was significantly improved in women who switched to

anastrozole (HR, 0.57; 95% CI, 0.38 to 0.85). There was no significant difference in overall survival between therapy arms.

- The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 and German Adjuvant Breast Cancer Group Arimidex/Nolvadex (ARNO)-95 trials had arms identical to the ITA trial described above. At 28-months median follow-up, a combined analysis showed significantly improved disease-free survival for women who switched to anastrozole (HR, 0.60; 95% CI, 0.44 to 0.81). Distant metastases-free survival was also significantly longer with anastrozole (HR, 0.61; 95% CI, 0.42 to 0.87). There was no significant difference in overall survival.
- A meta-analysis of the ABCSG-8, ARNO-95, and ITA trials found improvements in disease-free survival (HR, 0.59; 95% CI, 0.48 to 0.74; p<0.0001), distant recurrence-free survival (HR 0.61, 95% CI 0.45 to 0.83, p=0.002), and overall survival (HR, 0.71; 95% CI, 0.52 to 0.98; p=0.04) for women who switched to anastrozole.
- 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) and in those who received more than five years of tamoxifen (HR, 0.56; 95% CI, 0.33 to 0.97; p=0.04) but not in node-negative women (HR, 1.52; 95% CI, 0.76 to 3.06; p=0.24). Additional abstracts report on data at 4.5 years of median follow-up, at which time 73% of the placebo arm had crossed over to letrozole. Results indicate continued benefit in disease-free survival, but not overall survival, for all patients treated with letrozole including for those who had crossed over.

Qualifying Statements

- Tamoxifen remains an acceptable therapy option for several reasons. First, to date there has been no overall survival benefit detected for the use of anastrozole or letrozole alone over tamoxifen alone. Though a meta-analysis of trials indicated potential significant benefit in overall survival for switching to anastrozole in comparison to continued tamoxifen, consistent advantage in overall survival has not been observed, particularly for other aromatase inhibitors and in other treatment settings. Second, evidence indicates that patients treated with aromatase inhibitors experience a greater incidence of fractures and a greater loss of lumbar spine and hip bone mineral density (the latter specific to anastrozole; see Recommendation #5).
- Switching to aromatase inhibitors following less than two years of adjuvant tamoxifen therapy:

  Women in the IES, ITA, and ABCSG-8/ARNO-95 trials received tamoxifen for at least two years, to three years maximum. Decisions regarding initiating aromatase inhibitors in those women who have taken tamoxifen for less than two years will have to be individualized, and there is no evidence to support a decision process at this time.
- Use of aromatase inhibitors following five years of adjuvant tamoxifen:

  Patients in the MA.17 trial were treated within three months of stopping tamoxifen and had received tamoxifen for 4.5 to six 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.

- There is not enough evidence to evaluate the use of exemestane or anastrozole following five years of tamoxifen. The ABCSG-6a trial was developed as a continuation of the ABCSG-6 trial and compared three years of anastrozole or no further treatment following five years of adjuvant tamoxifen. At 60 months median follow-up, this trial, reported in abstract form, found significantly better disease-free survival in patients treated with anastrozole after five years of tamoxifen, with or without aminoglutethimide. No difference in overall survival was reported. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 trial was amended to compare five years of exemestane or placebo following five years of adjuvant tamoxifen. After the release of the MA.17 results, accrual was halted, the trial was unblinded, and placebo patients were offered exemestane. At 30 months median follow-up, an abstract reported no significant difference in disease-free or overall survival.

Precautions

Recommendations

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

Key Evidence

- Compared with tamoxifen alone, evidence from the ATAC and BIG 1-98 trials indicate a higher incidence of fracture for aromatase inhibitors alone (11.0% vs. 7.7%, p<0.0001 for anastrozole alone; 8.6% vs. 5.8%, p<0.001 for letrozole alone), and greater decline in both lumbar spine mineral density (-8.1% [95% CI -10.1% to -6.1%, p<0.0001) and hip bone mineral density (-7.4% [95% CI -9.6% to -5.3%, p<0.0001) for patients treated with anastrozole alone. However, no patient in the ATAC trial with normal bone density at outset developed osteoporosis after five years of anastrozole.
- A Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) International trial substudy also indicated that patients treated with exemestane alone experienced a mean decrease of −0.24 (p=0.02) and −0.25 (p=0.005) for spine and hip bone mineral density in comparison to tamoxifen alone.
- When switching to an aromatase inhibitor after two to three years of tamoxifen was compared to continued tamoxifen, evidence from the IES, and ABCSG-8/ARNO-95 trials indicate a higher incidence in fracture (7.0% vs. 4.9%, p=0.003 for exemestane; 2% vs.1%, p=0.015 for anastrozole), osteoporosis (9.2% vs. 7.2%, p=0.01 for exemestane), and a greater decline in lumbar spine and hip bone mineral density (-1.4%, 95% CI -0.8% to −1.9%; and −2.7%, 95% CI −2.0% to −3.4%; respectively for exemestane at six months).
- Additional evidence from the MA.17 trial indicates a higher incidence of osteoporosis (8.1% vs. 6.0%, p=0.003) in women placed on letrozole following five years of tamoxifen compared to placebo.

Qualifying Statements

- Data on clinical cardiac outcomes and lipid profile changes are mixed. Adverse effects on lipids in some of the aromatase inhibitor trials may be due to the discontinuation of the protective effect of tamoxifen. 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.
- Evidence exists to suggest that aromatase inhibitors reduce the occurrence of venous thromboembolic and gynecologic events.

- Compared with placebo, letrozole may adversely affect quality of life and increase the occurrence of arthritis and/or arthralgia. Further evidence across various trials suggests that aromatase inhibitors increase the occurrence of arthralgia regardless of comparison group and mode of treatment.
- Aromatase inhibitors are contraindicated in premenopausal women.

Predictors of Treatment Response

Recommendations

6. Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on HER2/*neu* status can be made at this time.

Qualifying Statements

- 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% vs. 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.

RELATED GUIDELINES

- Practice Guideline Report #1-5: *The Role of Aromatase Inhibitors in the Treatment of Postmenopausal Women with Metastatic Breast Cancer* (4) is related and may be of interest

Funding

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Evidence-based Series #1-18: Section 2

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

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 (PEBC), Cancer Care Ontario,
Developed by the PEBC Breast Cancer Disease Site Group

Current Report Date: February 26, 2008
Original 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 $p185^{HER2/neu}$ glycoprotein expression?

INTRODUCTION

In the mid-1990s, a new class of oral hormone agents, the third-generation aromatase inhibitors, became available for use in postmenopausal women with metastatic breast cancer. These agents comprise two categories: 1) the reversible inhibitors anastrozole (Arimidex®, AstraZeneca Pharmaceuticals LP) and letrozole (Femara®, Novartis Pharmaceuticals Corporation) and 2) the irreversible inhibitor exemestane (Aromasin®, Pfizer Inc). Evidence from phase III clinical trials suggests that anastrozole and letrozole are modestly superior to tamoxifen as first-line therapy for postmenopausal women with metastatic breast cancer (1). By extension, the hypothesis that aromatase inhibitors may also be superior to tamoxifen in the

adjuvant setting was generated. This systematic review was developed to review the evidence for the use of third-generation aromatase inhibitors as adjuvant therapy for postmenopausal women with early-stage, hormone receptor-positive tumours, addressing the following questions:

1. Compared with tamoxifen for five years, do aromatase inhibitors for five years improve clinically meaningful outcomes (disease-free or overall survival)?
2. Compared with tamoxifen for five years, do 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 tamoxifen improve clinically meaningful outcomes?
4. Compared with tamoxifen or placebo, what are the harms associated with aromatase inhibitors?
5. Do the relative efficacies of aromatase inhibitors, compared with tamoxifen, depend on HER-2/*neu* status?

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle[1]. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected by one methodologist (HM) and reviewed directly by four members of the PEBC Breast Cancer Disease Site Group (DSG) (AE, MT, WS, and SS) and one methodologist (HM). The entire Breast Cancer DSG was given opportunity to review the systematic review and provide input and consensus.

The systematic review is a convenient and up-to-date source of the best available evidence on the use of third-generation aromatase inhibitors as adjuvant therapy for postmenopausal women with early-stage, hormone receptor-positive tumours. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of the recommendations developed by the Breast Cancer DSG found in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

MEDLINE was searched through to May 9, 2007 using a disease-specific medical subject heading descriptor ("breast neoplasms"), a treatment-specific descriptor ("chemotherapy, adjuvant"), and agent-specific descriptors ("aromatase/antagonists and inhibitors"). The Excerpta Medica database was also searched through to May 9, 2007 using a disease-specific Excerpta Medica Tree term ("breast cancer"), a treatment-specific keyword ("adjuvant chemotherapy"), and agent-specific terms ("anastrozole" or "letrozole" or "exemestane"). These terms and various synonyms were then combined with search terms for the following publication types: randomized controlled trial, systematic review, or meta-analysis.

The Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews were also searched through to May 9, 2007. Online conference proceedings from the American Society of Clinical Oncology Annual Meetings from 1999 to 2006 (http://www.asco.org) and the San Antonio Breast Cancer Symposia from 2001 to 2006 (http://www.sabcs.org) were also searched.

[1] Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13(2):502-12.

Relevant articles and abstracts were selected by one reviewer (HM). The reference lists from all sources were searched for additional trials.

Study Selection Criteria

Articles were selected for inclusion in this systematic review, based on following criteria:

- Third generation aromatase inhibitors (anastrozole, letrozole, or exemestane) as adjuvant therapy were evaluated in a randomized controlled trial or meta-analysis.
- Trial primary outcomes included disease/event/relapse-free survival and/or overall survival.
- Clinical trial results were reported in full papers or abstracts.

Non-English trials were excluded, as translation capabilities were not available. Also, in order to concentrate on the most relevant data, trials designed solely to study toxicity or quality of life with no efficacy outcome were excluded from data abstraction, although their references are reported below.

Synthesizing the Evidence

The Review Manager software (RevMan 4.1)[2] provided by the Cochrane Collaboration (Metaview © Update Software) was used to create forest plots of time-to-event data. When necessary and possible, hazard ratios and confidence intervals for disease-free and overall survival were derived from reported data using the methods described by Parmar et al (2).

RESULTS

Nine randomized controlled trials (3-14) and one meta-analysis (15) with published efficacy data were eligible for inclusion in this systematic review. Table 1 provides a summary of key characteristics of these trials and their patients. An additional three trials with efficacy primary outcomes have reported quality of life and/or toxicity data but have not yet reported efficacy data; these trials are described below.

All major trials under review were multicentre trials. All trials except the Italian Tamoxifen Arimidex (ITA) (9) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 (12) trials reported an appropriate method of randomization. The point at which randomization occurred in trials of two to three years tamoxifen therapy followed by aromatase inhibitor, designated as “switching” trials, differed: in the Breast International Group (BIG) 1-98 and Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 trials, patients were randomized before the start of any hormonal therapy (tamoxifen included) whereas in the German Adjuvant Breast Cancer Group’s Arimidex/Nolvadex (ARNO)-95, ITA, and Intergroup Exemestane Study (IES) trials, patients were randomized after receiving two to three years of tamoxifen. The ABCSG-8 and ARNO-95 trials were the only trials, among those where patient characteristics were openly reported, that recruited patients without prior chemotherapy. All major trials reported double blinding, except for the ABCSG-8 and ARNO-95 trials (10), which were open label, and the ITA trial, which did not report any blinding. All major trials were appropriately powered. The IES trial (8), the ABCSG-8, and the ARNO-95 trials all met pre-specified stopping rules. The ITA and NSABP B-33 trials did not reach their planned sample sizes (see below for more details). All the major trials, except the ABCSG-6a (13,14) used intent-to-treat analysis. Major trials differed in their definitions of postmenopausal status, as listed in Table 2. Unless noted otherwise, all trials used the following doses: tamoxifen, 20 mg daily; anastrozole, 1.0 mg daily; letrozole, 2.5 mg daily; and exemestane, 25 mg daily.

[2] Review Manager (RevMan) [Computer program]. Version 4.1 for Windows. Oxford, England: The Cochrane Collaboration, 2008.

Six other trials (16-21) were identified but not systematically reviewed as they did not have efficacy measures as primary endpoints. These trials investigated the following issues: lipid metabolism (16-19), bone toxicity and side effects (17,18,20), gynecological toxicity and side effects (21), and quality of life (17).

Table 1. Randomized controlled trials comparing aromatase inhibitors to tamoxifen as adjuvant hormone therapy; characteristics of included trials that reported efficacy data.

Trial	Treatment Arms	Pts	Expected Effect, Power, and Significance	Age	Nodal Status	Tumour Size	Hormone-Receptor Status	Primary Therapy
ATAC[a] (3,4)	A T	3125 3116	DFS HR no greater than 1.25 for non-inferiority, at least 0.80 for superiority, 80% power at 5% significance	Mean 64.1 yrs	61% node negative	64% tumour ≤ 2 cm	84% ER+ and/or PgR+	Mastectomy: 47% Radiotherapy: 63% Chemotherapy: 20%-22%
BIG 1-98 (5,6)	L T	2463 2459	DFS HR 0.80, 80% power at 5% significance	Median 61 yrs	57% node negative	62% tumour ≤ 2 cm	ER+ and/or PgR+ required	Mastectomy: 43% Radiotherapy: 72% Chemotherapy: 25%
IES (7,8)	T→E T	2352 2372	Absolute diff. of 3.6% in DFS at 3 years, 88% power at 4.3% significance	<60 yrs: 32% 60-69 yrs: 42.8%	52% node negative	48% tumour ≤ 2 cm	ER+/unk required, 2% ER- and PgR-/unk	Mastectomy: 51% Chemotherapy: 32.6%
ITA (9)	T→A T	225 223	30% decrease in annual risk of recurrence, 80% power at 5% significance	Median 63 yrs	Node positive required	44-49% tumour ≤ 2 cm	ER+ required	Mastectomy: 52-55% Radiotherapy: 49-54% Chemotherapy: 67%
ABCSG 8-ARNO 95 (10)	T→A T	1618 1608	HR 0.7 for EFS, 80% power at 5% significance	Median 62 yrs	74% node negative	70% tumour ≤ 2 cm	ER+ and/or PgR+ required	Mastectomy: 23-24% No previous radiotherapy or chemotherapy
MA.17 (11)	T→L T→placebo	2593 2594	HR 0.78 for DFS, 80% power at 5% significance	Median 62 yrs	49-50% node negative	NR	97% ER+ and/or PgR+	Mastectomy: 51-52% Chemotherapy: 45-46%
NSABP B-	T→E	1598	21.3% reduction in DFS	49%	52% node	T1-3	NR	NR

Trial	Treatment Arms	Pts	Expected Effect, Power, and Significance	Age	Nodal Status	Tumour Size	Hormone-Receptor Status	Primary Therapy
33 (12)	T→placebo		HR, 80% power at 5% significance	<60 yrs	negative	required		
ABCSG-6a (13,14)	T[b]→A T[b]	387 469	See text		68% node negative	63% tumour ≤ 2 cm	ER+ and/or PgR+ required	NR

[a] The ATAC trial also included an anastrozole/tamoxifen combination arm, whose results are not reported here as that arm does not address the questions in this systematic review.

[b] Patients were previously randomized to five years tamoxifen or five years tamoxifen plus aminoglutethimide. They were then randomized to three years anastrozole or no further treatment.

Abbreviations: A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; BMD, bone mineral density; DFS, disease-free survival, disease-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; L, letrozole; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; PgR, progesterone receptor; Pts, patients; T, tamoxifen; TEAM, Tamoxifen and Exemestane Adjuvant Multicentre; unk, unknown; yrs, years.

Table 2: Definition of postmenopausal status used in the included trials. Included randomized controlled trials that have reported efficacy data.

Trial	Definition of Postmenopausal Status
ABCSG-6a (13,14)	Not reported
ABCSG-8/ ARNO-95 (10)	Assumed for women whose last menstruation took place at least 12 months before study entry, who had undergone bilateral ovariectomy, or whose follicle-stimulating hormone and luteinising hormone concentrations indicated postmenopausal status.
ATAC (3)	Bilateral oophorectomy; > 60 years of age; 45-59 years of age with intact uterus and amenorrheic for at least 12 months; or, for those amenorrheic for < 12 months, follicle-stimulating hormone concentrations within postmenopausal range.
BIG 1-98 (5)	Regardless of HRT or hysterectomy: • Surgical bilateral oophorectomy AND any age • Radiation castration AND amenorrheic for ≥ 3 months AND any age • Not postmenopausal at the start of adjuvant chemotherapy AND completed ≥ 6 cycles CMF or ≥ 4 cycles AC AND age ≥ 45 AND FSH/LH/E2 postmenopausal levels No HRT: • Hysterectomy AND age < 55 AND FSH/LH/E2 postmenopausal levels prior to chemotherapy • Hysterectomy AND age ≥ 55 No HRT and No Hysterectomy: • Amenorrhea > 1 year AND age < 50 • Amenorrhea > 6 months AND age ≥ 50 HRT (Regardless of hysterectomy): • HRT stopped for ≥ 1 month AND age < 55 AND FSH/LH/E2 postmenopausal levels prior to chemotherapy • HRT stopped for ≥ 1 month AND age ≥ 55 FSH/LH/E2 postmenopausal levels prior to chemotherapy and not categorized above HRT=Hormone replacement therapy, received within three months of randomization. HRT received more than 3 months prior to randomization is considered “No HRT.”
IES (7)	≥ 55 years of age with amenorrhea for more than two years or amenorrhea for more than one year at the time of diagnosis
ITA (9)	Missing regular menses for at least 1 year or women more than 50 years with hysterectomy. Also, confirmed amenorrheic because of chemotherapy. When status unclear, plasma follicle-stimulating hormone and estradiol levels were evaluated.
MA.17 (11)	≥ 50 years of age at start of tamoxifen; < 50 years of age but postmenopausal at tamoxifen initiation; < 50 years of age but underwent bilateral oophorectomy; premenopausal; < 50 years of age at start of tamoxifen but became amenorrheic

Trial	Definition of Postmenopausal Status
	during chemotherapy or treatment with tamoxifen; or any age but with postmenopausal levels of luteinizing hormone or follicle-stimulating hormone prior to study enrolment.
NSABP B-33 (12)	Not reported

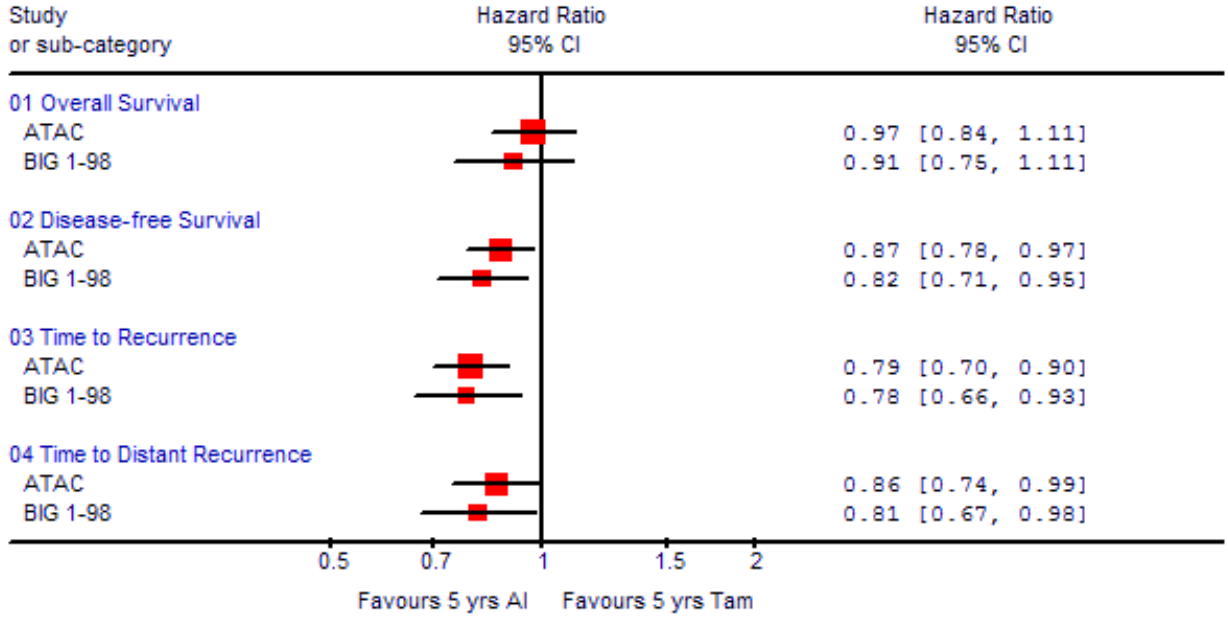
Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AC, doxorubicin, cyclophosphamide; ARNO, Arimidex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; CMF; Cyclophosphamide, Methotrexate And 5-Fluorouracil; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Arimidex; LH, luteinizing hormone; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Aromatase Inhibitors Alone Versus Tamoxifen Alone

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (3) compared three treatment regimens: five years of tamoxifen, five years of anastrozole, or five years of both agents given in combination. The primary outcome was disease-free survival (DFS; defined as the time to the earliest occurrence of either local or distant recurrence, new primary contralateral breast cancer [invasive or ductal carcinoma in situ], or death). At 68 months of follow-up, the intent-to-treat analysis showed significantly improved DFS, time to recurrence (TTR), and time to distant recurrence (TDR; see Figure 1) for anastrozole over tamoxifen, while overall survival (OS) was similar (4). Contralateral incidence was also significantly reduced (62% to 12%, p=0.01). The absolute difference in four-year DFS was 2.4% (86.9% with anastrozole versus 84.5% with tamoxifen). A retrospective subgroup analysis from this trial (22) found no significant efficacy interaction between the form of endocrine therapy and whether or not patients had received various prior chemotherapies (TTR hazard ratio [HR] for anastrozole versus [vs.] tamoxifen 0.89 in patients with chemotherapy vs. 0.74 in those without, p=0.21 for interaction).

The BIG 1-98 trial (5,6) compared four different treatment arms: five years of letrozole, five years of tamoxifen, two years of tamoxifen followed by three years of letrozole, or two years of letrozole followed by three years of tamoxifen. The analysis reported here (6) compares only patients randomized to five years of either tamoxifen or letrozole and does not include patients randomized to sequential therapy. However, an earlier analysis (5) included these patients and found very similar results. The primary endpoint under study was DFS. Disease events were defined as invasive breast cancer recurrence, invasive contralateral breast cancer, non-breast second primaries, and deaths without recurrence. After a median follow-up of 51 months, DFS favoured letrozole over tamoxifen, and there were significant benefits to letrozole for TTR and TDR, but there was no significant benefit to OS (Figure 1). The absolute difference in four-year DFS was 2.9% (87.5% in the letrozole group, 84.6% in the tamoxifen group).

Figure 1. Efficacy results of randomized controlled trials comparing aromatase inhibitors alone to tamoxifen alone as adjuvant hormone therapy.

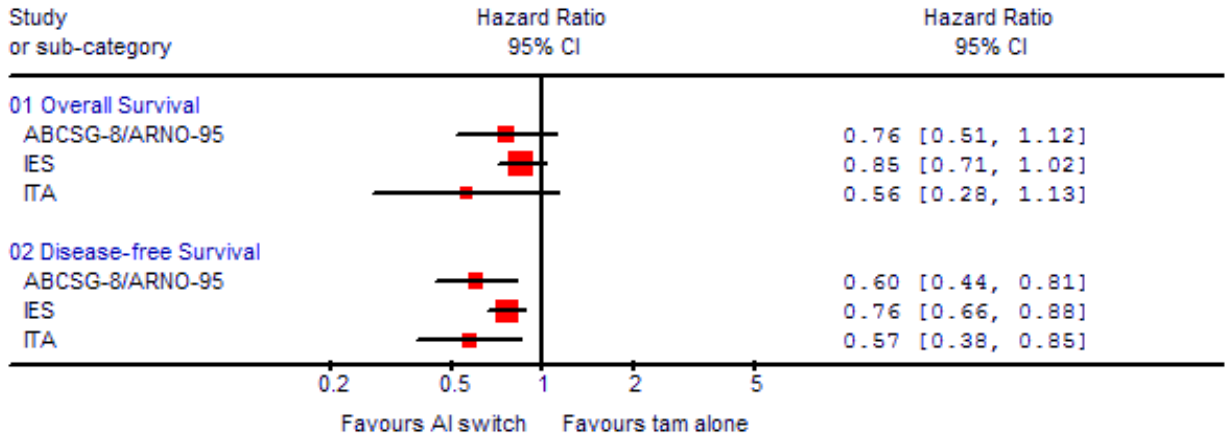


Note: HR CIs may differ slightly (±0.02) from originally reported CIs due to errors in rounding.
References: ATAC (4), BIG 1-98 (6).
Abbreviations: AI, aromatase inhibitor; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG, Breast International Group; CI, confidence interval; HR, hazard ratio; tam, tamoxifen.

Aromatase Inhibitors After Tamoxifen Versus Tamoxifen Alone

The IES study randomized women who had completed two to three years of tamoxifen to receive exemestane or further tamoxifen for a total of five years of treatment (7,8). The primary outcome was DFS (defined as the time from randomization to either recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause). At 55.7 months median follow-up, the trial showed an improvement in DFS but no significant difference in OS (Figure 2). Time to contralateral breast cancer (HR, 0.57; 95% confidence interval [CI], 0.33 to 0.98), TTR (HR, 0.70; 95% CI, 0.58 to 0.83), and TDR (HR, 0.83; 95% CI, 0.71 to 0.99) were also significantly improved with exemestane. In an updated subgroup analysis that excluded patients with estrogen receptor (ER)-negative disease (8), the OS was significantly improved in the exemestane arm (HR, 0.83; 95% CI, 0.69 to1.00).

Figure 2. Efficacy results of randomized controlled trials comparing tamoxifen followed by aromatase inhibitors for a total of five years to tamoxifen alone as adjuvant hormone therapy.



Note: HR CIs may differ slightly (±0.02) from originally reported CIs due to errors in rounding. ABCSG-8/ARNO-95 overall survival HRs and CIs were derived from raw data using methods as described by Parmar et al (2).

References: ABCSG-8/ARNO-95 (10), IES (8), ITA (23).

Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AI, aromatase inhibitor; ARNO, Arimidex/Nolvadex; CI, confidence interval; HR, hazard ratio; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; tam, tamoxifen.

The ITA trial (9,23) randomized women who had received two or more years of tamoxifen to receive anastrozole or further tamoxifen for a total of five years of treatment. Accrual to this trial was much slower than expected due to other competing trials. An interim analysis (9) was conducted in response to the release of the ATAC trial results, and because of the ATAC results, the significant results identified in the ITA interim analysis, and the slow accrual, recruitment to the ITA trial was halted. A more recent analysis (23) with a longer median follow-up of 64 months has since been published. Women in the ITA trial who switched to anastrozole experienced significantly longer DFS, but not OS, than those that remained on tamoxifen (Figure 2). In the earlier analysis, at 36 months median follow-up, there was no significant difference in distant metastases-free survival (DMFS; HR, 0.49; 95% CI, 0.22 to 1.05).

The ABCSG-8 and ARNO-95 trials had arms similar to the ITA trial. The results of these two separate trials were combined in a preplanned interim analysis (10). Tamoxifen dosage was 20 mg for ABCSG-8 and 20 or 30 mg daily for ARNO-95. Due to differences in randomization between the two trials, the survival analysis was conducted beginning with the

completion of the first two years of tamoxifen, as opposed to the beginning of tamoxifen therapy. At 28-months median follow-up, women in these trials who switched to anastrozole experienced significantly longer DFS but no significant difference was found in OS (Figure 2). DMFS was also significantly longer with anastrozole (HR 0.61, 95% CI 0.42 to 0.87). A separate analysis of the ARNO-95 trial (24) was reported at 30.1-months median follow-up and included 979 patients. It reported both DFS (HR, 0.66; 95% CI, 0.44 to 1.00; p=0.049) and OS (HR, 0.53; 95% CI, 0.28 to 0.99; p=0.045) to be significantly improved in the tamoxifen followed by anastrozole arm. A separate analysis of the ABCSG-8 trial has also been published (25) at a median follow-up of 30 months, including 3,700 patients. In that analysis, time-to-event DFS was measured from the beginning of all therapy, and not from the switch to anastrozole following two to three years of tamoxifen. It reported significantly better DFS in the tamoxifen followed by anastrozole arm (HR, 0.68; 95% CI, 0.49 to 0.91; p=0.02).

A meta-analysis of the ABCSG-8, ARNO-95, and ITA trials has been reported (15). This meta-analysis found improvements in DFS (HR, 0.59; 95% CI, 0.48 to 0.74, p<0.0001), distant recurrence-free survival (RFS) (hazard ratio 0.61, 95% confidence interval 0.45 to 0.83; p=0.002) and OS (HR, 0.71; 95% CI, 0.52 to 0.98; p=0.04).

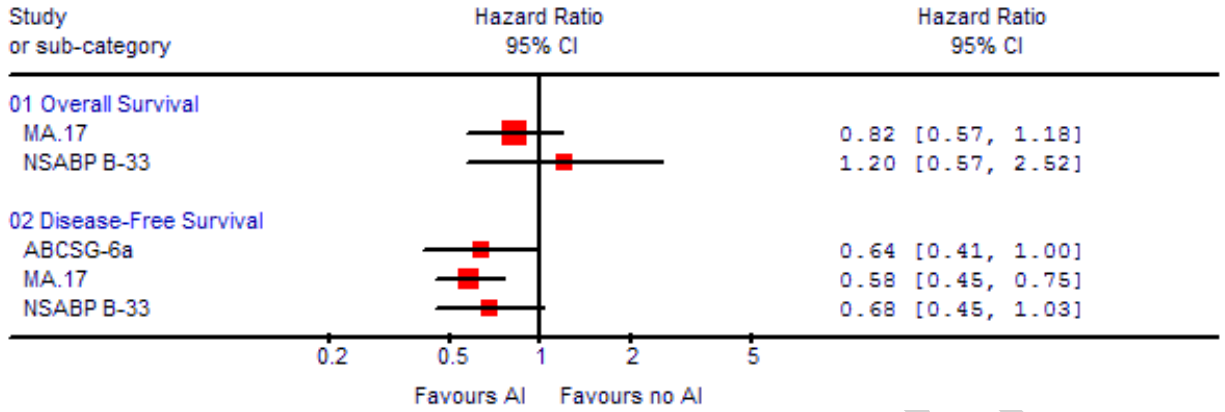
Two additional meta-analyses (26,27) of the three trials described directly above have been published, but both analyses also included the GROCTA 4B trial of aminoglutethimide, an agent not under review, and therefore are not abstracted in detail here. However, the results of both analyses were similar to those described above.

Aromatase Inhibitors After Five-Years of Tamoxifen

The National Cancer Institute of Canada MA.17 trial randomized women who had completed approximately five years of tamoxifen to receive five years of letrozole or five years of placebo (11). Patients could not have discontinued tamoxifen more than three months before randomization. The primary outcome was DFS (defined as the time from randomization to the diagnosis of either metastatic breast cancer, recurrent cancer in the treated breast, chest wall or regional nodes, or contralateral breast cancer). At 30-months median follow-up, women in the MA.17 trial who received letrozole after five years of tamoxifen experienced significantly longer DFS but not OS (Figure 3). DMFS survival was also significantly longer with letrozole (HR, 0.60; 95% CI, 0.43 to 0.84) but time to contralateral breast cancer was not (HR, 0.63; 95% CI, 0.18 to 2.21). Prespecified subgroup analyses revealed an OS benefit with letrozole in the node-positive group (HR, 0.61; 95% CI, 0.38 to 0.98; p=0.04) and in those who received more than five years of tamoxifen (HR, 0.56; 95% CI, 0.33 to 0.97; p=0.04). Proportionate reductions in local recurrences, new primaries, and distant recurrences were seen in the node-positive and node-negative subgroups. Another abstract (28) reported an unplanned analysis of DFS by ER and progesterone-receptor (PgR) status and found the following DFS hazard ratios (less than 1 favours letrozole): both ER and PgR positive, HR 0.50 (95% CI 0.36 to 0.68); ER positive and PgR negative, HR 1.19 (95% CI 0.62 to 2.29); and ER negative and PgR positive, HR 0.62 (95% CI 0.17 to 2.31).

A detailed analysis (29) from the MA.17 trial of the effect of letrozole versus placebo over time has been published. In this analysis, the trend in DFS, distant disease-free survival (DDFS), and OS hazard ratios was analyzed out to 48 months letrozole duration. A significant trend was found with both DFS (p<0.0001) and DDFS (p=0.0013), indicating that the benefit of letrozole compared to placebo was increasing over time out to 48 months. No trend was identified for OS (p=0.33). When the analysis was stratified by node status, a significant trend for increasing benefit for letrozole was identified in node-positive patients in terms of all three outcomes (DFS p=0.0004, DDFS p=0.0005, OS p=0.038), but only for DFS in node-negative patients (DFS p=0.027, DDFS p=0.22, OS p=0.34). The number of node-positive and node-negative patients was roughly the same (2,360 vs. 2,568).

Figure 3. Efficacy results of randomized controlled trials comparing aromatase inhibitors after five years of tamoxifen versus no further therapy or placebo as adjuvant hormone therapy.



Note: HR CIs may differ slightly (±0.02) from originally reported CIs due to errors in rounding. NSABP B-33 CIs were constructed from raw data using methods as described by Parmar et al (2).
References: ABCSG-6a (13,14), MA.17 (11), NSABP B-33 (12).
Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Three additional reports (30-32) in abstract form have presented results from the MA.17 trial at 54-months median follow-up. These results are not summarized in Table 3 as the trial was unblinded after the analysis described above, and patients on the placebo arm were offered letrozole—73% crossed over. In one of the reports (30), DFS (HR, 0.64; 95% CI, 0.52 to 0.79; p=0.00002) and DDFS (HR, 0.76; 95% CI, 0.58 to 0.99; p=0.041) were still improved in patients who were originally randomized to letrozole. OS was not significantly different (HR, 1.00; 95% CI, 0.78 to 1.28; p=0.99). In the other reports (31,32), patients who crossed over to letrozole after being randomized to placebo were compared to patients who had not crossed over. Patients who crossed over were significantly different from those that did not in that they were older (80% versus [vs.] 66% over age 70), had lower performance status (92% vs. 96% Eastern Cooperative Oncology Group [ECOG]=0), were significantly less likely to be node-negative (49% vs. 57%), and were more likely to have prior chemotherapy (49% vs. 33%). Patients who recurred or died prior to unblinding were not included in the analysis, and the reported hazard ratios were adjusted for the factors above. Patients who crossed over to letrozole had significantly better DFS (HR, 0.31; 95% CI, 0.18 to 0.55; p<0.0001), DDFS (HR, 0.28 95% CI, 0.13 to 0.62; p=0.002), contralateral breast cancer incidence (HR, 0.23; 95% CI, 0.07 to 0.77; p=0.017), and OS (HR, 0.53; 95% CI, 0.28 to 1.00; p=0.05, reported as significant).

The NSABP B-33 trial (12) was originally designed to randomize women who had received five years of adjuvant tamoxifen to either two years of exemestane or placebo. It was later amended to five years of exemestane or placebo. After the release of the MA.17 results, accrual was halted, the trial was unblinded, and placebo patients were offered exemestane. An analysis of this trial has been reported in abstract form. The primary outcome was DFS; the definition of 'disease free' was not reported. At 30-months median follow-up, no significant difference in DFS or OS was reported (Figure 3). There was significantly longer relapse-free survival (HR, 0.50; p=0.03) reported in patients who received exemestane.

The ABCSG-6a trial (13,14) was developed as a continuation of the ABCSG-6 trial. The ABCSG-6 trial was designed to compare five years of tamoxifen versus five years of tamoxifen plus aminoglutethimide. When the ABCSG-6 trial found no significant differences between the arms, it was extended as a trial of three years of anastrozole or no further treatment following five years of tamoxifen. At 60-months median follow-up, this trial, reported in abstract form,

found significantly better DFS in patients treated with anastrozole after five years of tamoxifen, with or without aminoglutethimide (Figure 3). No difference in OS was reported (p-value or point estimate not reported).

Harms Associated With Aromatase Inhibitors

A comprehensive paper (33) on adverse effects and side effects has been published from the ATAC trial. Serious adverse events (defined as death, life-threatening event, event causing extended hospitalization, event causing disability, or event needing intervention to prevent permanent impairment) occurred more frequently with tamoxifen (36%) than with anastrozole (33%, p=0.03). Treatment-related serious adverse events were also more common on tamoxifen (9% vs. 5%, p<0.0001). In addition, two global health time-to-event indices were constructed that incorporated the occurrence of serious adverse events into DFS. Patients treated with anastrozole experienced better global health according to both indices (p≤0.0015 for both).

Data on cardiovascular, cerebrovascular, and venous thromboembolic events are summarized in Table 3. Data on the lipid metabolism changes associated with aromatase inhibitors are available from the BIG 1-98 (5), ITA (9), and MA.17 trials (34), as well as two Tamoxifen and Exemestane Adjuvant Multicentre (TEAM) substudies (35,36).

In the BIG 1-98 trial (5), patients receiving initial tamoxifen had reduced total cholesterol levels from baseline, while those receiving initial letrozole had levels that were unchanged (six months, 0% vs. -12.0%; twelve months, 0% vs. -13.5%; and 24 months, -1.8% vs. -14.1%; significance test not reported). Of the letrozole group 43.6%, compared with 19.2% of the tamoxifen group, had hypercholesterolemia reported at least once during treatment (significance test not reported). In the ITA trial (9), the rate of lipid metabolism disorders was significantly lower in the tamoxifen-alone arm (4.0%) than in the tamoxifen followed by anastrozole arm (9.3%, p=0.04).

In a companion study (34) to the MA.17 trial that included 347 patients (183 receiving letrozole and 164 receiving placebo), a number of lipid parameters were measured at multiple time points. No significant difference was found between the number of patients receiving letrozole after tamoxifen and the number receiving placebo, with the following conditions, at any time point in the study: total cholesterol ≥ 6.2 mmol/L or low-density lipoprotein (LDL) cholesterol ≥ 4.9 mmol/L without prior history of coronary heart disease and < 2 risk factors (53.8% vs. 55.7%, p=0.49); as above but with ≥ 2 risk factors (62.5% vs. 54.5%, p=0.77); LDL cholesterol ≥ 3.4 mmol/L with prior history of coronary heart disease (80% vs. 71.4%, p=1.00); high-density lipoprotein (HDL) cholesterol <0.9 mmol/L (3.1% vs. 3.7%, p=1.00); or HDL cholesterol <10% from baseline (79.2% vs. 72.0%, p=0.13).

Table 3. Randomized controlled trials comparing aromatase inhibitors to tamoxifen as adjuvant hormone therapy: summary of cardiovascular, cerebrovascular, and thromboembolic results.

Trial	Trmt Arms	Cardiovascular	Cerebrovascular	Thromboembolic
ATAC (4,33,76)	A vs.T	Ischemic cardiovascular disease: 4.1% vs. 3.4%, p=0.1 Cardiovascular deaths: 2% vs. 1%, p=NR	**Ischemic cerebrovascular events: 2.0% vs. 2.8%, p=0.03** Cerebrovascular deaths: <1% vs. 1%, p=NR	**Venous thromboembolic events: 2.8% vs. 4.5%, p=0.0004, OR 0.61, 95% CI 0.46 to 0.80** **Deep venous thromboembolic events: 1.6% vs. 2.4%, p=0.02**
BIG 1-98 (6)	L vs.T	All cardiac events: 5.5% vs. 5.0%, p=0.48 Ischemic heart disease: 2.2% vs. 1.7%, p=0.21 Cardiac failure: 1.0% vs. 0.6%, p=0.14 **Other cardiovascular events: 0.8% vs. 0.2%, p=0.014**	Cerebrovascular accident or TIA: 1.4% vs. 1.4%, p=0.90	**Thromboembolic events: 2.0% vs. 3.8%, p<0.001**
IES (8)	T→E vs.T	Cardiovascular events: 20.8% vs. 18.9%, p=0.09 Ischemic cardiovascular disease: 9.9% vs. 8.6%, p=0.12	NR	**Thromboembolic events: 1.9% vs. 3.1%, p=0.01**
ITA (9)	T→A vs.T	**Cardiovascular diseases: 7.9% vs. 9.3%, p=0.04**	NR	NR
ABCSG-8/ARNO-95 (10)	T→A vs.T	Myocardial infarction: <1% vs. <1%, p=1.0	NR	Embolism: <1% vs. <1%, p=0.064 **Thromboses: <1% vs. <1%, p=0.034**[a]
MA.17 (11)	T→L vs. T→placebo	Cardiovascular disease: 5.8% vs. 5.6%, p=0.76 Myocardial infarction: 0.3% vs. 0.4% New or worsening angina: 1.2% vs. 0.9% Angina requiring PTCA: 0.1% vs. 0.3% Angina requiring CABG: 0.2% vs. 0.5%	Stroke/TIA: 0.7% vs. 0.6%	Thromboembolic event: 0.4% vs. 0.2%

Note: Significant differences are shown in bold face.

[a] Favours anastrozole.

Abbreviations: →, followed by; A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; CABG, coronary artery bypass graft; CI, confidence interval; E, exemestane; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; L, letrozole; NR, not reported; OR, odds ratio; PTCA, Percutaneous Transluminal Coronary Angioplasty; T, tamoxifen; TIA, Transient Ischemic Attack; Trmt, treatment; vs., versus.

Data on bone-related toxicity are summarized in Table 4. Additional data are provided below. The ATAC study (4) also compared the rate of fracture by site, as follows, for anastrozole versus tamoxifen: hip (1.2% vs. 1.0%, p=0.5), spine (1.5% vs. 0.9%, p=0.03), wrist/Colles' (2.3% vs. 2.0%, p=0.4), and all other fractures (7.1% vs. 4.6%, p<0.0001). Two ATAC trial substudies have been reported in abstract form. In the first substudy (37), patterns of time to fracture in the ATAC trial between anastrozole and tamoxifen were assessed up to five years. Time to fracture was worse for women taking anastrozole versus tamoxifen at each interval. In the second subprotocol (38), lumbar spine and total hip bone mineral density were measured in 167 women from the ATAC trial. Anastrozole was associated with decreases in both lumbar spine and total hip bone mineral density loss at five years (percentage decrease of BMD on anastrozole relative to tamoxifen, -8.1% [95% CI, -10.1% to -6.1%; p<0.0001], and -7.4% [95% CI, -9.6% to -5.3%; p<0.0001], respectively). No patient with normal bone mineral density at baseline had osteoporosis at five years.

A substudy associated with the MA.17 trial, MA.17B (39), of 226 patients, had as its primary objective the change from baseline bone mineral density in patients treated with letrozole versus placebo. After a median follow-up of 1.6 years, patients on letrozole had a significantly greater decrease in total hip bone mineral density (-3.6% versus -0.71%, p=0.044) as well as a significantly greater decrease in lumbar spine bone mineral density (−5.35 versus −0.70%, p=0.008) compared to those on placebo. No significant difference was found in the rate of osteoporosis in the total hip or lumbar spine. Additionally, in the report described above (31,32) that, post-unblinding, compared patients in the MA.17 trial who crossed over to letrozole to those who did not, more patients in the cross-over group experienced new osteoporosis than did those who did not cross-over (~4.0% vs. ~1.5%, p=0.007).

Data on endometrial cancer are summarized in Table 5. Additionally, two subprotocols of the ATAC trial have been reported separately in abstract form. The first subprotocol included 271 patients who received anastrozole, tamoxifen, or a combination of the two (40,41). At six years (41), the rates of abnormalities in the anastrozole and tamoxifen groups were 27% and 44%, respectively (odds ratio, 0.52; 95% CI, 0.20 to 1.32; p=0.17). The median endometrial thickness was unchanged from baseline in the anastrozole group (3.0 mm) but had increased from 3.0 mm to 5.0 mm in the tamoxifen group. At two years (40), the majority of abnormalities were polyps (7% and 16%, respectively). Atypical hyperplasia was found in one woman (2%) in the tamoxifen group.

The second substudy of the ATAC trial assessed the incidence of endometrial malignancy (42). Observed rates of endometrial cancer were lower than expected in the anastrozole group (standardized incidence rate ratio 0.73 [95% CI, 0.15 to 2.12]), while those for tamoxifen were higher than expected (standardized incidence rate ratio 2.68 [95% CI, 1.34 to 4.80]).

Data on a selection of menopausal symptoms across trials are summarized in Table 6. Menopausal symptoms during the first year of exemestane or tamoxifen treatment were assessed in 997 evaluable patients accrued to the TEAM trial (43). Self-reported symptoms were assessed at baseline and every six months. Vaginal bleeding, mood alteration, impaired word finding, low energy, decreased libido, difficulty sleeping, vaginal discharge, dryness, and bone/muscle aches were assessed as none, mild, moderate, or severe. A score for hot flashes was used to capture more detail. Vaginal dryness (p=0.0.0004), impaired word finding (p=0.0057), bone/muscle aches (p<0.0001), decreased libido (p=0.0343), and difficulty sleeping (p=0.0346) were worse in patients receiving exemestane, while vaginal discharge (p<0.0001) and hot flashes (p=0.0253) were worse in women receiving tamoxifen.

Table 4. Randomized controlled trials comparing aromatase inhibitors to tamoxifen as adjuvant hormone therapy: summary of bone toxicity results.

Trial	Trmt Arms	Fractures	Time to fracture	Osteoporosis	Hip BMD	Lumbar spine BMD
ATAC (4,37)	A vs.T	**11.0% vs. 7.7%, p<0.0001**	**HR 1.54 (1.30 to 1.84)[a]**	NR	See text	See text
BIG 1-98 (6)	L vs.T	**8.6% vs. 5.8%, p<0.001**	**Shorter on L (p<0.001)[a]**	NR	NR	NR
IES (8,77)	T→E vs.T	**7.0% vs. 4.9%, p=0.003**	NR	9.2% vs. 7.2%, p=0.01	**With E, -1.4% (95% CI -0.8% to -1.9%, p<0.0001) at 6 months, -0.8% (95% CI -0.29% to -1.39%, p=0.003) at 24 months** No sig. diff. with T	**With E, -2.7% (95% CI -2.0% to -3.4%, p<0.0001) at 6 months, -1.0% (95% CI -0.39% to -1.70%, p=0.002) at 24 months** No sig. diff. with T
ITA (9)	T→A vs.T	1.0% vs. 1.3%, p=0.06	NR	NR	NR	NR
ABCSG-8/ARNO-95 (10)	T→A vs.T	**2% vs. 1%, p=0.015**	NR	NR	NR	NR
MA.17 (11)	T→L vs. T→placebo	5.3% vs. 4.6%, p=0.25	NR	**8.1% vs. 6.0%, p=0.003**	See text	See text
NSABP B-33 (12)	T→E vs. T→placebo	28 fractures vs. 20 fractures, p=0.33	NR	NR	NR	NR
TEAM sub-study (78,79)	E vs.T	NR	NR	NR	**Worse with E, p=0.005**	**Worse with E, p=0.02**
Asmar et al.[b] (80)	E (2 yrs) vs. T (2 yrs)	NR	NR	NR	No sig. diff. at 12 (p=0.26) or 24 months, (p=0.73)	**Worse with E at 12 months, p=0.0006** No sig diff. at 24 months, p=0.39

Note: Significant differences are shown in bold-face type.
[a] From earlier report (5) including all patients not just those randomized to only letrozole and tamoxifen.

[b] Based on similarities in arm and sponsorship, this report is believed to be associated with the trial described as “Pfizer” (65) in Table 7, and is therefore included here.

Abbreviations: →, followed by; A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; BMD, bone mineral density; CI, confidence interval; E, exemestane; HR, hazard ratio; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; L, letrozole; NR, not reported; NS, not significant; NSABP, National Surgical Adjuvant Breast and Bowel Project; sig, significant; TEAM, Tamoxifen and Exemestane Adjuvant Multicentre; T, tamoxifen; Trmt, treatment; vs., versus.

Table 5. Randomized controlled trials comparing aromatase inhibitors to tamoxifen as adjuvant hormone therapy: summary of endometrial cancer and other gynaecological toxicity results.

Trial	Trmt Arms	Results
ATAC (4)	A vs. T	**Vaginal bleeding: 5.4% vs. 10.2%, p<0.0001** **Vaginal discharge: 3.5% vs. 13.2%, p<0.0001** **Endometrial cancer: 0.2% vs. 0.8%, p=0.02**
BIG 1-98 (6)	L vs. T	**Vaginal bleeding: 3.8% vs. 8.3%, p<0.001** **Endometrial biopsies: 2.3% vs. 9.1%, p<0.001[a]** Invasive endometrial cancers: 0.1% vs. 0.3%, p=0.18[a]
IES (8)	T→E vs. T	**Serious gynaecological events: 7.0% vs. 10.6%, p=0.0001** **Vaginal bleeding: 5.2% vs. 7.6%, p=0.002** Vaginal discharge: 3.1% vs. 4.1%, p=0.06 **Endometrial hyperplasia: 0.2% vs. 1.2%, p=0.0002** **Uterine polyps/fibroids: 1.6% vs. 4.6%, p<0.0001** Endometrial cancer did not differ significantly between the arms
ITA (9)	T→A vs. T	Gynecological symptoms: 7.4% vs. 8.0%, p=0.5 **Gynecological changes, including endometrial carcinoma: 1.0% vs. 11.3%, p=0.0002**
ABCSG-8/ARNO-95 (10)	T→A vs. T	Endometrial cancer: <1% vs. <1%, p=0.069 Vaginal bleeding/discharge (ABCSG-8 only): 18% vs. 17%, p=0.9348
MA.17 (11)	T→L vs. T→placebo	**Vaginal bleeding: 6% vs. 8%, p=0.005** Endometrial cancer: 4 pts vs. 11 pts, p=0.12

Note: Significant differences are shown in bold face.
[a] From earlier report (5) including all patients not just those randomized to only letrozole and tamoxifen.
Abbreviations: →, followed by; A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; E, exemestane; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; L, letrozole; pts, patients; T, tamoxifen; Trmt, treatment; vs., versus.

Table 6. Randomized controlled trials comparing aromatase inhibitors to tamoxifen as adjuvant hormone therapy: summary of other symptoms.

Trial	Trmt Arms	Hot Flashes		Fatigue/ Asthenia		Insomnia		Bone Pain		Arthralgia		Arthritis		Muscle Pain	
		%	p	%	p	%	p	%	p	%	p	%	p	%	p
ATAC (4)	A T	**35.7** **40.9**	**<0.0001**	18.6 17.6	0.3	NR	NR	NR	NR	**35.6** **29.4**	**<0.0001**	NR	NR	NR	NR
BIG 1-98 (6)	L T	**32.8** **37.4**	**<0.001**	NR	NR	NR	NR	NR	NR	**20.0** **13.5**	**<0.001**	NR	NR	7.1 6.1	0.19
IES (8)	T→E T	42.4 39.9	0.08	24.5 24.1	0.75	**20.8** **18.2**	**0.03**	NR	NR	**20.8** **15.1**	**<0.0001**	**17.5** **14.6**	**0.008**	**25.7**[a] **20.3**[a]	**p<0.0001**[a]
ITA (9)	T→A T	NR	NR	2.0 0	0.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ABCSG-8/ARNO-95 (10)	T→A T	50 48	0.3209	3 3	0.3880	NR	NR	16 19	0.0546	NR	NR	NR	NR	NR	NR
MA.17 (11)	T→L T→pl.	**58** **54**	**0.003**	39 39	0.95	6 5	0.06	5 6	0.67	**25** **21**	**<0.001**	6 5	0.07	**15** **12**	**0.004**
NSABP B-33 (12)	T→E T→pl.	NR	NR	0.9[b] 0.5[b]	NR	NR	NR	0.5[b] 0.7[b]	NR	1.0[b] 0.5[b]	NR	NR	NR	NR	NR

Note: Significant differences are shown in bold-face type.
[a] Musculoskeletal pain
[b] Grade 3/4 toxicity only
Abbreviations: →, followed by; A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex/Nolvadex; ATAC, Arimidex , Tamoxifen, Alone or in Combination; BIG, Breast International Group; E, exemestane; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; L, letrozole; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; pl., placebo; T, tamoxifen; Trmt, treatment.

A separate abstract from the ATAC trial (44) reported that, at 68-months median follow-up, 35.6% of patients receiving anastrozole and 29.4% receiving tamoxifen had experienced joint symptoms (p<0.0001). Most events occurred within 24 months of initiating treatment. The rate of serious adverse events was similar (10.6% with anastrozole and 10.4% with tamoxifen), and a few patients withdrew from treatment due to these symptoms (2.1% with anastrozole and 0.9% with tamoxifen).

Quality-of-life data have been reported for the ATAC (45), MA.17 (46), IES (47), and National Surgical Adjuvant Study for Breast Cancer (NSAS BC) 03 (48) trials and the TEAM trial NSAS BC 04 substudy (49). In the ATAC subprotocol (45), 1,021 patients were evaluated, with measurements made at baseline, three months, six months, and every six months thereafter. No significant differences in the Treatment Outcome Index (summary score of the breast cancer scale and the physical and function well-being subscales of the Functional Assessment of Cancer Therapy [FACT] questionnaire) were detected between the anastrozole and tamoxifen groups (p=0.23). All groups showed an improvement between Treatment Outcome index (TOI) scores at baseline and three months. Between baseline and three months, the hormone sub-score decreased slightly for all three treatments and then stabilized.

In the MA.17 trial (46), 3,582 patients were evaluated, with measurements made at baseline, six months, twelve months, and every twelve months thereafter. No significant differences in mean change scores (up to 36 months) were detected between the letrozole and placebo groups. Small (<0.1 standard deviation) but statistically significant differences (favouring placebo) were seen for the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) physical functioning (at six and 12 months), SF-36 bodily pain (at six months), SF-36 vitality (at six and 12 months), and Menopause Specific Quality of Life Questionnaire (MENQOL) physical domains (at 12 months). Moderately (between 0.2 and 0.3 standard deviations) significant differences favouring placebo were detected for the MENQOL vasomotor (at six, 12, and 24 months) and sexual domains (at 12 and 24 months). Absolute increases in the proportion of patients reporting a worsening in their quality of life at any time on letrozole compared to placebo for the different domains were as follows: SF-36 physical functioning (6%, p<0.001), SF-36 bodily pain (5%, p=0.001), SF-36 vitality (5%, p=0.005), MENQOL vasomotor (8%, p<0.001), MENQOL physical (5%, p=0.004), and MENQOL sexual (4%, p=0.02).

In the IES trial (47), 582 patients were evaluated, with measurements taken at baseline and at three, six, nine, 12, 18, and 24 months. No clinically meaningful differences were found between treatment arms in overall quality of life, as measured by TOI or FACT with Endocrine Subscale (FACT-ES) scores.

Results from the quality of life substudy of the NSAS BC 03 trial (48) have been published in abstract form. The NSAS BC 03 trial randomized patients who had been treated with one to four years of tamoxifen without recurrence to either an additional five years of tamoxifen or five years of anastrozole. In this trial, the FACT breast cancer (B) and general (G) instruments were used, as well as the FACT-ES. Patients who received tamoxifen instead of anastrozole reported significantly better quality of life on the FACT-G (p=0.012), FACT-B (p=0.010), and FACT-ES (p=0.015) instruments.

In the TEAM sub-study NSAS BC 04 (49), FACT-B, -G, and -ES scores did not significantly differ between the three arms (five years anastrozole, exemestane, or tamoxifen). All patients, regardless of arm, experienced significant worsening of scores on the FACT-ES.

Effect Of HER2/*Neu*-Status

No evidence was identified for the relative efficacy of any aromatase inhibitor compared to tamoxifen analyzed by the HER2/*neu* status of the patient. A report in abstract from the ATAC trial (50) indicates that an analysis by HER2 status has been performed in that trial, but

the abstract itself provides no data, and no presentation associated with this trial could be located. See the "Discussion" section for further information.

Ongoing Trials Of Adjuvant AI's

A number of relevant phase III trials are ongoing with unreported results. The National Cancer Institute's clinical trials online database (http://www.cancer.gov/search/clinical_trials/) was searched to November 2007 for reports of new or ongoing trials. Trials that had not yet published efficacy data (51-65) are summarized in Table 7. Several of these trials are comparisons of two different aromatase inhibitors or comparisons of varying lengths of aromatase inhibitor therapy and are included here for reference. In addition to these trials, an extension of the MA.17 trial, the MA.17R trial (66), is underway. This trial re-randomizes patients who complete the five-year letrozole arm of MA.17 to either an additional five years of letrozole or placebo. It is also important to note that full data from all four arms of the BIG 1-98 trial have not yet been published.

Table 7. Ongoing, third-generation aromatase inhibitor randomized controlled trials for which no efficacy data or results have been reported.

Trial (Reference)	Protocol ID, NLM Identifier	Lead Group(s)	Treatment Arms*	Target Accrual	Accrual Status
TEAM (51)	CRC-TU-TEAM, NCT00032136	Cancer Research UK Clinical Trials Unit - Birmingham	5 yrs E 5 yrs T	4400	Active
Pfizer trial (52)	NCT00279448	Pfizer	5 yr E 2-2.5 yrs T → E to 5 yrs	1500	Active
IBCSG-1-98 (53)	NCT00004205	IBCSG, DBCCG, FNCLCC	L T	5180	Active
NSAS BC 03 (54)	Not found in PDQ	CSPOR-BC	1-4 yrs T → A to 5yrs 1-4 yrs T → T to 5 yrs 5 yrs T → 5 yrs placebo	2500	Unknown
ICCG-BIG-97/02 (55)	NCT00003418	ICCG, EORTC, FCLCC	5 yrs T 2-3 T → E	4400	Active
ICCG trial (56)	NCT00038467	Pfizer, ICCG	5 yrs T 2-3 yr T → E	4400	Active
NSABP-B-42 (57)	NCT00382070	NSABP, NCI	5 yrs AI / T → L 5 yrs AI / T → placebo	3840	Active
MA.27 (58)	CAN-NCIC-MA27, NCT00066573	NCIC	5 yrs E 5 yrs A	6840	Active
FACE (59,60)	CFEM345D2411, NCT00248170	Novartis	5 yrs L 5 yrs A	4000	Active
SALSA (61)	1033AU/0003, NCT00295620	AstraZeneca	5 yrs endocrine therapy → 2 yrs A 5 yrs endocrine therapy → 5 yrs A	NR	Active
AstraZeneca trial (62)	D5392NL0003, NCT00301457	AstraZeneca	2 to 3 yrs T → 3 yrs A 2 to 3 yrs T → 6 yrs A	NR	Active
AstraZeneca trial (63)	NCT00295620	AstraZenaca	5 yrs ET → 2 yrs A 5 yrs ET → 5 yrs A	3500	Active

Trial (Reference)	Protocol ID, NLM Identifier	Lead Group(s)	Treatment Arms*	Target Accrual	Accrual Status
GIM-3-FATA (64)	NCT00541086	GIM	T → E / L / A E / L / A	10000	Active
Pfizer trial (65)	971-ONC-0028-081, NCT00036270	Pfizer	5 yrs E 2.5 to 3 yrs T → E to 5 yrs	NR	Closed

Note: All studies required patients to be postmenopausal and cancers to be hormone-receptor positive.
Abbreviations: A, anastrozole; CSPOR-BC, Comprehensive Support Project for Oncological Research of Breast Cancer (Japan); DBCCG, Danish Breast Cancer Cooperative Group; E, exemestane; EORTC; European Organization for Research and Treatment of Cancer; ET, endocrine therapy; FNCLCC; Federation Nationale des Centres de Lutte Contre le Cancer; GIM, Gruppo Italiano Mammella; ICCG, International Collaborative Cancer Group; L, letrozole; NCI, National Cancer Institute; NCIC, National Cancer Institute of Canada; NLM, National Library of Medicine; NSABP, National Surgical Adjuvant Breast and Bowel Project; NSAS BC, National Surgical Adjuvant Study of Breast Cancer (Japan); PDQ, Physician Data Query; SALSA, Secondary Adjuvant Long-term Study with Arimidex; T, tamoxifen; TEAM, Tamoxifen and Exemestane Adjuvant Multicentre; yrs, years.

DISCUSSION

In the trials identified in this systematic review, aromatase inhibitors have been consistently associated with longer DFS than has therapy with tamoxifen alone (Figures 1 through 3). This benefit seems independent of the way in which the aromatase inhibitor is administered: upfront, instead of tamoxifen; switching after two to three years of tamoxifen; or switching after five years of tamoxifen. Of the nine trials that have reported efficacy data, only the NSABP B-33 trial did not report significantly longer DFS in patients receiving aromatase inhibitors compared to those that were not, although relapse-free survival was prolonged, and this trial closed prematurely (12).

Differences in OS, however, have not been consistently observed across reviewed trials. The only reported significant improvements in OS with aromatase inhibitors have been in a meta-analysis of the ABCSG-8, ARNO-95, and ITA trials (15), in the individual ARNO-95 trial (24) analysis, among node-positive patients and patients who had received more than five years of tamoxifen in the MA.17 trial (11), and in the IES trial when receptor-negative patients were excluded (8). This lack of consistent OS benefit may be due to the follow-up period in many of the trials; even the trials with the longest follow-up had median follow-up times roughly equal to the duration of therapy. However, given the survival rate in the tamoxifen-only arms of the included trials, it may be that these trials do/will not have sufficient power to detect differences in OS. Of note, in the trials of five years of adjuvant tamoxifen therapy, the majority of the reduction in breast cancer mortality was not seen until after five years follow-up (67).

The differences in efficacy between the trials might also be explained by the variation in treatment received before aromatase inhibitor therapy was initiated, and when patients were randomized to aromatase inhibitor therapy. The ABCSG-8 and ARNO-95 trials excluded patients who had received prior chemotherapy and/or radiotherapy, and in the other trials, prior chemotherapy varied from 20% to 67% (Table 1). The point of randomization to an aromatase inhibitor after tamoxifen differed across the "switching" trials. In the ABCSG-8 and BIG 1-98 trials, patients were randomized before the start of any hormonal therapy (tamoxifen included), whereas in the ARNO-95, ITA, and IES trials, randomization occurred after some duration of tamoxifen therapy. Thus, patients who were randomized two to three years after their initial diagnosis represent a selected, favourable-prognosis, hormone-responsive group who did not experience early relapse, and thus may be more likely to do better on any endocrine therapy.

The choice of a particular aromatase inhibitor should be guided by the trial evidence available. Anastrozole and letrozole are both acceptable options for five years therapy, instead of tamoxifen. Switching to either exemestane or anastrozole after two to three years tamoxifen is also acceptable. In comparison to five years of tamoxifen, only letrozole over five years has been shown to provide any consistent efficacy benefit. The ongoing MA.27 (58) and FACE (59,60) trials will be useful in aiding clinicians to decide between the aromatase inhibitors once data becomes available from them.

Given the obvious benefits to DFS, the question of which aromatase inhibitor strategy—instead of tamoxifen, switching after two to three years of tamoxifen, or subsequent therapy after five years of tamoxifen—becomes important. There is little evidence at this point to assist the clinician in choosing between these different methods as no trials have yet reported direct comparisons. There is, however, some limited non-randomized evidence that suggests either five years of an aromatase inhibitor or two to three years of tamoxifen followed by an aromatase inhibitor may be preferable (68,69). The letrozole versus tamoxifen followed by letrozole comparison from the BIG 1-98 trial (5), when reported, will provide some insight, as will data from a similar comparison with exemestane from an ongoing Pfizer trial (65) (Table 7).

The optimal length of aromatase inhibitor therapy similarly remains undefined pending future study. Two ongoing trials (61,62) are investigating this question in different ways (Table 7). In addition, the extension of the MA.17 trial (66) will provide some direct evidence. It is, however, important to note that as the length of therapy increases, the costs associated with

that therapy will inevitably increase. Furthermore, the potential for increased adverse toxicity effects with long-term exposure may dictate the choice of therapy.

Concern has been raised about the potential cardiovascular toxicity of the aromatase inhibitors. Similar effects on lipid profile were observed across the majority of trials under review. Tamoxifen use was associated with decreased total cholesterol and LDL cholesterol, and the elevation of triglycerides, whereas initial therapy with aromatase inhibitors was associated with no or minor lipid changes. In the "switching" trials, the observed adverse effects of aromatase inhibitors on lipids could potentially be attributable to withdrawal from tamoxifen. Changes in lipids have not necessarily translated into significant differences in cardiovascular disease. The initial report of increased ischemic heart disease associated with exemestane use in the IES trial was not substantiated in a subsequent report (7,8), and a consistent increase in cardiovascular toxicity was not seen across all trials (Table 3).

Data on cerebrovascular toxicity is limited. The ATAC trial found significantly higher rates of ischemic cerebrovascular events with tamoxifen compared to anastrozole, but only two other trials reported on this toxicity and found no difference (Table 3). Tamoxifen is consistently associated with roughly twice the rate of thromboembolic events associated with aromatase inhibitors and a greater incidence of endometrial cancer. The aromatase inhibitors have all been associated with bone loss, but whether this translates into meaningful differences in clinically significant osteoporosis is debatable.

Anastrozole as an initial therapy (45) and exemestane beginning after two to three years of tamoxifen did not differ from tamoxifen with respect to quality of life (47). Compared with placebo after tamoxifen, letrozole after tamoxifen adversely affected several factors related to quality of life, including vitality, bodily pain, and physical, vasomotor, and sexual factors (46).

While much of the evidence for harms associated with aromatase inhibitors is derived from substudies with small numbers of patients, these findings are consistent with the larger body of evidence for harms associated with this class of agents. Given the increased risk of osteoporosis and/or fractures in women receiving aromatase inhibitors (Table 4), women should be closely monitored for changes in bone mineral density. The data for cardiac outcomes and lipid profile changes with aromatase inhibitors are not conclusive but are a cause for concern. Due to theoretical concerns and the lack of long-term results in the trials, clinical cardiac outcomes and lipid profile changes, as well as other harms associated with aromatase inhibitors in this setting, should be closely monitored.

No reported data were identified that met the inclusion criteria regarding the effect of HER2/*neu* status on the relative efficacy of any aromatase inhibitor compared to tamoxifen in adjuvant therapy. However, there is evidence from other treatment settings that may be relevant. Three trials were identified that have reported results of aromatase inhibitors versus tamoxifen by HER2/*neu* status. Two of these trials were conducted in the neoadjuvant setting: a study of letrozole versus tamoxifen conducted by Duke University Medical Center (70,71),and the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial (72) of anastrozole versus tamoxifen versus the combination of anastrozole and tamoxifen. An additional trial, conducted in the metastatic setting (73), compared letrozole to tamoxifen. Tests for an interaction between treatment arm assignment and HER2/*neu* status were not reported in any of the trials. The evidence from these three trials is mixed, with no clear picture emerging regarding the relationship, if any, between HER2/*neu* status and aromatase inhibitor efficacy compared to tamoxifen.

Whether or not the benefit of aromatase inhibitor therapy in the adjuvant setting differs according to the status of the PR has also been a matter of debate. Initial reports from the ATAC trial suggested that time to recurrence was better for ER-positive, PgR-negative patients than for ER-positive, PgR-positive patients (74), but when ER and PgR status were centrally reviewed, the benefits of anastrazole were seen in ER-positive patients, regardless of PgR status (M Dowsett, personal communication). A similar analysis of the efficacy of letrozole

versus tamoxifen following the central review of ER and PR status in the BIG 1-98 trial has been published (75). In this analysis, the benefits of letrozole were also not affected by PR expression. These two studies highlight the importance of central pathology review and standardization of hormone-receptor assays in multicentre trials.

CONCLUSIONS

Aromatase inhibitors provide an alternative to tamoxifen as adjuvant therapy for post-menopausal, hormone receptor-positive breast cancer patients. The trials systematically reviewed here have consistently identified a small but significant improvement in DFS, compared to tamoxifen alone. Additionally, at least one trial, a meta-analysis, and two subgroup analyses from larger trials have demonstrated significant improvements in OS with the use of these agents. Longer follow-up, new results from ongoing studies, and perhaps further meta-analyses may demonstrate whether this survival benefit proves to be a robust finding.

CONFLICT OF INTEREST

The members of the Breast Cancer DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. Two of the lead authors (AE, MT) reported related research involvement. These authors reported receiving honoraria or consultant fees from pharmaceutical companies that manufacture the aromatase inhibitors covered by this review.

JOURNAL REFERENCE

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Draft Evidence-based Series #1-18: Section 3

The Role of Aromatase Inhibitors in Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-positive Breast Cancer: EBS Development Methods and External Review Process

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 (PEBC), Cancer Care Ontario,
Developed by the PEBC Breast Cancer Disease Site Group

Current Report Date: February 26, 2008
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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Breast Cancer DSG of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

External Review by Ontario Clinicians

Following review and discussion of Sections 1 and 2 of this evidence-based series, the Breast Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review April 2004)

Target Population
Postmenopausal women with early-stage, hormone receptor-positive breast cancer:

Question 1
Compared with adjuvant tamoxifen alone for five years, do adjuvant aromatase inhibitors alone for five years improve clinically meaningful outcomes?

Draft Recommendations

- 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.

Qualifying Statements

- Data is available for 47 months (3.9 years) of anastrozole therapy.

Key Evidence

- The Arimidex (anastrozole) and Tamoxifen Alone or in Combination study (n=9,366) compared tamoxifen versus anastrozole versus tamoxifen plus anastrozole. At 47 months (3.9 years), disease recurrence was improved in the anastrozole group versus the tamoxifen group (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.76 to 0.99; 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 data are not yet available.

Question 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?

Draft Recommendations

- 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.

Qualifying Statements

- 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.
- 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.

Key Evidence

- 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. At 2.6 years, recurrence rates favoured exemestane after tamoxifen (HR, 0.68; 95% CI, 0.56 to 0.82; p<0.001). Three-year disease-free survival estimates 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). Overall survival was not different at the time of this analysis (HR, 0.88; 95% CI, 0.67 to 1.16; p=0.37).
- 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 (2 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).

Question 3

Compared with placebo, do aromatase inhibitors after five years of adjuvant tamoxifen therapy

improve clinically meaningful outcomes?

Draft Recommendation

- 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).

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.

Key Evidence

- The MA-17 study (n=5,187) compared letrozole to placebo following 4.5 to 6 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).

Question 4

Compared with tamoxifen or placebo, what are the harms associated with aromatase inhibitors?

Draft Recommendation

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

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.

Key Evidence

- Compared with tamoxifen, preliminary evidence exists to suggest that aromatase inhibitors reduce the occurrence of circulatory and gynecologic events. Compared with tamoxifen or placebo, aromatase inhibitors likely increase the occurrence 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.

Question 5
Compared with tamoxifen, does the efficacy of aromatase inhibitors depend on $p185^{HER2/neu}$ glycoprotein (HER2/*neu*) expression?

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

Qualifying Statement
- Aromatase inhibitors may be the preferred treatment in women with HER2/*neu*-overexpressing breast cancer.

Key Evidence
- No eligible trials on the efficacy of aromatase inhibitors according to HER2/*neu* status 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.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 127 practitioners in Ontario (74 medical oncologists, 33 radiation oncologists, and 20 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 4, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

Results

Sixty-nine responses were received out of the 127 surveys sent (54.3% response rate). Responses included returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 54 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number[a] (%)[b]		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	53 (98.1%)	0	1 (1.9%)
There is a need for a clinical practice guideline on this topic.	53 (98.1%)	1 (1.9%)	0
The literature search is relevant and complete.	48 (88.9%)	3 (5.6%)	2 (3.7%)
The results of the trials described in the report are interpreted according to my understanding of the data.	50 (92.3%)	2 (3.7%)	2 (3.7%)
The draft recommendations in this report are clear.	52 (96.3%)	1 (1.9%)	1 (1.9%)
I agree with the draft recommendations as stated.	47 (87.0%)	3 (5.6%)	3 (5.6%)
This report should be approved as a practice guideline.	47 (87.0%)	5 (9.3%)	2 (3.7%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	50 (92.6%)	1 (1.9%)	1 (1.9%)

[a] For some items, numbers may not total 54 due to missing responses.
[b] For some items, percentages may not total 100 due to rounding error.

Summary of Written Comments

Twelve respondents (30.8%) provided written comments, the main points being:

- The guideline is too confusing. It does not present a unified summary of the recommendations, and the formatting is difficult to understand. It also provides too many alternatives without clear recommendations as to which is or are preferable.
- Elements of the guideline are premature, and should not be published until the full results of the ATAC study are presented.
- The guideline, when implemented, will cause increased call-back of patients to the cancer clinic after they have been placed under a family doctor's care.
- The qualifying statements in questions 1 and 2 should be more strongly written to more clearly emphasize the fact that aromatase inhibitors are a standard of care.
- The guideline may be difficult to implement due to difficulty in funding aromatase inhibitors after tamoxifen, especially in those less than 65 years of age.
- The guideline states on page iv that aromatase inhibitors "reduce the occurrence of circulatory…events." The evidence shows that this is true for venous thromboembolic events, but may not be true for ischemic heart disease.

Modifications/Actions and Response to Comments

In response to the practitioner feedback, the following actions were taken:

- Recent results of several trials published in 2004 were included into the final systematic review, to ensure completeness.
- The references to circulatory events were altered to make clearer the types of events that were being reported.

In addition, several of the comments above generated no action, but deserve comment:

- The third and fifth comments above deal with fiscal and policy issues that the PEBC and the Breast Cancer DSG cannot address. The charge of the PEBC and the Breast Cancer DSG is to develop practice guidelines based on the best scientific evidence available.

- In response to the second comment above, the Breast Cancer DSG reviewed the recommendations and decided that the current wording is appropriate. Both aromatase inhibitors and tamoxifen are recommended standards of care depending on the situation, and the current wording reflects this accurately.

Changes after Practitioner Feedback

After the practitioner feedback process was complete, a new EBS format was designed by the PEBC, as described above. The original draft was reformatted according to this EBS template.

Additional results from the ATAC and IES trials were reported at the 2004 San Antonio Breast Cancer Symposium, with the ATAC results published by *The Lancet* electronically (3-5). In addition, results from the combined ABSCG/ARNO trial analysis were also reported at the same meeting (5). Results from the BIG 1-98 trial were reported at the 9th International Conference on Primary Therapy of Early Breast Cancer at Saint Gallen, Switzerland in January 2005 (6). All of those results were included in Section 2: Evidentiary Base of this EBS after practitioner feedback was complete, and some additional qualifying statements have been added to Section 1: Guideline Recommendations.

Report Approval Panel

The final EBS report was reviewed and approved by one member of the PEBC Report Approval Panel with expertise in clinical and methodology issues. The principal issue raised by this member concerned the continued recommendation for tamoxifen and whether the document fully explained the Breast Cancer DSG position on this topic. The concern was whether a continued recommendation for tamoxifen warranted additional details, in light of the disease-free survival (DFS) benefit identified by the ATAC trial (3) and the IES (4) with aromatase inhibitors either versus single-agent tamoxifen or in addition to tamoxifen. In response to this concern, additional qualifying statements and discussion were added to explain the differences in toxicity (bone mineral density and cardiac) and the lack of an established overall survival benefit were the key issues that led the Breast Cancer DSG to continue to recommend tamoxifen as a standard of care.

Implications for Policy

Based on a draft of this practice guideline, the Breast Cancer DSG submitted funding requests to the Program Advisory Committee (PAC) for 1) anastrozole instead of tamoxifen for postmenopausal women with hormone receptor-positive tumours and a contraindication or intolerance to tamoxifen and 2) letrozole after tamoxifen for postmenopausal women with hormone receptor-positive tumours who had completed five years of adjuvant tamoxifen therapy in 2004.

February 2008 Update to Evidentiary Base

In response to comments made by the *Cancer Treatment Reviews* editor during a process for manuscript publication, the evidentiary base was updated to May 2007 (and accepted for publication in January 2008). The process primarily provided updated results for data previously presented in abstract form, and no new trials of significant relevance were identified. As the February 2008 revision did not significantly alter the recommendations of the October 2005 practice guideline, no internal (report approval) or external (practitioner feedback) review was undertaken. All updated components were, however, reviewed by all authors of the practice guideline and approved by the Breast Cancer DSG during an annual consensus meeting.

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