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Endocrine Therapy for Early Breast Cancer: Updated Review

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Background: Although breast cancer is still the second most common cause of cancer-related deaths, breast cancer mortality has been declining because of advances in the use of adjuvant therapies.

Methods: We summarize clinical trials involving endocrine therapies used to treat early breast cancer and discuss their inception and recent advances.

Results: Endocrine therapies such as tamoxifen have revolutionized the treatment of breast cancer, resulting in significant decreases in cancer-related mortality. Aromatase inhibitors such as anastrozole and letrozole have further improved breast cancer survival.

Conclusion: With the implementation of such therapies resulting in decreased mortality, patients with breast cancer are living longer than ever before. The focus of research is now directed toward the length of treatment and prediction models for recurrence.

Keywords: *Aromatase inhibitors, breast cancer, estrogen receptor antagonists, tamoxifen*

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide, with an incidence of 246,660 cases in 2016 in the United States alone, and is the second most common cause of cancer-related deaths among females, with 40,450 deaths from breast cancer in 2016 in the United States.[1] Despite these numbers, breast cancer mortality rates have steadily declined since the 1970s. This decline is thought to be partly the result of advances in adjuvant therapy.[2] In this review, we focus on the inception of and recent advances in endocrine therapies.

Estrogen and progesterone are the primary regulators of breast tissue growth and differentiation. Both steroid hormones are primarily produced in the ovaries. They exert their cellular effects through binding to and activating specific nuclear receptors, the estrogen receptors (ERs) and progesterone receptors (PRs). Once activated, the receptors exhibit transcriptional and membrane localized signaling activities. ERα and ERβ are the 2 major ERs. The majority of breast cancers express ERα (70%), while ERβ is less well characterized.[3]

The potential role of estrogen in breast tissue was first noted by George T. Beatson who noted that oophorectomy in rabbits resulted in a loss of lactation.[4] Based on this result, Beatson performed an oophorectomy on June 15, 1895, on a premenopausal patient with unresectable breast cancer. She had complete remission and survived another 4 years.[4] Beatson's early work provided the foundations on which hormonal therapy was built. Stanley N. Boyd confirmed the utility of this therapy in a series of 46 cases of unresectable breast cancer in premenopausal females treated with oophorectomy.[5] In 1923, Edgar Allen and Edward Doisy discovered an ovarian hormone, estrogen, that regulates mammary tissue.[6] During the next several decades, a full range of ablative hormonal therapies was researched and developed, leading to the discovery of tamoxifen in 1967 by Harper and Walpole.[7]

TAMOXIFEN TRIALS

Tamoxifen has been extensively researched to treat early breast cancer and has strong evidence supporting its use as an adjuvant endocrine therapy.[8] Tamoxifen is a nonsteroidal antiestrogen that the US Food and Drug Administration (FDA) approved in the 1970s for the treatment of metastatic breast cancer in postmenopausal females.[9] The role of tamoxifen expanded to the adjuvant setting with the treatment of postmenopausal females with positive nodes and ER-positive tumors under recommendations from the 1985 National Institutes of Health Consensus Conference on Breast Cancer Chemotherapy.[10] Subsequently, the Nolvadex Adjuvant Trial Organization studies analyzed 1,285 patients who underwent total mastectomy with axillary node clearance or sampling followed by randomization to

Table 1. Aromatase Inhibitor Trials

Trial	Treatment Regimens	Number of Subjects	Endpoints	Findings
ATAC, 2005[19]	5 years of 1-mg anastrozole vs 20-mg tamoxifen vs combination therapy	9,366	DFS, safety, incidence of contralateral breast cancer, time to distant recurrence, and OS	After a median follow-up of 68 months, anastrozole significantly prolonged DFS (575 events vs 651 events; HR 0.87; P=0.01)
BIG 1-98, 2006[21]	5 years of 20-mg tamoxifen vs 5 years of 2.5-mg letrozole vs 2 years of 20-mg tamoxifen followed by 3 years of 2.5-mg letrozole vs 2 years of 2.5-mg letrozole followed by 3 years of 20-mg tamoxifen	8,010	DFS, OS, systemic DFS, and time to distant recurrence	Letrozole increased DFS (84.0% vs 81.4%), reduced distant recurrences, and prolonged time to distant metastasis
FACE, 2017[24]	5 years of 2.5-mg letrozole vs 5 years of 1-mg anastrozole	4,136	Safety and efficacy	5-year DFS rate was 84.9% for letrozole vs 82.9% for anastrozole (HR 0.93; 95% CI 0.80-1.07; P=0.3150)
EBCTCG, 2015[25]	5 years of an AI (group 1) vs 5 years of tamoxifen (group 2) vs 2-3 years of tamoxifen followed by an AI to year 5 (group 3) vs 2-3 years of an AI followed by tamoxifen to year 5 (group 4)[a]	31,920	Recurrence, breast cancer mortality, death without recurrence, and all-cause mortality	AIs reduced recurrence rates by nearly 30% compared to tamoxifen

AI, aromatase inhibitor; ATAC, Arimidex, Tamoxifen Alone or in Combination; BIG, Breast International Group; DFS, disease-free survival; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; FACE, Femara Versus Anastrozole Clinical Evaluation; HR, hazard ratio; OS, overall survival.
[a]Dosage varied with metaanalysis.

tamoxifen therapy for 2 years or no further treatment.[11] The study demonstrated that 2 years of adjuvant tamoxifen was associated with a reduction in recurrence and death. Additionally, the improvement in overall survival was independent of menopausal, ER, or nodal status. Since 1958, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted numerous randomized controlled trials evaluating different aspects of adjuvant and surgical therapies.[12] The NSABP B-14 trial evaluated 2,644 patients with receptor-positive, node-negative disease who were randomized to 5 years of tamoxifen or 5 years of placebo after surgery.[13,14] The study found a significant benefit in disease-free survival (DFS) among females treated with tamoxifen compared to placebo.[14] Extended follow-up of these patients after 10 years showed continued DFS benefit in the tamoxifen group compared to placebo, 69% vs 57%, respectively, as well as a significant survival advantage: 80% in the tamoxifen group vs 76% in the placebo group.[15] Furthermore, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reviewed 194 randomized controlled trials and found that 5 years of adjuvant tamoxifen in patients with ER-positive breast cancer resulted in a reduction in the breast cancer mortality rate by 31% and was more effective than 1 or 2 years of tamoxifen therapy.[16] In a follow-up metaanalysis, the EBCTCG noted that 5 years of adjuvant tamoxifen in patients with ER-positive breast cancer significantly reduced disease recurrence throughout the first 10 years and reduced breast cancer mortality by approximately one-third throughout the first 15 years.[17] Because of the multitude of positive studies, treatment with tamoxifen for 5 years has been the backbone of adjuvant hormonal therapy, especially for premenopausal patients with breast cancer.[8] However, duration of therapy has been debated extensively, specifically treatment extended beyond 5 years (we address extended therapy below).

AROMATASE INHIBITORS

In postmenopausal females, estrogen is no longer produced by ovarian tissue and is predominantly synthesized from nonglandular sources via the aromatase enzyme. Aromatase can be found in a number of tissues including subcutaneous fat, liver, and muscle; the enzyme has also been isolated in breast cancer cells.[3] Because of the prior success with estrogen inhibition, inhibition of aromatase has been extensively explored as a treatment modality for breast cancer (Table 1).

The first 2 generations of aromatase inhibitors (AIs) were effective in treating breast cancer but caused significant side effects because they inhibited other steroid hormones such as cortisol and aldosterone. Third-generation AIs have increased specificity for aromatase and are either categorized as steroidal (type I) or nonsteroidal (type II). Steroidal inhibitors lead to irreversible inhibition of enzymatic activity, while nonsteroidal inhibitors are reversible competitive inhibitors. Third-generation AIs were initially studied in patients with metastatic breast cancer. In 1998, Buzdar et al noted a statistically and clinically significant response with

the use of anastrozole, a type II AI, instead of the standard treatment at the time, megestrol acetate, for postmenopausal females with advanced breast carcinoma that progressed on tamoxifen.[18] Subsequent studies, discussed below, demonstrated the superiority of AIs over tamoxifen in postmenopausal females with advanced disease.

When the effectiveness of AI therapy was identified in metastatic breast cancer, the focus shifted to its use in the adjuvant setting. Many patients being treated with tamoxifen experienced recurrence because of drug resistance or developed side effects such as endometrial cancer and venous thromboembolic disease. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial compared anastrozole with tamoxifen for 5 years in 9,366 postmenopausal females with localized breast cancer.[19] After a median follow-up of 68 months, anastrozole significantly prolonged DFS (575 vs 651 events; hazard ratio [HR] 0.87; 95% confidence interval [CI] 0.78-0.97; P=0.01), time to recurrence (402 vs 498 days; HR 0.79; 95% CI 0.70-0.90; P=0.0005), overall benefit in time to distant recurrences (324 vs 375 days; HR 0.86; 95% CI 0.78-0.97; P=0.04), and rate of contralateral breast cancer development (35 vs 59 cases; 42% relative risk [RR] reduction; P=0.01). The investigators reported fewer side effects and discontinuations of anastrozole. However, they reported significantly more fractures at 120 months of median follow-up with anastrozole compared to tamoxifen, (451 vs 351 events; odds ratio [OR] 1.33; 95% CI 1.15-1.55; $P<0.0001$). At the completion of treatment, the incidence of fractures was similar in the anastrozole and tamoxifen groups (66 vs 78 events; OR 0.84; 95% CI 0.60-1.19; P=0.3). The risk of venous thromboembolic events, endometrial cancer, and hot flashes was lower in patients treated with anastrozole.[20]

Letrozole, another type II AI, was compared to tamoxifen in a head-to-head trial in the Breast International Group (BIG) 1-98 Collaborative Group study. The phase 3, double-blind trial randomized 8,010 patients to tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years followed by letrozole, or letrozole for 2 years followed by tamoxifen.[21] After a median follow-up of 25.8 months, the initial analysis compared the 2 groups assigned to receive letrozole initially with the 2 groups assigned to receive tamoxifen initially. The letrozole group had an improved 5-year survival rate compared to the tamoxifen group (84.0% and 81.4%, respectively). The study also found that thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. BIG 1-98 also found significantly increased rates of fractures with letrozole compared to tamoxifen (5.7% vs 4%; $P<0.001$).[21] A companion study to the MA.17 trial evaluated the effect of letrozole on bone mineral density (BMD) prospectively and monitored BMD over time. At 24 months, patients taking letrozole had significant decreases in their BMD in the total hip and lumbar spine compared to patients receiving placebo.[22]

Based on these studies, along with the 51-month follow-up in the BIG 1-98 trial,[23] the FDA approved anastrozole and letrozole for initial adjuvant therapy of hormone-sensitive early-stage breast cancer. The recent randomized phase 3 trial, Femara Versus Anastrozole Clinical Evaluation (FACE), compared the efficacy and safety of letrozole with anastrozole.[24] The FACE trial evaluated 4,136 postmenopausal females who had hormone receptor–positive and node-positive breast cancer and found that letrozole was not significantly superior with regard to safety or efficacy compared to anastrozole, despite prior pharmacodynamic studies that demonstrated more effective estradiol suppression by letrozole.[24]

In addition, the EBCTCG performed a metaanalysis of the randomized trials for AIs vs tamoxifen in early breast cancer.[25] They divided 31,920 postmenopausal females with ER-positive early breast cancer into multiple therapy subgroups and compared the groups. The subgroups were 5 years of an AI (group 1), 5 years of tamoxifen (group 2), 2-3 years of tamoxifen followed by an AI to complete 5 years (group 3), and 2-3 years of an AI followed by tamoxifen (group 4).[25] The comparison of 5 years of an AI and the switching strategy of 2-3 years of tamoxifen followed by an AI to year 5 showed a recurrence reduction during the first year among the AI group, but that benefit was lost when both groups were taking an AI. When comparing the data from groups 1 and 2, groups 1 and 3, and groups 2 and 3, a greater recurrence reduction was noted in patients taking an AI during any point in the trial, even with varied treatment regimens. Overall, AIs reduced recurrence rates by nearly 30% compared to tamoxifen.

SWITCH TRIALS

AIs have also been studied as sequential therapy after 2-3 years of tamoxifen. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 conducted a combined analysis with the Arimidex-Nolvadex 95 (ARNO 95) trial in which they evaluated the efficacy of switching to anastrozole for 3 years after completing 2 years of adjuvant tamoxifen therapy.[26] The researchers identified 3,224 postmenopausal hormone receptor–positive females who had received 2 years of tamoxifen and randomized them to receive 1 mg of anastrozole, 20 mg of tamoxifen, or 30 mg of tamoxifen. After a median follow-up of 28 months, a 40% decrease in risk for an event was noted with anastrozole (67 events with anastrozole vs 110 with tamoxifen; HR 0.60; 95% CI 0.44-0.81; P=0.0009).[26] The Intergroup Exemestane Study (IES) evaluated exemestane, a type I AI, for sequential therapy after tamoxifen in the adjuvant setting.[27] The investigators examined 4,742 postmenopausal females with ER-positive or ER-unknown breast cancer who had no evidence of disease after 2-3 years of adjuvant tamoxifen and who were randomized to either switching to exemestane or continuing tamoxifen therapy for a total of 5 years. After a median follow-up of 30.6 months, they found a 32% risk reduction, corresponding to an absolute benefit in terms of DFS of 4.7% at 3 years after randomization, in the exemestane group.[27] These switch trials showed evidence that the sequential use of AIs and tamoxifen provided additional benefits. The correct sequence and duration of treatment need further clarification.

EXTENDED THERAPY TRIALS

As data from 5-year trials began to emerge, interest on extending the duration of adjuvant therapy and late recurrence increased (Table 2). The NSABP explored continuing tamoxifen therapy beyond 5 years. They evaluated the outcomes of patients in the B-14 trial through 10 years and the effects of 5 more years of tamoxifen vs

Table 2. Extended Trials

Trial	Treatment Regimens	Number of Subjects	Endpoints	Findings
ATLAS, 2013[28]	After 5 years of 20-mg tamoxifen, patients were randomized to stop tamoxifen or continue to year 10	12,894	Recurrence, side effects, breast cancer mortality, and overall mortality	Reduced recurrence for ER-positive disease (617 recurrences in women who continued vs 711 in control group; P=0.002) and reduced breast cancer mortality (639 deaths vs 722 deaths; P=0.01)
aTTom, 2013[29]	After 5 years of 20-mg tamoxifen, patients were randomized to stop tamoxifen or continue to year 10	6,953	Recurrence, mortality, and hospital admissions	Continuing tamoxifen to year 10 produced further reduction in recurrence (580/3,468 vs 678/3,485; P=0.003) from year 7 onward
MA.17, 2016[30]	After 4.5-6 years of an AI, 5 years of 2.5-mg letrozole vs placebo within 2 years after completion of initial treatment	1,918	DFS, recurrence, OS, incidence of contralateral breast cancer, quality of life, and long-term safety	5-year DFS was 95% in the letrozole group compared to 91% in the placebo group
NSABP B-42, 2016[31]	After 5 years of an AI or tamoxifen, 5 years of 2.5-mg letrozole vs placebo	3,966	DFS, second primary cancer, death, OS, and breast cancer–free interval	No significantly improved DFS or OS but improved breast cancer–free interval (6.7% vs 10.0%; HR=0.71; P=0.003) and distant recurrence rate (3.9% vs 5.8% events; HR=0.72; P=0.03)
IDEAL, 2016[32]	5 years vs 2.5 years of 2.5-mg letrozole after 5 years of hormone therapy	1,824	DFS, OS, distant DFS, and contralateral breast cancer	5 years of letrozole did not improve DFS (88.4% for 2.5 years and 87.9% for 5 years; HR 1.08; P=0.59) compared to 2.5 years
DATA, 2016[33]	6 years vs 3 years of 2.5-mg anastrazole after 2-3 years of 20-mg tamoxifen	1,912	Adapted DFS (DFS beyond 3 years after randomization)	6 years did not improve rates of adapted DFS (HR 0.79 with 83.1% for 6 years and 79.4% for 3 years)

AI, aromatase inhibitor; ATLAS, Adjuvant Tamoxifen: Longer Against Short; aTTom, Adjuvant Tamoxifen–To Offer More?; DATA, Different Durations of Anastrozole and Tamoxifen; DFS, disease-free survival; HR, hazard ratio; IDEAL, Investigation on the Duration of Extended Adjuvant Letrozole; MA.17, National Cancer Institute of Canada Trial; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival.

placebo.[15] A significant advantage was noted in DFS (69% vs 57%; P=0.001; RR 0.66; 95% CI 0.58-0.71), with 10 years of follow-up between the placebo and tamoxifen groups. However, no additional advantage was seen between the 5-year and 10-year groups of tamoxifen therapy (94% vs 96% 4-year survival; P=0.08).[15] The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial compared 12,894 females with early breast cancer who had completed 5 years of treatment and randomly assigned them to continue tamoxifen for 10 years or to stop at 5 years.[28] The investigators knew 5 years of tamoxifen were more effective than 1-2 years, and they wanted to explore whether 10 years of treatment would have a greater effect. Greater protective effects against ER-positive breast cancer were noted with 10 years of tamoxifen, resulting in reductions in recurrence and mortality.[28] These results were mirrored in the Adjuvant Tamoxifen–To Offer More? (aTTom) trial that compared 6,953 females who were randomized to stop adjuvant tamoxifen at 5 years or continue to year 10.[29] This trial confirmed that the continuation of tamoxifen to year 10 resulted in reductions in recurrence and breast cancer deaths.[29]

Extending adjuvant therapy in postmenopausal women with early ER-positive breast cancer using AIs was also examined in a hope to further reduce late recurrences. The MA.17 extended adjuvant phase 3, randomized, double-blind, placebo-controlled trial examined the effects of treatment with an AI for 10 years.[30] The investigators randomized postmenopausal women with primary breast cancer who had already received 4.5-6 years of adjuvant therapy with an AI to either receive placebo or letrozole daily for another 5 years. They found that the 5-year DFS was

95% in the extended letrozole group compared to 91% in the placebo group (HR 0.66; P=0.01). Ultimately, the trial showed benefit in the prevention of disease recurrence that was independent of nodal status. However, 5-year overall survival was not higher in the extended letrozole group (93% vs 94%; HR 0.97; P=0.83).[30]

The NSABP B-42 trial evaluated the benefit of an additional 5 years of hormonal therapy with letrozole after an initial 5 years of an AI or tamoxifen.[31] The study's endpoint was DFS with median follow-up from randomization at 6.9 years. Results showed a nonsignificant 15% reduction in DFS at approximately 7 years in the extended letrozole group. However, the study found improvement in the 7-year cumulative incidence of breast cancer–free intervals (6.7% vs 10.0% events; HR 0.71; P=0.003) and distant recurrence (3.9% vs 5.8% events; HR 0.72; P=0.03) in the extended letrozole group compared to placebo.[31]

The Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial from the Netherlands randomized patients to 2.5 or 5 years of letrozole after 5 years of hormone therapy.[32] DFS was 88.4% with 2.5 years and 87.9% with 5 years. However, approximately 74% of patients completed 2.5 years of letrozole, and only 57% of patients completed 5 years of letrozole. Overall survival was 93% in both groups.[32] The Different Durations of Anastrozole and Tamoxifen (DATA) trial from the Netherlands studied 3 vs 6 years of anastrozole after 2-3 years of tamoxifen in 1,912 patients.[33] The trial was designed to detect an increase in adapted DFS (ADFS) after 6 years vs only 3 years, but instead the HR was 0.79 (P=0.07). ADFS is DFS after randomization (in this case 3 years). The 5-year ADFS was 83.1% in the 6-year group and 79.4% in the 3-year group. These findings did not support the use of extended adjuvant AI but suggested a benefit for node-negative disease and ER-positive/PR-positive disease with a 5-year HR for ADFS events of 1.01 (95% CI 0.62-1.63; P=0.9817) and 0.68 (95% CI 0.51-0.90; P=0.0072), respectively.[33]

THE BREAST CANCER INDEX

The Breast Cancer Index (BCI) is a computer algorithm that uses a gene expression assay–based signature to predict the early (defined as 0-5 years) and late (defined as >5 years) risk of distant recurrence in patients.[34] The algorithm was developed using a combination of 2 independent gene expression profiles, the HOXB13/IL17BR (H:I) and the molecular grade index (MGI).[35] While the MGI was a better prognostic predictor from 0-5 years and H:I was a better prognostic predictor beyond 5 years, the BCI was designed to be a continuous risk index.[34] The BCI model was created using a cohort of patients from the Stockholm study, a randomized trial with 2,738 patients with early-stage breast cancer that compared 2 or 5 years of adjuvant tamoxifen to no endocrine therapy.[36] Zhang et al provided validation for the BCI using tumors from 600 early-stage patients with ER-positive, node-negative breast cancer from the Stockholm study along with an additional 358 patients from a multi-institutional cohort comprising ER-positive, node-negative, tamoxifen-treated patients from 2 other medical centers.[34] They found the BCI to be a significant prognosticator of both early and late distant recurrence.[34] The BCI has been further validated and compared to other prognostication tools. Sgroi et al compared the BCI to the Oncotype DX (Genomic Health, Inc.), a 21-gene recurrence score, and to IHC4, an immunohistochemical prognostic model, with regard to prognostic capabilities.[37] The study assessed tumors from 665 ER-positive, node-negative breast cancer patients who were a part of the translational substudy of the ATAC trials (TransATAC) and tested the ability of the prognostic tools to predict risk of recurrence.[37] Of the prognostic tools evaluated, only the BCI was able to significantly predict the risk of both early and late distant recurrence.[37] The BCI has been adapted to assess patients with node-positive disease.[38] The expansion of the BCI to node-positive patients was programmed based on 219 ER-positive tumor samples from patients with 1-3 positive nodes from the TransATAC trials.[38] This BCI model was validated by Zhang et al who looked at 402 ER-positive, node-positive patients; the BCI detected a significant number of node-positive patients considered to be low risk for distant recurrence after chemotherapy and 5 years of endocrine therapy.[39] The BCI is thus able to provide prognostic data on whether a patient will have a high or low likelihood of benefiting from extended endocrine therapy.[34,37,40] As a result, patients and clinicians are able to use the BCI tool to help make challenging treatment decisions, leading to less anxiety and decisional conflict.[41]

CONCLUSION

The management of hormone receptor–positive breast cancer has changed significantly since the 1970s. After the adoption of adjuvant endocrine therapy with tamoxifen and AIs, investigators have attempted to determine the optimal duration of adjuvant therapy. Current efforts are focusing on how best to identify patients at risk for late recurrence and how best to manage them. As technology continues to advance and become readily available, treatment plans can become personalized to the individual patient and the particular characteristics of the tumor. The incorporation of these tools may improve patient outcomes.

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