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Extended Adjuvant Aromatase Inhibitor Therapy in Post-Menopausal Women

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Abstract

Purpose of the review—To understand the evidence for extending adjuvant aromatase inhibitor (AI) therapy from 5 to 10 years in post-menopausal women with hormone receptor positive (HR+) breast cancer.

Recent findings—Multiple large trials have investigated this question. The two trials most representative of the dilemma faced in clinical practice are the MA.17R and NSABP-B42 trials, which both investigated the benefit of continuing versus stopping AI therapy beyond 5 years. Both trials showed that extended AI therapy led to a reduction in new or recurrent breast cancers, but had no effect on survival outcomes when death from any cause was included.

Summary—The decision to extend AI therapy beyond 5 years remains a personalized one based on a discussion of the projected risk of recurrence, the expected benefits of prolonged AI treatment, and the patient's ability to tolerate side effects so that quality of life is preserved.

Keywords

Aromatase inhibitor; hormone receptor positive breast cancer; estrogen receptor positive breast cancer; extended adjuvant therapy

Introduction

For hormone receptor-positive (HR+) breast cancer, anti-estrogen therapy is the cornerstone of treatment.¹ Anti-estrogen treatment has important roles in many facets of breast cancer including breast cancer prevention,² the management of ductal carcinoma in situ,³ and the treatment of invasive breast cancer.⁴

In the adjuvant setting – after surgical resection of an invasive breast cancer – 5 years of endocrine therapy in patients with HR+ disease reduces breast cancer mortality by

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Compliance with Ethics Guidelines

Conflict of Interest

Maura N. Dickler has served as a consultant for Roche/Genentech, Novartis, Astra Zeneca, Puma, G1 Therapeutics, TapImmune, Pfizer, and Syndax.

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Human and Animal Rights and Informed Consent

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approximately one third.⁴ Tamoxifen, a selective estrogen receptor modulator (SERM), and the aromatase inhibitors (AIs) represent two classes of endocrine therapies used to treat HR+ breast cancer. While tamoxifen is beneficial in both pre- and post-menopausal patients requiring adjuvant endocrine therapy, the efficacy of AIs is limited to post-menopausal women, in whom data has shown slight superiority of AIs as compared to tamoxifen.⁵ Since HR+ breast cancer may recur many years after surgery,⁶ an important research question has been whether extending endocrine therapy beyond 5 years leads to better outcomes. While robust data has led the American Society of Clinical Oncology (ASCO) to recommend offering 10 years of adjuvant tamoxifen therapy to pre- and peri-menopausal women with HR+ breast cancer,⁷ the optimal duration of adjuvant AI therapy for post-menopausal women is less well defined.

In this article, we review the data investigating extended adjuvant AI therapy in post-menopausal women and offer recommendations to help guide treatment decisions in clinical practice.

Adjuvant AI treatment for post-menopausal women

AIs represent a class of drugs that function by preventing peripheral tissue conversion of adrenal androgens into estrogen by aromatase.⁸ This is the only mechanism of estrogen production in post-menopausal women. AIs include anastrozole, letrozole, and exemestane. The first approval of AI therapy in breast cancer was for anastrozole, which showed superiority to megestrol acetate in the treatment of HR+ metastatic breast cancer in post-menopausal patients who previously progressed on tamoxifen therapy.⁹ Anastrozole subsequently replaced tamoxifen as the preferred first line treatment in post-menopausal patients with HR+ metastatic disease after being found to improve median time to progression (11.1 months vs. 5.6 months, $p=0.005$), reduce the occurrence of thromboembolic events (4.1% vs. 8.2%), and reduce vaginal bleeding (1.2% vs. 3.8%) as compared to tamoxifen.¹⁰ These promising results of AI therapy in the metastatic setting led to trials investigating its utility in the adjuvant setting.

The pivotal adjuvant Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial found that 5 years of AI therapy was superior to 5 years of tamoxifen in post-menopausal woman with resected HR+ breast cancer. This large trial found that as compared to tamoxifen, 5 years of anastrozole improved rates of disease-free survival (DFS; HR 0.86, $p=0.003$), time to recurrence (HR 0.79, $p=0.0002$), and time to distant recurrence (HR 0.85, $p=0.02$).⁵ Patients randomized to anastrozole had increased rates of bone fractures (odds ratio 1.33, $p<0.0001$) and decreased rates of endometrial cancer (odds ratio 0.25, $p=0.001$) as compared to patients receiving tamoxifen.⁵ Of note, the initial trial design included a combination tamoxifen plus anastrozole group, which was discontinued due to a lack of benefit of combined treatment over tamoxifen alone.¹¹ The Breast International Group (BIG) I-98 trial similarly found that 5 years of adjuvant letrozole was superior to tamoxifen in post-menopausal women with HR+ disease, leading to reductions in distant recurrences (HR 0.73, $p=0.001$) and improved rates of DFS (84% vs. 81.4%).¹² Furthermore, a large meta analysis of 31, 920 post-menopausal patients with HR+ breast cancer showed that 5 years of adjuvant AI therapy reduced rates of breast cancer mortality by 15% compared to 5 years of

adjuvant tamoxifen.¹³ Overall however, the choice of appropriate adjuvant endocrine therapy remains individualized and must also take into account the side effects of each agent.

Extended tamoxifen therapy in pre- and peri-menopausal women

HR+ breast cancers often recur many years after initial diagnosis.⁶ Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTG) found that even stage 1 HR+ breast cancers treated with 5 years of endocrine therapy have a cumulative distant recurrence rate during years 5 to 20 of 14%.¹⁴ As a result of the long natural history of HR+ breast cancer, an important research question has been whether more than 5 years of endocrine therapy is beneficial.

Two large studies investigated the optimal duration of adjuvant tamoxifen and found that extending tamoxifen treatment to 10 years in patients whom had already completed 5 years of tamoxifen improved breast cancer-specific survival. The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial showed an absolute breast cancer mortality rate reduction of 2.8% for women receiving longer tamoxifen therapy.¹⁵ Interestingly, the benefit of 10 years of tamoxifen became more pronounced further out from surgery, with a breast cancer mortality ratio of 0.97 during years 5–9, and 0.71 in years 10 and beyond. As compared to stopping at 5 years of tamoxifen, extending tamoxifen to 10 years led to increased rates of developing pulmonary emboli (RR 1.87; $p=0.01$; mortality rate of 0.2% in both treatment groups) and endometrial cancer (RR 1.74; $p=0.0002$; mortality rate 0.4% versus 0.2%). In contrast, extended tamoxifen treatment led to decreased rates of myocardial ischemia as compared to stopping at 5 years (RR 0.75; $p=0.02$). The second large study was the adjuvant tamoxifen – To offer more? (aTTOM) trial, which similarly showed a reduction in breast cancer-specific mortality in patients treated with 10 years versus 5 years of tamoxifen therapy, with benefits most pronounced after year 10 (rate ratio 1.05 during years 5–9; rate ratio 0.86 later).¹⁶ Based on these studies, ASCO currently recommends offering 10 years of adjuvant tamoxifen to pre- and peri-menopausal women with breast cancer requiring adjuvant endocrine therapy.⁷

Extended adjuvant AI therapy trials

Multiple large clinical trials have been conducted to answer the question of whether the benefits observed with extended adjuvant tamoxifen also apply to adjuvant AI therapy in post-menopausal patients with HR+ breast cancer. To incorporate these trial results into evidence-based treatment, it is important to understand the similarities and differences between these trial designs and their results. Here we review the 5 important trials of extended adjuvant AI therapy in post-menopausal patients with HR+ breast cancer, summarized in figure 1.

MA.17 Trial¹⁷—The MA.17 trial tested the benefit of 5 years of letrozole versus placebo in 5,187 post-menopausal patients who previously completed 5 years of adjuvant tamoxifen treatment.¹⁷ Eligible patients must have been greater than 50 years old at the time of initiation of tamoxifen (76% of patients), less than 50 years old but considered post-menopausal before the time of tamoxifen initiation (approximately 10.5%), or became amenorrheic during treatment with tamoxifen (approximately 23.5%). After a median

follow-up period of 2.4 years, the trial was terminated early due to improved 4 year DFS rates in patients randomized to letrozole versus placebo (93% vs, 87%, respectively). The hazard ratio of local or distant recurrence as compared to placebo was 0.57 ($p=0.00008$), and unplanned sub-group analysis showed this benefit was independent of nodal status (HR 0.60 in node-positive disease; HR 0.47 for node-negative disease). However, improvements in overall survival associated with letrozole were seen only in patients with lymph node positive disease (HR 0.82, $p=0.3$ for all patients; HR 0.61, $p=0.04$ for patients with lymph node positive disease).¹⁸ Women who received letrozole had statistically more hot flashes, anorexia, arthralgia, myalgia, and alopecia. However, there was no statistically significant effect of letrozole on bone fractures or cardiovascular events.

MA.17R Trial¹⁹—Extrapolation of MA.17 results in combination with the extended tamoxifen data led many patients and physicians to discuss continued use of AI treatment beyond 5 years. To provide data to understand the utility of extended AI therapy, the North American MA.17R trial randomized 1,918 post-menopausal women who previously completed 4.5–6 years of AI therapy to receive an additional 5 years of letrozole or placebo. Of note, 68.5% of patients also received 4.5–5.5 years of initial treatment with tamoxifen prior to AI therapy, and only 20.7% of patients received no upfront tamoxifen. The primary end point was DFS defined as local or distant recurrence of breast cancer or a new primary breast cancer. Importantly, second primary non-breast cancer events and death from any cause were not included in the DFS definition, and patients who died without breast cancer recurrence were censored at time of death. After a median follow-up of 6.3 years, extended letrozole therapy versus placebo led to a statistically significant improvement in 5 year DFS (HR of disease recurrence or new primary breast cancer was 0.66, $p=0.01$), and this benefit was independent of nodal status. The strongest effect of extended letrozole versus placebo was in the reduction of contralateral breast cancer development from 3.2% to 1.4%, respectively (HR 0.42, $p=0.007$). Importantly, when the definition of DFS included death, there was no longer a statistically significant benefit of extended letrozole therapy versus placebo (HR 0.80, $p=0.06$). There was no difference in overall survival between the extended letrozole and placebo groups (HR for death 0.97, $p=0.83$).

This trial also investigated the effect of extended letrozole therapy on bone health and quality of life. Patients randomized to extended letrozole therapy versus placebo had increased rates of T scores of the lumbar spine less than -2.5 at any time after baseline (10% vs. 7%, respectively, $p=0.03$) and increased rates of fractures while on letrozole (14% vs. 9%, respectively, $p=0.001$) despite having similar rates of calcium, vitamin D, and bisphosphonate use. Quality of life scores including bodily pain overall tended to be worse in patients receiving extended letrozole, but most subscales did not show statistically significant effects.

NSABP-B42 Trial²⁰—In the NSABP-B42 trial, 3,923 post-menopausal patients who previously completed 5 years of endocrine therapy were randomized to receive an additional 5 years of AI therapy with letrozole or placebo.²⁰ Prior endocrine therapy allowed included 5 years of AI therapy (61% of patients), or up to 3 years of tamoxifen followed by subsequent AI therapy to complete 5 years before randomization (39% of patients).

Therefore, NSABP-B42 tested 10 versus 5 years of adjuvant AI therapy similar to the MA.17R trial discussed above. The primary endpoint was DFS, defined as local or distant breast cancer recurrence, new contralateral breast cancer, a second primary non-breast cancer, or death from any cause. Based on a pre-defined statistical significance level of $p=0.0418$, extended letrozole therapy versus placebo did not have a statistically significant impact on DFS (HR 0.85, $p=0.048$) or overall survival (HR 1.15, $p=0.22$). The researchers did however find that extended letrozole led to a statistically significant reduction in cumulative breast cancer-free interval (BCFI) events from 10% to 6.7% (HR 0.71, $p=0.003$) and cumulative incidence of distant recurrence from 5.8% to 3.9% (HR 0.72, $p=0.03$), without an increase in osteoporotic fractures (HR 1.19, $p=0.27$). Quality of life was not assessed.

Importantly, although the NSABP-B42 and MA.17R trials at first glance seem contradictory, it is important to recognize the differences in each trial's definition of DFS. The definition of DFS in NSABP-B42 included second non-primary breast cancers and death from any cause, which is consistent with previously proposed standard definitions of *survival* outcomes in breast cancer.²¹ In contrast, DFS as defined in the MA.17R study excluded both of these outcomes and included only breast cancer recurrence or the development of a new primary breast cancer, more consistent with standard definitions of breast cancer free *interval* outcomes.²¹ In fact, the definition of DFS in MA.17R is synonymous with the definition of the secondary endpoint BCFI in NSABP-B42. With this in mind, both the MA.17R and NSABP-B42 trials showed similar effects of extended AI therapy beyond 5 years on reducing breast cancer recurrence or the development of a new primary breast cancer (HR 0.66, $p=0.01$; HR 0.71, $p=0.003$, respectively), and neither showed improvements on survival when death from any cause was included.

IDEAL Trial²²—The IDEAL trial was conducted in the Netherlands and tested the benefit of an additional 5 versus 2 years of letrozole therapy in 1,824 post-menopausal patients who previously completed 5 years of adjuvant tamoxifen or AI therapy.²² This trial slightly differs from MA.17R and NSABP-B42 because all patients in the IDEAL study who previously completed 5 years of AI therapy got at least 2 years of additional AI treatment. Eligible patients were post-menopausal at time of adjuvant endocrine therapy initiation. The study found no statistically significant effect on their primary endpoint DFS (HR 0.96, $p=0.70$) after a median follow-up of 6.5 years. There was similarly no effect on overall survival (HR 1.08, $p=0.59$) or distant metastasis-free survival (HR 1.08, $p=0.64$). However, the researchers did find that extended letrozole treatment reduced rates of developing a secondary primary DCIS or invasive breast cancer (HR 0.37, $p=0.008$).

DATA Trial²³—The DATA trial randomized 1,912 post-menopausal patients who previously completed 2–3 years of adjuvant tamoxifen therapy to receive an additional 6 versus 3 years of AI therapy with anastrozole.²³ Of note, this trial design differs from designs of the MA.17R, NSABP-B42, and IDEAL trials, which all randomized at least a subgroup of patients with approximately 5 years of prior AI therapy to receive extended AI treatment. Minimum follow-up time in the DATA trial was at least 6 years after randomization. The primary endpoint was adapted DFS (aDFS), defined as DFS beginning 3 years after randomization. Events included in their DFS analysis included local and distant

breast cancer recurrence, the development of a new secondary malignancy, and death from any cause. The trial found that 6 years of AI therapy had no statistically significant effect on aDFS as compared to 3 years of therapy (HR 0.79, $p=0.07$). However, in a subgroup analysis including patients with HER2-negative, lymph node positive, high risk disease that required chemotherapy, extended AI therapy improved aDFS (HR 0.58, $p=0.01$). Longer AI therapy had no effect on adapted overall survival (HR 0.91, $p=0.60$).

Summary of extended adjuvant AI trials—Although all 5 trials above investigated the role of extended AI therapy, it is important to recognize the heterogeneity of their trial designs (figure 1). For example, the duration of AI therapy significantly varied across trials. The MA.17 and DATA trials included patients who had previously received only tamoxifen and randomized them to receive up to a total of 5 or 6 years of AI therapy, respectively. The MA.17 study found that AI therapy led to improved rates of overall survival only in patients with lymph node positive disease,¹⁸ and the DATA trial similarly showed improved aDFS only in patients with lymph node positive disease that was also HER2 negative and with high risk features requiring chemotherapy.²³

However, in clinical practice, the common problem oncologists face is whether to continue AI therapy in post-menopausal patients with HR+ disease who have already completed 5 years of AI treatment. Only the MA.17R and NSABP-B42 trials addressed this question (since all patients in the IDEAL study who received 5 years of prior AI therapy continued at least 2 more years of AI treatment), and both showed a reduction in rates of recurrence and new primary breast cancers but no effect on survival outcomes when death from any cause was included.

Potential decision making tools to determine patients needing extended AI therapy

Breast Cancer Index (BCI)—The breast cancer index (BCI) tool reports both an individual's risk of late (defined as years 5–10 after surgery) breast cancer recurrence, as well as the likelihood of benefit from extended endocrine therapy beyond 5 years. This tool was first developed and validated using retrospective tissue samples from patients with HR+, lymph node negative disease randomized to tamoxifen in the Stockholm trial ($n=317$) or from a multi-institutional cohort ($n=358$).²⁴ BCI was subsequently compared to the 21 gene recurrence score (Oncotype DX) and an immunohistochemical prognostic score (IHC4 - composed of ER, PR, HER2, and Ki67) to determine which test best predicted a patient's risk of 10 year recurrence using archival tumor blocks from the TransATAC tissue bank.²⁵ The authors found that BCI was the only tool able to identify patients at risk for late (years 5–10) breast cancer recurrence.

BCI is also marketed as having predictive utility to understand if a patient has a high likelihood of benefit from endocrine therapy beyond 5 years.²⁶ However, this predictive benefit has been validated only in patients who participated in the MA.17 trial, which randomized patients who previously received 5 years of tamoxifen to receive an additional 5 years of endocrine therapy with letrozole versus placebo.¹⁷ The more common scenario faced by clinicians is whether to extend adjuvant AI therapy in post-menopausal patients who have already received 5 years of AI therapy. Since BCI has not yet been tested (or at

least with results published) in this setting, ASCO currently recommends against the use of BCI or any other multiparameter gene expression or protein assays to guide decisions on extended adjuvant therapy.²⁷

Conclusions and recommendations

Despite multiple trials investigating extended adjuvant AI therapy, the decision to extend AI treatment beyond 5 years remains an individual one based on the tradeoff between additional benefit and side effects. The two trials most representative of the dilemma faced in clinical practice are the MA.17R and NSABP-B42 trials, which both investigated the benefit of continuing versus stopping AI therapy beyond 5 years. Both trials showed that extended AI therapy beyond 5 years led to a reduction in new or recurrent breast cancers, but had no effect on overall survival.^{19,20} This benefit must be weighed against common side effects of AI treatment, a patient's tolerability of the initial 5 years of AI treatment, bone health, and quality of life. In the end, the decision to extend AI therapy beyond 5 years remains a personalized one based on a discussion of the projected risk of recurrence, the expected benefits of prolonged AI treatment, and the patient's ability to tolerate side effects so that quality of life is preserved.

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Figure 1.
Overview of extended adjuvant AI therapy trial schemas.