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REVIEW

Clinical Utility of Aromatase Inhibitors as Adjuvant Treatment in Postmenopausal Early Breast Cancer

Arturo Loaiza-Bonilla, Francisco Socola and Stefan Glück

Department of Medicine, Division of Hematology and Oncology, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL. Corresponding author email: sgluck@med.miami.edu

Abstract: Breast cancer is the most frequently diagnosed malignancy in women, with over 200,000 new cases diagnosed each year. Adjuvant systemic endocrine therapy has demonstrated its benefits in reducing the risk of occult micro metastatic infiltration by preventing breast cancer cells from receiving endogenous estrogen stimulation. Initial adjuvant treatment with an aromatase inhibitor (AI) is considered the standard of care for most postmenopausal women with node-positive and high-risk node-negative estrogen receptor (ER)-positive breast cancer. Aromatase inhibitors (AIs) are generally preferred over tamoxifen due to their effectiveness in preventing breast cancer recurrence post surgery and when tamoxifen side effects are to be avoided. When compared with tamoxifen, AIs are associated with significantly improved disease-free survival, however no OS advantage has been noted. Potential toxicities such as bone loss, dyslipidemia, musculoskeletal and cardiovascular health issues should be taken into consideration when AIs are to be used.

Keywords: adjuvant, aromatase inhibitors, breast cancer, hormonal therapy, postmenopausal

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Introduction

Breast cancer is the most frequently diagnosed malignancy in women, with over 200,000 new cases diagnosed each year. This disease is the second leading cause of cancer death in women in the United States. It is estimated that 458,400 women died of this disease in 2008, most of them with metastatic disease. Patients diagnosed with breast cancer face the risk of local and distant recurrence, most often in the form of distant metastasis, being the main cause of death.[1–5] Data from one retrospective cohort study showed that the 10-year survival in women with loco-regional recurrence was 56% (95% confidence interval [CI]: 45–65), compared with 9% (95% CI: 7–13) in those with distant recurrence. The median survival rate was 12.9 ± 5.4 years and 2.2 ± 0.3 years, respectively.[5]

Early detection through better screening and imaging techniques has resulted in a greater number of patients presenting with early-stage breast cancer. Advances in treatment options have improved overall survival (OS) and led to a reduced rate of death due to breast cancer worldwide, decreasing it from 0.4% (1990–95) to −1.9% (1998–2006) in the United States alone.[6,7] Treatments aiming to decrease the risk of breast cancer recurrence, especially distant metastasis, have the potential to allow women to remain disease-free and improve OS in women with early-stage breast cancer. Adjuvant systemic (chemotherapy or hormone) therapy has demonstrated its benefits in reducing the risk of occult micro metastatic infiltration, and is now the recommended clinical practice for patients with node-positive and high-risk node-negative breast cancer.[6] The purpose of this article is to review the clinical utility of aromatase inhibitors as adjuvant treatment in postmenopausal, estrogen-receptor-positive, early breast cancer.

Definition of early breast cancer

Early stage invasive breast cancer is defined as a malignancy derived from the mammary gland that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ, stage I, stage IIA, stage IIB and stage IIIA breast cancers.[8] Currently more than half of the women presenting with breast cancer in the US have an early-stage form of the disease.[9]

The main treatment for this group of patients is surgery with or without adjuvant chemotherapy or

Anatomic stage/prognostic groups

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1*	N0	M0		T1*	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1*	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1**	M0		T3	N2	M0
	T1*	N1**	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
* T1 includes T1mi				**Stage IV**	Any T	Any N	M1

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB

- M0 includes M0(i+)
- The designation pM0 is nto valid; any M0 should be clinical
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neeoadjuvant therapy
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0

NCCN National Comprehensive Cancer Network®

Figure 1. Breast Cancer Staging.
Edge SB, Byrd DR, Compton CC, et al, editors. AJCC (American Joint Committee on Cancer). Cancer Staging Manual, 7th ed. New York: Springer-Verlag; 2010:347.

hormone therapy; however, there is also a risk for distant relapse. Prognostic factors associated with risk of distant relapse include large tumor size, involvement of lymph nodes ad vascular invasion, tumor type and grade 3, high proliferation rate (as measured by Ki-67), hormone receptor status and human epidermal growth factor receptor 2 (HER-2/neu) status.[10,11] Risk of distant metastasis is also directly related to the number of axillary lymph nodes involved, but even patients with node-negative disease are at risk for developing distant metastasis.[12,13] Patients with poorly-differentiated ductal carcinoma in situ (DCIS) are also at a higher risk for distant metastasis than those with well-differentiated DCIS. Vicine et al[14] reported that local recurrence had two peaks in the rate of distant metastasis (at 2.5 years and at 6.5 years), compared to only one peak (at 1.5 years) for patients who did not develop local recurrence.

In early breast cancer, nodal status is a very important prognostic indicator, as the risk of distant metastasis has been directly related to the number of involved axillary nodes. The most commonly used stratification in clinical trials is based on four nodal groups, according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) data: negative nodes, 1–3 positive nodes, 4–9 positive nodes, and 10 or more positive nodes. The 5-year survival rate for patients with node-negative disease is 82.8%

compared with 73% for 1–3 positive nodes, 45.7% for 4–12 positive nodes, and 28.4% for ≥13 positive nodes. Similarly, tumor size also plays a significant role. Patients with tumors ≤ 1 cm had a five-year OS of nearly 99% compared with 86% for patients with tumors between 3 and 5 cm in size.[15,16]

Regarding the timing for potential recurrence, the Early Breast Cancer Trialist Collaborative Group (EBCTCG) identified that women with hormone-receptor positive breast cancer retain approximately 50% of their initial recurrence risk after year five. Furthermore, the risk of recurrence, particularly distant metastasis, remained as late as 15 years after diagnosis.[17]

Metastasis occurs when tumor cells detach from the primary tumor and migrate through the circulation to a new environment, with subsequent micro- and macro-metastatic disease growth along with simultaneous neo-angiogenesis.[18] The pathogenesis of micro-metastatic disease is partially explained by what is called the "spectrum theory", proposed by Harris and Hellmen.[19,20] According to this theory, tumor cells spread via lymphatic vessels in early-stage breast cancer and via hematogenous routes in late-stage breast cancer. Consequently, failure to achieve initial loco-regional control may allow the later migration of tumor cells to distant sites, with a deleterious effect on the patient's long-term survival.

Treatment for early breast cancer

Multimodal therapy is the treatment of choice for early-stage breast cancer and involves surgery, radiotherapy and adjuvant or neoadjuvant systemic therapy with chemotherapy and/or endocrine agents for hormone receptor-positive disease, as well as trastuzumab[28] for HER-2-positive breast cancer.[8,21] The aim of adjuvant therapy is to reduce the risk of local and distant recurrence following surgery.[22–24] Systemic endocrine therapy is indicated in patients with hormone-receptor-positive breast cancer, and it can be done in pre- and post-menopausal women. In premenopausal women, tamoxifen 20 mg/day orally for 5 years is recommended, and this therapy would be extended with an aromatase inhibitor after menopause is reached. In postmenopausal women with early breast cancer, a regimen of 5-year monotherapy treatment with any aromatase inhibitor or sequential therapy with 2–3 years of tamoxifen and then 2–3 years of aromatase inhibitor for total 5 years have become the standard of care.[25–28]

Aromatase inhibitors as part of adjuvant treatment

Aromatase inhibitors deplete estrogen by blocking conversion of adrenal androgens in peripheral tissues to estrone and estradiol. This group of drugs is considered a standard part of treatment in postmenopausal women with hormone-receptor-positive breast cancer, and they may be given as initial adjuvant hormonal therapy or sequentially after treatment with tamoxifen. If given in premenopausal women, these drugs require ovarian suppression with a luteinizing hormone-releasing hormone (LHRH) agonist to block ovarian estrogen production, or oophorectomy.[29–32]

AIs include the non-steroidal reversible aromatase inhibitors anastrozole and letrozole, and the steroidal irreversible aromatase inhibitor exemestane.

Aromatase inhibitors efficacy as group

AIs may improve survival and reduce breast cancer recurrence compared to tamoxifen in postmenopausal women with estrogen receptor (ER)-positive early breast cancer. Overall, AIs have proven to have a superior efficacy of between 15% and 25% compared to tamoxifen in terms of reducing the relative risk of recurrence, with some cohorts reporting reduced distant metastatic recurrence by up 27% over tamoxifen, particularly in the first two years post surgery. Major pivotal clinical trials have shown that AIs are better than tamoxifen in term of distant disease-free survival (DFS), defined as the time from random assignment to the earliest time of invasive recurrence in local, regional, or distant sites, a new invasive breast cancer in the contralateral breast, any second (non-breast) malignancy, death from any cause and contralateral breast cancer. However, no OS advantage has been found.[33,34]

Hind et al[35] published a systematic review of seven randomized trials comparing AI to tamoxifen for 5 years in postmenopausal women with ER-positive early breast cancer. AIs were used as switching therapy (changing to an aromatase inhibitor after a period of time on tamoxifen) or extended therapy (3–5 years of treatment with an aromatase inhibitor in women who were disease-free after 5 years of tamoxifen). Based on meta-analysis of 3 trials,

OS was improved only in the anastrozole-switching strategy, with no significant differences in OS established with letrozole or exemestane. In terms of disease-free survival (DFS) rates, this analysis reported DFS improvement with anastrozole and letrozole as primary adjuvant therapy, and with exemestane-switching therapy. Similar benefits were noted regarding breast cancer recurrence in all AI-related treatment groups.

Another meta-analysis of 7 trials performed by Dowsett et al[36] evaluating AI versus tamoxifen for breast cancer in postmenopausal women with ER-positive tumors, analysis was done separately in 2 cohorts. In the first cohort 9,856 patients from 2 trials were followed for a mean of 5.8 years, comparing 5 years of aromatase inhibitor therapy to 5 years of tamoxifen therapy. The reported recurrence rate was significantly lower in the AI group, being 9.6% versus 12.6% ($P < 0.00001$), but there was no statistically significant difference in cancer mortality; 4.8% versus 5.9% ($P = 0.1$), respectively.

In the second cohort, 9,015 patients from 4 trials were followed for a mean of 3.9 years to compare patients who switched after 2–3 years to AI therapy versus Patients who underwent 5 years of continuous tamoxifen therapy. The recurrence rate was significantly lower in the AI-switched therapy group versus tamoxifen (5.0% versus 8.1% [$P < 0.00001$]) as was cancer mortality (1.7% versus 2.4% [$P = 0.02$]), respectively.[36]

Anastrozole—clinical trials

Anastrozole 1 mg orally once daily is currently approved by the Food and Drug Administration (FDA) for adjuvant endocrine therapy in postmenopausal women with early hormone-receptor-positive breast cancer based on the following studies.

In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Table 1 and 2 randomized clinical trial, 9366 postmenopausal women with ER-positive localized breast cancer were enrolled, comparing anastrozole versus tamoxifen as monotherapy. After a median follow-up of 33.3 months, DFS at 3 years was 89.4% with anastrozole, 87.4% with tamoxifen and 87.2% with combination ($P = 0.013$ versus tamoxifen; $P = 0.006$ versus combination). These results lead to the initial conclusion that anastrozole appears to be more effective for improving DFS than tamoxifen when given as monotherapy.[37]

Results after median follow-up 68 months into the same study showed that anastrozole had an improved DFS ($P = 0.01$) and time to recurrence ($P = 0.0005$) in comparison with tamoxifen. Anastrozole was also associated with lower rates of distant metastases ($P = 0.04$) and contralateral breast cancers ($P = 0.01$), in addition to eliciting fewer side effects than tamoxifen, especially gynecological problems and vascular events. However, arthralgia and fractures were increased ($P < 0.001$). No significant difference was found in OS.[38]

An update of ATAC after a median follow-up of 100 months reported that the anastrozole group had a lower recurrence rate of 17% versus 21.8%; however, the incidence of fractures during active treatment was higher (2.93% versus 1.9%) than while off of treatment (1.56% versus 1.51%).[39]

The ABCSG-8 trial (Austrian Breast and Colorectal Cancer Study Group 8), a randomized trial (RT) without blinding, assessed treatment for 3,714 receptor-positive postmenopausal breast cancer women receiving tamoxifen for 2 years followed by anastrozole for 3 years versus tamoxifen alone. The first group was associated with a small improvement in the distant relapse-free survival (94.1% versus 92.5% [$P = 0.046$]); however, the difference in recurrence-free survival was not significant.[40]

Exemestane—clinical trials

Exemestane 25 mg once a day orally is currently approved by the FDA for two indications. The first is during adjuvant treatment of ER-positive early breast cancer in postmenopausal women who have received 2–3 years of tamoxifen and switch to exemestane to complete treatment, totaling 5 consecutive years of treatment. The second involves treatment of advanced breast cancer in postmenopausal women who exhibit disease progression following tamoxifen therapy.[41,42]

The Intergroup Exemestane Study (IES) Table 1 and 2 was a double-blind RCT that included 4,742 postmenopausal patients with ER-positive early breast cancer previously who were treated with surgery followed by tamoxifen for 2–3 years. The patients were randomized to switch to exemestane or to continue taking tamoxifen for 5 years. After a median follow-up of 30.6 months, DFS was higher in the exemestane group (92.3% versus 88.8% respectively, [$P < 0.001$]); however, overall mortality was the

Table 1. Aromatase inhibitor pivotal trials with Disease free survival (DFS) and overall survival (OS) data results.[39,40,45–47,50]

Trial name	Aromatase inhibitor [number of patients]	Comparator [number of patients]	Median follow-up	DFS	*P* value	Overall survival
TEAM[46]	Exemestane 5 y [4904]	Tamoxifen 2.5–3 y + Exemestane 2.5–2 y [4875]	60 months	86% vs. 85%	$P = 0.60$	Non significant
IES[45]	Tamoxifen 2–3 y + Exemestane 2–3 y [2362]	Tamoxifen 5 y [2380]	55.7 months	84.9% vs. 80.8%	$P = 0.0004$	Non significant
BIG-1–98[49]	Letrozole 5 y [3203]	Tamoxifen 5 y [3224]	97.2 months	76.4% vs. 72%	$P < 0.05$	Significant*
ABCSG-8[40]	Tamoxifen 2 y + Anatrozole 3 y [1865]	Tamoxifen 5 y [1849]	60 months	Non significant	$P = 0.33$	Non significant
ATAC[39]	Anastrozole 2.8 y [3092]	Tamoxifen 2.8 y [3094]	68 months	81.4% vs. 78.9%	$P = 0.01$	Non significant
Goss et al[50]	Tamoxifen 5 y + letrozole 2.4 y [2593]	Tamoxifen 5 y + placebo 2.4 y [2594]	28.8 months	93% vs. 87%	$P \leq 0.001$	Non significant

Note: *85.5% vs. 81.4% ($P < 0.05$).

same (3.9% versus 4.5%; not significant). The rate of contralateral breast cancer was 0.4% for the exemestane group versus 0.8% with tamoxifen ($P = 0.04$).[43]

The most commonly reported adverse effects with exemestane included diarrhea (4.3% versus 2.3%, $P < 0.001$), arthralgia (5.3% versus 3.6%, $P = 0.01$), visual disturbances (7.4% versus 5.7%, $P = 0.04$), osteoporosis (7.4% versus 5.7%, $P = 0.05$) and fractures (3.1% versus 2.3%, $P = 0.08$). The treatment discontinuation rate due to adverse events was the same between groups (5.8% versus 5.1%).[43]

Results after median follow-up 55.7 months into the same study showed that the tamoxifen + exemestane group's DFS was 84.9% versus 80.8% in the tamoxifen group alone ($P = 0.0004$), however overall mortality was not significantly different at 9.4% versus 11% respectively ($P = 0.08$).[44] An updated analysis of IES at a median follow-up of 91 months confirmed the protective effect of switching to exemestane compared with continuing on tamoxifen on risk of relapse or death; such an effect was maintained for at least 5 years post-treatment and it was associated with a continuing beneficial impact on OS (hazard ratio [HR], 0.86; 95% CI: 0.75 to 0.99; $P = 0.04$).[45]

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) Table 1 and 2 phase 3 trial included 9,779 patients with hormone-receptor-positive breast cancer who were randomly assigned in a 1:1 ratio to open-label exemestane (25 mg once a day, orally) alone or following tamoxifen (20 mg once a day, orally for 2.5–3 years) for a total of 5 years. After the treatment period ended, the DFS was not significantly different for both groups (86% versus 85%, respectively). In addition, the exemestane sequential treatment group was associated with a higher incidence of gynecological symptoms (942 [20%] of 4814 versus 523 [11%] of 4852), venous thrombosis (99 [2%] versus 47 [1%]), and endometrial abnormalities (191 [4%] versus 19 [< 1%]) than the exemestane alone group. Musculoskeletal adverse events (2448 [50%] versus 2133 [44%]), hypertension (303 [6%] versus 219 [5%]), and hyperlipidemia (230 [5%] versus 136 [3%]) were reported more frequently with exemestane alone. A higher discontinuation rate was also reported in the sequential group, being 29.5% versus 55.3% in exemestane group.[46]

Letrozole—clinical trials

Letrozole 2.5 mg a day orally is approved by the FDA for postmenopausal women in the adjuvant treatment of hormone-receptor-positive early breast cancer, extended adjuvant treatment of early breast cancer after 5 years of tamoxifen, and advanced breast cancer with disease progression following antiestrogen therapy. It is also approved for hormone-receptor-positive or hormone-receptor-unknown, locally-advanced, first-line, or second-line treatment of advanced or metastatic breast cancer.

In the Breast International Group (BIG) Table 1 and 2 1–98 trial, 8,028 early breast cancer hormone-receptor-positive postmenopausal patients

Table 2. Absolute differences (AD) and Number needed to harm (NNH) associated with one adverse event of each type*.[39,40,45–47]

Trial name	Cardiovascular disease		Cerebrovascular disease		Venous thrombosis		Bone fractures		Endometrial carcinoma		Other second cancers		Death without recurrence	
	AD (%)	NNH	AD (%)	NNH	AD (%)	NNH	AD (%)	NNH	AD (%)	NNH	AD(%)	NNH	AD(%)	NNH
TEAM[46]	0.7	139	0.4	311	–1.1	–91	1.6	63	–0.2	–485	NS	NS	0.3	287
IES[45]	1.3	79	0	∞	–1.2	–34	2.1	43	–0.2	–479	–1.1	–93	–1	–102
BIG-1–98[49]	0.9	107	0	∞	–1.8	–56	2.8	36	–0.5	–204	–0.3	–349	0	∞
ABCSG-8[40]	<0.1†	16431†	NS	NS	–0.6	–179	1.1	91	–0.3	–268	NS	NS	–0.5	–225
ATAC[39]	0.8	129	–0.8	–115	–1.8	–59	4.6	22	0.6	–163	0.8	134	1.2	87

Notes: *Positive values indicate excess events with aromatase inhibitors and negative values indicate excess events with tamoxifen. †Myocardial infarctions only.
Abbreviations: NNH, number needed to harm; NS, not specified.

previously treated with surgery were randomized to 1 of 4 groups for adjuvant therapy: letrozole alone for 5 years, tamoxifen alone for 5 years, letrozole for 2 years then tamoxifen for 3 years, and tamoxifen for 2 years then letrozole for 3 years.[47]

In the first cohort letrozole was compared with initial treatment with tamoxifen; at a median follow-up of 25.8 months, the letrozole group significantly reduced the risk of distant recurrence (HR = 0.73, [95% CI: 0.6–0.88; $P = 0.001$]) and DFS, with estimated 5-year DFS of 84% versus 81.4% compared with tamoxifen (HR = 0.81, [95% CI: 0.7–0.93; $P = 0.003$]), however overall mortality was not significantly different (4.1% versus 4.8%). Letrozole treatment was associated with higher risk than tamoxifen for fractures (5.7% versus 4%, $P < 0.001$), cardiac failure (0.8% versus 0.4%, $P = 0.01$) and arthralgia (20.3% versus 12.3%, $P < 0.001$); letrozole was also associated with lower risk than tamoxifen for thromboembolic events (1.5% versus 3.5%, $P < 0.001$), vaginal bleeding (3.3% versus 6.6%, $P < 0.001$), endometrial biopsies (2.3% versus 9.1%, $P < 0.001$,), invasive endometrial cancers (0.1% versus 0.3%, not significant) and hot flashes (33.5% versus 38%, $P < 0.001$).[47]

An update of these results at a median follow-up of 71 months revealed the comparison between sequential treatments to letrozole alone was not significant for DFS, OS or time to distant recurrence. When letrozole was compared to tamoxifen monotherapy, OS was not significantly different (91.8% versus 90.9% [$P = 0.08$]), DFS was higher with letrozole (85.6% versus 82.6% [$P = 0.03$]), and distant recurrence was lower in the letrozole group (10.4% versus 12.1% [$P = 0.05$]). Thromboembolic events, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group.[48]

In the same study results after median follow-up of 8.1-years, when letrozole and tamoxifen monotherapy were compared, OS was significantly higher in the letrozole group (85.5% versus 81.4%; $P < 0.05$), the DFS was 76.4% versus 72% ($P < 0.05$) and distant recurrence was 87.9% versus 85.1% ($P < 0.05$) in favor of letrozole group. In regards to sequential treatment versus letrozole alone there were no significant differences for OS, DFS or time to distant recurrence.[49]

Another study from Goss et al,[50] which included 5,187 postmenopausal women who had received tamoxifen for 5 years for hormone receptor-positive

Table 3. Recommendations on the use of AIs per international guidelines.[25,63,64]

According to the American Society of Clinical Oncology (ASCO)[25]
Most postmenopausal women should consider aromatase inhibitor therapy during adjuvant treatment, either as primary therapy or after 2–3 years of tamoxifen.
Duration of aromatase inhibitor therapy should not exceed 5 years.
Total duration of adjuvant endocrine therapy (aromatase inhibitor therapy and tamoxifen therapy in either sequence) should be at least 5 years.
According to Cancer Care Ontario (CCO)[63]
Adjuvant therapy for hormone receptor-positive, early stage breast cancer are:
• Adjuvant tamoxifen 20 mg/day, anastrozole 1 mg/day, letrozole 2.5 mg/day all of them for 5 years;
• Adjuvant tamoxifen 20 mg/day for 2–3 years then switch to either adjuvant exemestane 25 mg/day or anastrozole 1 mg/day for a total of 5 years of hormone therapy.
Consider adjuvant letrozole 2.5 mg/day for 5 years after completing 5 years of adjuvant tamoxifen therapy.
Monitor for changes in bone mineral density in women taking aromatase inhibitors.
According to New Zealand Guidelines Group (NZGG) guideline[64]
Adjuvant endocrine therapy for early breast cancer should include 5 years of either aromatase inhibitor alone or sequence of aromatase inhibitor and tamoxifen.
Aromatase inhibitors should form at least part of adjuvant endocrine therapy regimen for early breast cancer, unless contraindicated.
Use of tamoxifen alone recommended only when aromatase inhibitor contraindicated or not tolerated.
Bisphosphonate recommended if osteoporosis.
Consider bisphosphonate if osteopenia, especially if other risk factors for bone loss, including: prior non-traumatic fracture, age $>$ 65 years, family history, tobacco use, low body weight.
Postmenopausal women taking aromatase inhibitors should start bisphosphonate treatment for T-score $<$ –2, or $<$ –1 in presence of vertebral fracture; exclude secondary causes of osteoporosis.
Bone density monitoring at least every 2 years recommended for patients on AI.

breast cancer and exhibited no evidence of recurrence, patients were randomized to daily oral administration of letrozole 2.5 mg or a placebo. After a median follow-up of 2.4 years, as compared with placebo, letrozole therapy showed significant improvement in disease-free survival, with a 4-year DFS in the letrozole group of 93% versus 87% in placebo group. The most common adverse effects in the letrozole group were hot flashes, arthralgia, arthritis and myalgias.[50]

Aromatase inhibitors side effects

In a systematic review of seven randomized trials comparing aromatase inhibitors to tamoxifen as adjuvant endocrine therapy for 5 years, 30,023 postmenopausal women with breast cancer were evaluated. In this analysis, AI use was associated with an increased risk of cardiovascular events (odds ratio [OR], 1.3, 95% CI: 1.06–1.61), increased risk of bone fractures (OR, 1.48, 95% CI: 1.31–1.67), decreased risk of venous thrombosis (OR, 0.57, 95% CI: 0.46–0.71) and decreased risk of endometrial carcinoma (OR, 0.22, 95% CI: 0.11–0.46). No significant differences were seen in terms of cerebrovascular events, other second cancers, or death without breast cancer recurrence.[51]

When AI for 5 years was compared to sequential therapy with tamoxifen for 2–3 years followed by AI for 2–3 years, the first group had an increased risk of cardiovascular events (OR, 1.37, 95% CI: 1.05–1.79) and an increased risk of bone fractures (OR, 1.48, 95% CI: 1.21–1.8). The group with sequential therapy exhibited an increased risk of bone fractures (OR, 1.44, 95% CI: 1.15–1.8), a decreased risk of death without breast cancer recurrence (OR, 0.75, 95% CI: 0.58–0.98), and lower incidence of venous thrombosis (OR, 0.57, 95% CI: 0.4–0.8), endometrial carcinoma (OR, 0.46, 95% CI: 0.23–0.92) and other second cancers (OR, 0.61, 95% CI: 0.41–0.93). No significant difference in risk of cardiovascular events was found.[51]

Effect of AI on cardiovascular disease and lipid disorders

According to the Framingham Heart Study, postmenopausal women are already at an increased risk for cardiovascular disease.[52] It is important to mention that in most studies comparing tamoxifen and AI,

the patient cohorts assessed may not be representative of the general population due to the trials' exclusion criteria of patients with pre-existing hypertension or cardiovascular disease.

In the ATAC study (anastrozole versus tamoxifen for 5 years), at a median follow-up of 68 months, it was reported that anastrozole-treated patients had a greater incidence of hypercholesterolemia (278 of 3092) than tamoxifen-treated patients (278 of 3092), and this difference was statistically significant (9% versus 3%, odds ratio, 2.73, $P \leq 0.001$. In addition, patients in the anastrozole group also experienced significantly more hypertension (402 events versus 349, HR, 1.18, $P = 0.04$) and a trend towards a higher incidence of ischemic cardiovascular events that did not reach statistical significance (most commonly mild-to-moderate angina) in the anastrozole group compared to the tamoxifen group (127 patients, 4.1% versus 104, 3.4%; $P = 0.1$). The incidence of all grades coronary artery disease, Myocardial infarction (MI) or ischemia was not different between the groups (2% for both; $P = 0.5$) even after 100 months of follow up (anastrozole 37 events versus tamoxifen 28 events).[38]

In the IES study (exemestane versus tamoxifen, N = 4564), at 55.7 months of follow up, the frequency of ischemic cardiovascular disease was 8% in the exemestane group versus 6.9% in the tamoxifen group ($P = 0.17$), and the frequency of MI was 1.3% in the exemestane group versus 0.8% in the tamoxifen group ($P = 0.08$). The overall incidence of cardiovascular events (ischemic events and MI) was not statistically significant between the two groups during treatment (exemestane group 382 of 2320 patients, 16.5%, versus 350 of 2338 patient, 15% on tamoxifen; $P = 0.16$).[44]

In the BIG 1–98 trial (letrozole versus tamoxifen) at a median follow-up of 25.8 months, serum cholesterol was stable in the letrozole group at 6, 12 and 24 months, and in the tamoxifen group it was decreased by 12%, 13.5% and 14.1%, respectively. Additionally, more patients in the letrozole group developed hypercholesterolemia (173 of 3203 patients [5.4%]) versus (40 of 3224 patients [1.2%]) in comparison with the tamoxifen group.[36] In terms of cardiovascular disease, at a median of 30.1 months of follow up, the overall incidence of cardiovascular events was not statistically significant between the two groups (191 of 3975 patients [4.8%] versus 188 of 3988 patients [4.7%], $P = 0.87$); however, the risk of any grade 3 through 5 cardiac event was higher in the letrozole group versus tamoxifen (HR, 1.63; $P = 0.04$).[47]

In the TEAM trial (exemestane versus tamoxifen) the incidence of hypercholesterolemia at 12 months was significantly lower with tamoxifen than with exemestane ($P = 0.012$).[46]

Importantly, the MA.17 trial, which examined the impact of extended adjuvant letrozole after approximately 5 years of tamoxifen, provides for the largest comparison of AIs with placebo. Results from this trial showed that at a median follow up of 30 months, there is an identical incidence of hypercholesterolemia (418 of 2572, 16%) for letrozole versus (411 of 2577, 16%) for placebo ($P = 0.79$). Furthermore, there was no difference in the rate of hypertension between both groups (5% in both, $P = 0.94$).[51]

Effect of AI on thromboembolic and cerebrovascular events

In the ATAC trial (anastrozole versus tamoxifen for 5 years) at median follow up of 68-months, there was a significantly reduced incidence of thrombotic events (87 of 3092 patients, 2.8% versus 140 of 3094 patients 4.5%; $P = 0.004$) and deep vein thrombosis (DVT) (48 of 3092 patients, 1.6% versus 74 of 3094 patients, 2.4%; $P = 0.02$). A subsequent analysis also showed that anastrozole decreased in 39% the incidence of vascular thrombotic events compared with tamoxifen (OR, 0.61; $P = 0.0001$). After 100 months of follow up, the incidence of cerebrovascular disease accidents continued to be lower during treatment with anastrozole (20 events, 0.64% versus 34 events, 1.1% OR, 0.59; $P = 0.56$) but this trend did not persist while off treatment.[38]

The BIG 1–98 (letrozole versus tamoxifen) trial revealed a significantly lower incidence of thromboembolic events favoring letrozole (61 of 3975 patients, 1.5% versus 140 of 3988 patients, 3.5%; $P = 0.001$), and similar incidence of strokes and transient ischemic attacks (39 of 3975 patients, 1%, versus 41 of 3988 patients 1%; $P = 0.91$).[47]

In the IES trial (exemestane versus tamoxifen), at a median follow up of 55.7 months, vascular thrombotic events occurred in 28 of 2320 patients (1.2%) who were switched to exemestane, compared with 54 of 2338 (2.3%) of patients who continued on tamoxifen ($P = 0.004$). The incidence of cerebrovascular

events during treatment was the same in both groups.[44]

Finally, in the National Cancer Institute of Canada—Clinical trial group, MA.17 (MA.17) trial, vascular thrombotic events occurred at a low frequency regardless of the treatment group (11 of 2572 patients 0.4% on letrozole versus 6 of 2577 patients, 0.2% on placebo), and the incidence of cardiovascular disease was not statistically different ($P = 0.76$) between letrozole and placebo.[51]

Based on the available data, it can be stated that the increased prevalence of dyslipidemia seen in the AI versus the tamoxifen group may reflect the lipid-lowering effect of tamoxifen; however, more studies comparing AIs to placebo should be pursued in order to clarify this issue. Most of these pivotal studies have shown that the incidence of cardiovascular events between AI and tamoxifen is almost the same, and the calculated risks of cardiovascular events are similar to those observed in an age-matched, non-breast cancer population.[28,33,47,51,52] In terms of thromboembolic and thrombotic events, it seems that AI provides a benefit in lowering the incidence of DVT, pulmonary embolism and stroke when it is compared with tamoxifen.

Management of cardiovascular risk in breast cancer patients

Regardless of treatment choice, all breast cancer patients should have regular assessment, monitoring and management of potential cardiovascular risks and complications according to current institutional guidelines for primary and secondary prevention of cardiovascular disease. Lifestyle modifications, regular exercise, smoking cessation and dietary changes aimed to decrease cardiovascular risks are also important. Overall, the benefit of AI therapy in patients with ER-positive early breast cancer far outweighs the risk of any potential side effects, and this should be taken into account when considering treatment options for this patient population.[52–56]

Clinical and economic benefits of AI

Due to the significant impact on quality of life and mortality that breast cancer distant recurrence can have, as well as the increased cost for the intervention and management of these complications, it is important to consider that therapies reducing the risk of distant metastasis may improve not only long-term survival but also the cost-effectiveness of medical interventions. Emerging evidence-based data has demonstrated potential OS advantages for AIs related to distant recurrence. Amongst the AIs, letrozole appears to have an efficacy advantage by demonstrating an early effect on distant recurrence, and subsequently a potential significant OS benefit. When the economic burden to society is considered, it appears that all AIs are similarly beneficial on the basis of disease recurrence prevention and cost-effectiveness.[57–62]

Conclusion

Initial adjuvant treatment with an aromatase inhibitor (AI) is considered the standard of care for most postmenopausal women with node-positive and high-risk node-negative ER-positive breast cancer. Aromatase inhibitors (AIs) are generally preferred over tamoxifen due to their effectiveness in preventing breast cancer recurrence post-surgery, and when tamoxifen side effects are to be avoided. When compared with tamoxifen, AIs are associated with significantly improved disease-free survival, however no OS advantage has been noted. Potential toxicities such as bone loss, dyslipidemia, musculoskeletal and cardiovascular health issues should be taken into consideration when AIs are to be used.

Author Contributions

Conceived and designed the experiments: ALB, FS, SG. Analysed the data: ALB, FS, SG. Wrote the first draft of the manuscript: ALB, FS, SG. Contributed to the writing of the manuscript: ALB, FS, SG. Agree with manuscript results and conclusions: ALB, FS, SG. Jointly developed the structure and arguments for the paper: ALB, FS, SG. Made critical revisions and approved final version: ALB, FS, SG. All authors reviewed and approved of the final manuscript.

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