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REVIEW

Safety of aromatase inhibitors in the adjuvant setting

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Abstract The third-generation aromatase inhibitors (AIs) letrozole, anastrozole, and exemestane are replacing tamoxifen as adjuvant therapy in most postmenopausal women with early breast cancer. Although AIs have demonstrated superior efficacy and better overall safety compared with tamoxifen in randomized controlled trials, they may not provide the cardioprotective effects of tamoxifen, and bone loss may be a concern with their long-term adjuvant use. Patients require regular bone mineral density monitoring, and prophylactic bisphosphonates are being evaluated to determine whether they may protect long-term bone health. AIs decrease the risks of thromboembolic and cerebrovascular events compared with tamoxifen, and the overall rate of cardiovascular events in patients treated with AIs is within the range seen in age-matched, non-breast-cancer populations. AIs are also associated with a lower incidence of endometrial cancer and fewer vaginal bleeding/discharge events than tamoxifen. Compared with tamoxifen, the incidence of hot flashes is lower with anastrozole and letrozole but may be higher with exemestane. Generally, adverse events with AIs are predictable and manageable, whereas tamoxifen may be associated with life-threatening events in a minority of patients. Overall, the benefits of AIs over tamoxifen are achieved without compromising overall quality of life.

Keywords Adjuvant therapy · Aromatase inhibitors · Early breast cancer · Letrozole · Safety

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Introduction

Tamoxifen became the standard adjuvant therapy for women with early breast cancer following the first demonstration of efficacy more than 20 years ago [1]. Administration of tamoxifen for 5 years has been shown to reduce breast cancer recurrence by 41% and mortality by 34% in women with hormone-responsive tumors [2]. Nevertheless, many limitations of tamoxifen have emerged with widespread use. In the landmark National Surgical Adjuvant Breast and Bowel Project B-14 trial, 66% of tamoxifen-treated patients experienced side effects compared with 58% of patients given placebo [3]. Severe, potentially life-threatening events such as thrombosis were more likely to occur in patients aged >60 years [3]. Long-term adverse effects associated with 5 years' adjuvant tamoxifen include venous thromboembolic events, vaginal bleeding, vaginal discharge, ischemic cerebrovascular events, endometrial and uterine cancer, and hysterectomy [3, 4]. Experiencing side effects significantly increases the likelihood of patients discontinuing tamoxifen therapy (odds ratio 4.0; 95% confidence interval [CI] 1.1, 13.9 in women aged ≥ 55 years) [5]. Over time, resistance to tamoxifen may develop [6], and therapy beyond 5 years is not recommended because neither further disease-free survival nor survival benefit is gained [7].

The third-generation aromatase inhibitors (AIs) letrozole, anastrozole, and exemestane are rapidly replacing tamoxifen as initial adjuvant therapy [8, 9] or sequential adjuvant therapy after 2–5 years of tamoxifen [10–13]. By potently inhibiting the aromatase enzyme, which converts androgens to estrogen [14, 15], AIs achieve almost total suppression of total body aromatization and dramatic reductions in estrogen concentrations in postmenopausal women [16–18]. AIs are now recommended in

international guidelines for the management of breast cancer [19–21]. In addition, guidance is being developed for the management of common co-morbidities such as osteoporosis in postmenopausal women with hormone-sensitive breast cancer receiving AIs [20, 22]. This review examines the safety of AIs and assesses their advantages and disadvantages compared with tamoxifen. It also considers the impact of treatment on co-morbidities commonly encountered in this population.

Possible impact of treatment on common co-morbidities

Adjuvant therapy should be individualized on the basis of clinical and biologic risk factors [21], including the presence of co-morbidities [23–26]. The most prevalent co-morbidities in the postmenopausal patient population are hypertension, arthritis, heart disease, diabetes, chronic obstructive pulmonary disease, eye problems, anemia, depression, fractures, hearing problems, osteoporosis, Parkinson's disease, renal failure, and urinary tract problems [25]. Understanding the long-term effects of aromatase inhibition on bone and cardiovascular health are particularly important to consider because of the potential effects of altering estrogen concentrations.

Bone disease

Bone health typically may deteriorate as women age, particularly after reaching menopause [27, 28]. A decline in estrogen concentrations accelerates postmenopausal bone loss [29–31] while vitamin D deficiency also increases bone turnover and the risk of fracture [32, 33]. It is important to note that bone health is compromised in women with breast cancer compared with the general population [34]. In the Women's Health Initiative Observational Study, breast cancer survivors had significantly lower total body bone mineral density (BMD) and total hip BMD [34] and a significantly higher risk of clinical fractures [35]. Of concern, osteoporosis was undiagnosed in more than three quarters of breast cancer survivors and the reference population [34]. Multiple factors contribute to the increased risk of osteoporosis and fractures in postmenopausal women with breast cancer [34]. Furthermore, tumor cells can have a direct effect on bone remodeling [36], and breast cancer therapy can lead to cancer treatment-induced bone loss (CTIBL) [37–39]. In a large cohort study, patients with early breast cancer who received anticancer therapy had a 30% higher risk for osteoporosis/osteopenia (odds ratio 1.29; 95% CI 1.13, 1.46) [38]. The study also showed that other factors such as poor health status, history of smoking, and alcohol abuse can contribute to CTIBL.

The most serious consequence of CTIBL is an increased risk of fractures (Fig. 1) [35], which increase morbidity and healthcare costs [40]. The presence of bone metastases can contribute to CTIBL and lead to serious complications, including fractures, spinal compression, bone pain, and hypercalcemia of malignancy [41].

Aromatase inhibitors and bone disease

In a recent study, the bone health of 1,354 patients with breast cancer receiving an AI (anastrozole, exemestane, or letrozole) was compared with 11,014 controls [39]. Treatment with an AI increased the risk of bone loss (relative risk 1.3; 95% CI 1.1, 1.6; $P = 0.01$) and bone fracture (relative risk 1.4; 95% CI 1.2, 1.6; $P = 0.001$). The risks remained significantly higher for AI therapy after adjustment for age and co-morbidities [39]. An increase in the incidence of arthralgia is noted with all three AIs, when compared with tamoxifen.

Anastrozole

Howell and colleagues reported fracture rates after a median follow-up of 68 months in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [42]. Fractures were reported in 577 (9.3%) of the 6,186 patients and were more common with anastrozole than with tamoxifen (11 vs. 8%, respectively; $P < 0.0001$). The incidence of hip fractures was 1% in both groups. The rate of fractures was low at approximately 2% per year and decreased to baseline levels after completion of 5 years of treatment. The effects of anastrozole and tamoxifen on BMD were assessed in a

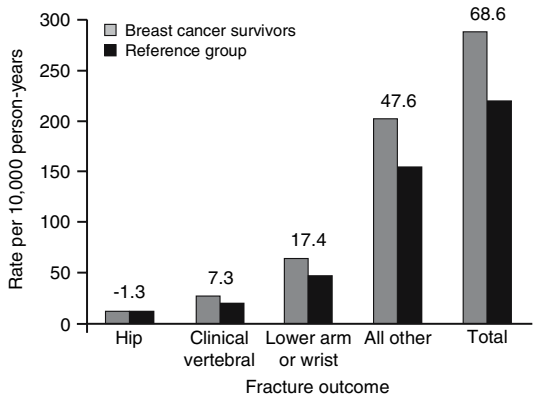

Fig. 1 Age-standardized fracture incident rates by survivor status. Standardized rates were calculated using the age distribution of the entire Women's Health Initiative Observational Study cohort. Excess numbers of fractures per 10,000 person-years are above each set of bars [35]. ©2005 American Medical Association. Reproduced with permission

sub-analysis of 167 patients from the ATAC trial [43]. Anastrozole-treated patients had significant decreases in lumbar spine BMD (–8.1%; 95% CI –10.1, –6.1; $P < 0.0001$) and total hip BMD (–7.4%; 95% CI –9.6, –5.3; $P < 0.0001$) relative to tamoxifen-treated patients, in whom small increases were observed. Bone loss was greatest in the first 2 years of anastrozole treatment, as reported previously [44], but the rate of loss appeared to slow down from years 2 to 5. In the updated analysis after a median follow-up of 68 months, osteopenia or osteoporosis was reported in 11% of patients receiving anastrozole compared with 7% receiving tamoxifen ($P < 0.0001$) [42, 45]. Another sub-analysis of the ATAC trial showed that the majority of joint symptoms occur within 24 months of initiating treatment [46]. After 68 months' median follow-up, joint symptoms were reported in 35.6 and 29.4% of patients in the anastrozole and tamoxifen arms, respectively. Most symptoms were mild in intensity, and 46% were reported as an exacerbation of a pre-existing condition. The incidence of serious joint symptoms was similar for anastrozole and tamoxifen (10.6 vs. 10.4%, respectively) and only 2.1 and 0.9%, respectively, discontinued treatment because of joint symptoms. After a median follow-up of 68 months, muscle cramps were less common with anastrozole than tamoxifen (4 vs. 8%, respectively; $P < 0.0001$), whereas carpal-tunnel syndrome was more common with anastrozole (3 vs. 1%, respectively; $P < 0.0001$) [42].

These updated results from the ATAC trial confirm that AIs are a well-tolerated initial treatment option in terms of bone health [43, 45, 46]. Although anastrozole is associated with BMD loss, no patient with normal bone at baseline became osteoporotic after 5 years of treatment, and the rate of bone loss in the lumbar spine region slowed down in years 2–5.

The ARNO/ABCSG8 trials investigated the efficacy and safety of switching to anastrozole after 2 years of tamoxifen [12]. Although there were significantly more fractures in patients switching to anastrozole (2.1%) than in those continuing on tamoxifen (1.0%) [12], the rate was lower than that seen at a similar point in the ATAC trial [12]. In the Italian Tamoxifen Anastrozole (ITA) trial, switching to anastrozole after 2–3 years of tamoxifen was not associated with an increase in fracture rate, although differences may emerge with longer follow-up [13].

Letrozole

In the Breast International Group (BIG) 1–98 trial of initial adjuvant therapy, there was a slight yet significant difference in the incidence of fractures (5.7% with letrozole vs. 4.0% with tamoxifen; $P < 0.001$) [8]. The MA.17 trial of extended adjuvant therapy showed that when compared with placebo, letrozole had no significant impact on fractures [10]. There was a small but significant difference in patient-reported diagnoses of new-onset osteoporosis (8% letrozole vs. 6% placebo, $P = 0.003$), and arthralgia and myalgia were significantly more common with letrozole than placebo [10]. A companion study to MA.17 demonstrated a significant decrease in lumbar spine BMD (–5.35 vs. –0.70%; $P = 0.008$) and total hip BMD (–3.6 vs. –0.71%; $P = 0.044$) over 2 years in patients treated with letrozole compared with placebo, although no patient went below the threshold for osteoporosis in total hip BMD [47]. Data from this companion study suggest that women with a BMD score of –1.0 or greater when starting letrozole after tamoxifen are less vulnerable to enhanced bone resorption and may not require prophylactic bisphosphonate therapy.

Exemestane

In a model of ovariectomized rats, the steroidal AI exemestane was shown to prevent bone loss, presumably via its androgenic properties (both exemestane and its metabolite 17-hydro-exemestane demonstrate affinity for the androgen receptor) [48]. However, a randomized study to compare the effects of progestins and AIs on bone remodeling markers in patients with metastatic breast cancer found that exemestane increased osteoclast activity [49]. In the adjuvant treatment setting, a randomized trial involving 147 patients with early breast cancer demonstrated a non-significant effect of exemestane compared with placebo on the annual rate of BMD loss in the lumbar spine (2.17 vs. 1.84%; $P = 0.568$) and a small but significant effect in the femoral neck (2.72 vs. 1.48%; $P = 0.024$) [50]. Of note was the finding that BMD may rapidly improve following AI discontinuation: this trial showed that bone resorption markers returned to or below baseline values, and bone formation markers remained moderately increased within 6 months of stopping exemestane [51].

In the Intergroup Exemestane Study (IES) of exemestane following 2–3 years of tamoxifen, fractures were reported more frequently with exemestane than with tamoxifen after a median follow-up of 30.6 months, although this difference was not statistically significant (3.1 vs. 2.3%; $P = 0.08$) [52]. However, the difference in incidence of fractures was statistically significant (7.0% with exemestane vs. 4.9% with tamoxifen; $P = 0.003$) after a median follow-up of 55.7 months [11]. The incidence of osteoporosis was also significantly higher with exemestane than with tamoxifen (9.2 vs. 7.2%, respectively; $P = 0.01$). Recent results from a 1-year sub-study revealed that patients on exemestane experienced a significant decrease in hip BMD, while patients on tamoxifen did not [53]. These results were confirmed by another recent study, which evaluated the effects of exemestane on bone turnover markers and BMD in 70 postmenopausal women

(62.0 ± 8.9 years) with early breast cancer who were switched to exemestane after 2–3 years on tamoxifen [54]. Patients in the exemestane group had a significant decrease in BMD and early parathyroid hormone (at month 6) and an increase in bone alkaline phosphatase (B-ALP) and the carboxy-terminal telopeptide of type I collagen after 24 months. These studies suggest that switching postmenopausal women from tamoxifen to exemestane causes a marked increase in bone turnover markers with a consequent reduction in BMD.

Arthralgia was also significantly more common with exemestane than with tamoxifen (5.4 vs. 3.6%, $P = 0.01$) in the IES [52]. A study by Lønning et al. discovered a high prevalence of vitamin D deficiency in postmenopausal women treated with exemestane (52 of 59 patients) or placebo (56 of 62 patients), and this could be the most important factor causing bone loss in both groups [55]. Vitamin D substitution is therefore recommended for postmenopausal women, particularly those with breast cancer receiving an AI. The incidence of carpal-tunnel syndrome in the IES was higher in the exemestane arm (2.8%) than in the tamoxifen arm (0.4%; $P < 0.001$) [11].

Comparative studies of aromatase inhibitors

A randomized trial (Letrozole, Exemestane, and Anastrozole Pharmacodynamics [LEAP]) of healthy volunteers demonstrated that letrozole, exemestane, and anastrozole have similar effects on bone biochemical measurements and all result in increases in bone turnover [56]. There were no statistically significant differences between the AIs in changes from baseline to 24 weeks for B-ALP, serum C-telopeptide crosslinks, and propeptide of type I procollagen. The only difference in the bone remodeling markers was a greater decrease in parathyroid hormone with exemestane than with anastrozole ($P = 0.04$).

Thus, all AIs seem to have similar effects on bone health. The ATAC bone sub-study results are reassuring for the entire AI class, and women with breast cancer who have normal BMD measurements at the onset of AI treatment may be able to undergo 5 years of therapy without the risk of developing osteoporosis. Patients at risk of clinically relevant BMD loss during treatment should be identified and managed according to evolving clinical guidelines [20, 57].

Bisphosphonates

In the American Society of Clinical Oncology (ASCO) guidelines postmenopausal patients with breast cancer who receive AIs are identified as being at high risk for osteoporosis, and it is recommended that they have baseline BMD evaluation and regular monitoring to guide subsequent therapeutic interventions such as bisphosphonates [20, 58]. Preliminary results have been reported from a small number of clinical trials of bisphosphonates in women receiving adjuvant AI therapy. In one trial, premenopausal breast cancer patients receiving goserelin plus anastrozole or goserelin plus tamoxifen were randomly assigned to the bisphosphonate zoledronic acid (ZA) (4 mg IV every 6 months) or placebo. After 36 months, it was shown that ZA given every 6 months helped prevent bone loss in these premenopausal patients in both the lumbar spine and hip regardless of endocrine therapy [59]. Two randomized trials have shown that bisphosphonates may be beneficial in postmenopausal patients at a higher risk of osteoporosis [60, 61]. In the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) (North American) trial, 602 postmenopausal women with hormone-responsive breast cancer starting adjuvant therapy with letrozole were randomized to receive upfront ZA (4 mg IV infusion every 6 months) or delayed ZA when indicated (either post-baseline T-score decreases < -2 SD or occurrence of fracture) [60, 62]. Preliminary results after 12 months' follow-up indicate that initial treatment with ZA may be used to prevent CTIBL, and results at 24 months confirm these initial findings [62, 63] although the rate of clinical fractures was not changed. In addition, the small proportion of patients (8%) requiring ZA in the first year highlights the short-term bone tolerability of letrozole [62]. Results from the similarly designed ZO-FAST (European; N = 1,065) trial also support the use of ZA to potentially manage CTIBL in postmenopausal women with early breast cancer receiving adjuvant letrozole [61].

Lipid metabolism: A cohort study demonstrated that total and low-density lipoprotein (LDL) cholesterol concentrations are positively correlated with years since diagnosis of breast cancer [64]. In addition, during menopause, women experience adverse changes in cardiovascular risk factors, including declines in concentrations of high-density lipoprotein (HDL) cholesterol and increases in concentrations of total cholesterol, LDL cholesterol, HDL3 cholesterol, and triglycerides [65, 66]. These changes are independent of age and body mass index.

Assessing the impact of AIs on lipid profiles is difficult in trials where tamoxifen is the comparator. The selective estrogen-receptor modulators (SERMs) such as tamoxifen are known to have lipid-lowering properties [67, 68]. What is clear is that the studies comparing AIs with tamoxifen indicate only that the AIs lack the lipid-lowering effects of tamoxifen.

Aromatase inhibitors and lipid metabolism

Anastrozole

In the ATAC trial, the incidence of hypercholesterolemia was higher in patients receiving anastrozole than tamoxifen (9 vs. 3%, respectively; $P < 0.0001$) [42]. In the ITA trial, lipid metabolism disorders were reported in 9.3% of patients treated with anastrozole and 4.0% receiving tamoxifen ($P = 0.04$) [13].

A recent multicenter study in patients with estrogen-receptor positive breast cancer investigated the effects of adjuvant anastrozole and toremifene, a SERM, on serum lipids [68]. Results showed that only toremifene had a beneficial effect on lipid profile, indicated by a decrease in total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, and an increase in HDL cholesterol and apolipoprotein A1. Changes in total cholesterol, HDL, LDL, and apolipoproteins were significantly different between toremifene and anastrozole at 6 and 12 months ($P < 0.05$).

Letrozole

In the BIG 1–98 trial, according to the protocol, cholesterol concentrations (fasting or non-fasting) were collected systematically in the case-report forms every 6 months and even patients with only a single measurement above the upper limit of normal were defined as hypercholesterolemic [8]. Hypercholesterolemia was reported in 5.4% of the letrozole arm compared with 1.2% of the tamoxifen arm in patients with baseline values within normal limits, who then had an increase of 1.5 times the upper limit of normal [69]. Hypercholesterolemia was typically a single event and in the majority of these patients (80%) occurred at only grade 1 intensity (meaning a slight numerical increase above normal, not requiring medications). Moreover, the majority of cases were single measurements collected in non-fasting patients. Furthermore, when looking at total serum cholesterol levels, there was a 12% median decrease from baseline in total cholesterol in the tamoxifen arm after 6 months, consistent with previous reports demonstrating the lipid-lowering effect of tamoxifen [67], while in the letrozole group total cholesterol values remained stable [8]. Hypercholesterolemia was not predefined as an adverse event in the ATAC trial, and lipid concentrations were not routinely assessed [42].

Exemestane

Hypercholesterolemia was not reported in the IES trial of sequential exemestane after tamoxifen [11, 52].

Another study examined the longitudinal changes in body composition and lipid profiles in 55 postmenopausal women with early breast cancer switched to exemestane after at least 2 years of tamoxifen treatment [70]. Fat mass significantly decreased ($P < 0.01$) while the fat-free mass to fat mass ratio significantly increased ($P < 0.05$) by month 12 in the exemestane but not in the tamoxifen group. In addition, triglycerides and HDL cholesterol significantly decreased ($P < 0.01$ and $P < 0.05$, respectively) in the exemestane group, while LDL cholesterol significantly increased ($P < 0.01$) at the end of the 1-year study period.

Aromatase inhibitors versus placebo

When compared with placebo (the most accurate way to assess the true impact of AIs on serum lipids), the final analysis of the MA.17 trial demonstrated the incidence of hypercholesterolemia was 16% in the letrozole and the placebo arms [10]. Results from an MA.17 lipid sub-study showed that in 347 postmenopausal women with primary breast cancer treated for up to 36 months, letrozole ($n = 183$) does not significantly alter lipid profile (samples drawn under fasting conditions) compared with placebo ($n = 164$) [71]. In a placebo-controlled study involving 147 postmenopausal women with early breast cancer, exemestane had no major effect on lipid profile except for a modest but significant decrease from baseline in HDL cholesterol ($P < 0.001$) and apolipoprotein A1 ($P = 0.004$) [50]. On the basis of these results, it is clear that when compared with placebo, AIs do not have a detrimental effect on lipid profile. However, it should be noted that there have been no placebo-controlled trials of adjuvant anastrozole in women with breast cancer.

Comparative studies of aromatase inhibitors

The LEAP trial directly compared safety parameters between the steroidal AI exemestane and the non-steroidal AIs anastrozole and letrozole in 90 healthy postmenopausal women (Table 1) [72]. Initial results from the trial showed that there were no significant differences between anastrozole and letrozole in effects on LDL:HDL ratios, triglyceride concentrations, and non-HDL concentrations. Exemestane was associated with an increase in LDL:HDL ratio (+17) ($P = 0.047$) compared with anastrozole. There was no median change from baseline in total serum cholesterol for letrozole, a slight increase for anastrozole (+0.4), and a non-significant decrease for exemestane (–3.9) ($P = 0.164$ vs. anastrozole) [72].

Table 1 Comparative effects of third-generation aromatase inhibitors on lipids [72]

Percentage change from baseline	Anastrozole (n = 29)	Letrozole (n = 29)	P value vs. anastrozole	Exemestane (n = 32)	P value vs. anastrozole
Total cholesterol					
Week 12	–2.3	–3.8	0.617	–5.5	0.262
Week 24	+0.4	–0.0	0.900	–3.9	0.164
Triglycerides					
Week 12	–2.9	+9.6	0.037	–7.7	0.417
Week 24	+0.3	+5.4	0.550	+2.1	0.827
Ratio of LDL-C:HDL-C					
Week 12	–0.0	–3.1	0.486	+8.8	0.048
Week 24	+4.6	+3.4	0.847	+17.0	0.047
Non-HDL-C					
Week 12	–2.7	–4.2	0.667	–3.5	0.820
Week 24	+1.3	+1.2	0.975	–0.6	0.630
Ratio of apo B:apo A1					
Week 12	–1.0	–3.3	0.452	+4.4	0.069
Week 24	+0.0	–0.8	0.842	+9.0	0.023

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein, *apo B* apolipoprotein B, *apo A1* apolipoprotein A1

Cardiovascular disease

Cardiovascular risk increases substantially and progressively in women aged ≥65 years [73–77]. Isolated systolic hypertension, associated with arterial stiffening, is predominant in middle- and older-aged hypertensives [75] and predisposes individuals to coronary heart disease, heart failure, stroke, vascular dementia, and chronic kidney disease [73]. The risk of cardiac disease is also influenced by ethnicity, smoking, obesity, physical inactivity, alcohol abuse, and the presence of co-morbid diseases such as diabetes.

In patients with breast cancer the presence of co-morbidities, including cardiovascular disease and diabetes, is associated with a poorer prognosis than when co-morbid disease is absent [78] and may explain disparities in outcome between different ethnic groups [79]. There is also evidence that breast cancer is associated with a higher prevalence of hypertension compared with other tumor types [80] and a significantly increased risk of stroke compared with the general population (relative risk 1.12; 95% CI 1.07, 1.17) [81]. Many breast cancer therapies increase the risk of cardiovascular events [82–88]; tamoxifen, however, may have some cardio-protective effects [89, 90].

Tamoxifen and cardiovascular disease

Several studies have demonstrated the potential cardioprotective properties of tamoxifen, including a reduction in hospital admissions due to cardiac disease [89–91] and decreased mortality from cardiac disease [92]. In a meta-analysis, tamoxifen was associated with a significantly decreased incidence of myocardial infarction (relative risk 0.90) and death from myocardial infarction (relative risk 0.62) [93]. This finding is consistent with results from an earlier cohort study [94] and the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which demonstrated decreases in the risk of cardiac death and overall mortality from vascular disease in patients receiving tamoxifen compared with those receiving placebo [2].

Aromatase inhibitors and cardiovascular disease

Assessing the impact of different AIs on cardiovascular disease in postmenopausal women with breast cancer is difficult and inter-trial comparisons are confounded by differences in data collection and end points; for example, in the BIG 1–98 trial all potential adverse events were predefined in the case-report forms whereas the ATAC trial used non-specific case-report forms to report adverse events [8, 95]. Furthermore, comparisons with tamoxifen are complicated by its cardioprotective properties. Placebo-controlled trials thus provide the best source of data to delineate the effects of AIs in a patient population with an inherently elevated risk of cardiac events.

Anastrozole

The ATAC trial provided data on the cardiovascular effects of anastrozole as initial adjuvant therapy compared with

tamoxifen. The incidence of ischemic cardiovascular disease was higher (but not significantly) with anastrozole than placebo (127/3092, 4.1% vs. 104/3094, 3.4%; $P = 0.1$). The incidence of angina was also higher with anastrozole (71/3092, 2.3% vs. 51/3094, 1.6%; $P = 0.07$), while myocardial infarction occurred with similar frequency (37/3092, 1.2% vs. 34/3094, 1.1%; $P = 0.7$ [42]. Hypertension was statistically significantly more common with anastrozole than with tamoxifen (13 vs. 11%, respectively; $P = 0.04$) [42]. In the ARNO95 trial vascular events, including hot flashes, ischemic cardiovascular events, deep vein thrombosis, and ischemic cerebrovascular events, occurred in 9.2% of the anastrozole arm compared with 8.8% of the tamoxifen arm [96].

Letrozole

The BIG 1–98 trial demonstrated a similar incidence of cardiac events in the letrozole and tamoxifen groups (4.1 vs. 3.8%, respectively; not significant). However, more women in the letrozole group had grade 3, 4, or 5 cardiac events (2.1 vs. 1.1%, respectively; $P < 0.001$), but these events remain rare [8]. Of note, a recent update of the monotherapy arms of BIG 1–98 after a longer median follow-up of 51 months showed that the overall incidence of cardiac events was comparable in the two groups (134 events [5.5%] in the letrozole group vs. 122 [5.0%] in the tamoxifen arm), thus confirming the safe cardiac profile of letrozole reported at 26 months [97].

Exemestane

In the IES, there was no significant difference between exemestane and tamoxifen in the incidence of combined cardiovascular disease/thromboembolic events (22.1 vs. 20.9%, respectively; $P = 0.34$) after a median follow-up of 55.7 months [11]. The incidence of myocardial infarction was higher with exemestane than with tamoxifen, although the difference between treatment groups was not significant (1.3 vs. 0.8%, respectively; $P = 0.08$) [11].

Overall, the rate of cardiovascular events in patients treated with AIs is well within the range seen in age-matched, non-breast-cancer populations; for example, for women 57–65 years of age, the rates of fatal myocardial infarction and other fatal coronary artery disease are 1.1 and 0.81 per 1,000 patient-years, respectively [98]. Similar rates were recorded in the UK General Practice Research Database and Swedish MI register [99]. Currently, there is insufficient information to fully determine the effect of AIs on cardiovascular disease, especially coronary heart disease.

Aromatase inhibitors versus placebo

Cardiovascular events occurred with similar frequency in the letrozole and placebo arms in the MA.17 trial (5.8 vs. 5.6%, respectively; $P = 0.76$) [10]. Similar incidences were reported in the letrozole and placebo arms for stroke/transient ischemic attack (0.7 vs. 0.6%, respectively), myocardial infarction (0.3 vs. 0.4%, respectively), new or worsening angina (1.2 vs. 0.9%), angina requiring coronary artery bypass graft (0.2 vs. 0.5%), and thromboembolic events (0.4 vs. 0.2%, respectively) [10]. These results clearly indicate that when compared with placebo, AIs do not have a detrimental effect on cardiovascular safety.

Gynecologic health

The onset of menopause is characterized by numerous adverse events associated with a decline in estrogen concentrations [100–102]. Early symptoms include abnormal vaginal bleeding, hot flashes, and mood changes, while vaginal dryness and irritation, osteoporosis, and heart disease are late symptoms [29, 103, 104]. Vasomotor symptoms, particularly hot flashes, are common during transition to menopause [105–109] and may lead to disturbed sleep, depressive symptoms, and significant reductions in quality of life [110–115]. Cigarette smoking may be associated with increased risk of hot flashes in menopausal women [116]. Sexual dysfunction is also prevalent in menopausal women and is associated with vaginal atrophy, vaginal/genital dryness, dyspareunia (pain during sexual intercourse), vaginitis, cystitis, and urinary tract infections [117].

Aromatase inhibitors and gynecologic health

Anastrozole

In the ATAC trial, the incidence of hot flashes was significantly lower with anastrozole than with tamoxifen (36 vs. 41%; $P < 0.0001$) [9]. In the latest analysis, anastrozole was associated with a significantly lower incidence of gynecologic events (endometrial hyperplasia, endometrial neoplasia, cervical neoplasm, and enlarged uterine fibroids: 3 vs. 10% with tamoxifen; $P < 0.0001$) [42]. A quality-of-life (QOL) analysis confirmed that vaginal discharge, vaginal itching/irritation, and vaginal bleeding were less common with anastrozole but found that vaginal dryness, pain during intercourse, and loss of interest in sex were more common [118]. After 2 years of treatment there was a non-significant trend towards a lower incidence of endometrial abnormalities with anastrozole than tamoxifen

(odds ratio 0.44; 95% CI 0.146, 1.314; $P = 0.14$) [119]. The latest update of the ATAC trial revealed reduced libido in significantly more patients receiving anastrozole (1%) than tamoxifen (<1%; $P = 0.0001$) [42]. Patients receiving anastrozole also experienced a significantly higher incidence of dyspareunia than those receiving tamoxifen (1 vs. < 1%, respectively; $P = 0.002$), whereas urinary incontinence and urinary tract infection were significantly less common among patients receiving anastrozole (urinary incontinence: 2 vs. 4%, respectively, $P < 0.0001$; urinary tract infection: 8 vs. 10%, respectively, $P = 0.002$).

In a randomized study of postmenopausal women in whom abnormal vaginal bleeding and/or asymptomatic endometrial thickening occurred during treatment with tamoxifen, switching to anastrozole was associated with a significant reduction in mean endometrial thickness compared with continuation of tamoxifen ($P < 0.0001$) [120]. Significantly fewer anastrozole patients required a repeat hysteroscopy and dilation and curettage compared with those taking tamoxifen (4.8 vs. 33.0%, respectively; $P < 0.0001$).

Letrozole

In the BIG 1–98 trial [8], endometrial biopsies were significantly less common in patients receiving letrozole than tamoxifen (2.3 vs. 9.1%, respectively; $P < 0.001$), and there was a trend towards fewer invasive endometrial cancers (0.1 vs. 0.3%, respectively; not significant). There was a significantly lower incidence of vaginal bleeding with letrozole than with tamoxifen (3.3 vs. 6.6%, respectively; $P < 0.001$), and the incidence of hot flashes was also significantly lower (33.5 vs. 38.0%, respectively; $P < 0.001$). In another study in patients intolerant of tamoxifen, switching to letrozole for 6 weeks was associated with a 53.7% decrease in hot flashes (hot-flash score 97.0–52.1; $P = 0.001$) [121]. In the MA.17 trial, letrozole was associated with less vaginal bleeding than placebo (6 vs. 8%, respectively; $P = 0.005$) but a greater incidence of hot flashes (58 vs. 54%, respectively; $P = 0.003$) [10]. There was no significant difference in the incidence of vaginal dryness between letrozole and placebo.

Exemestane

In the IES, there were no significant differences between the exemestane and tamoxifen treatment arms in the incidence of endometrial cancer (0.4 vs. 0.7%, respectively; $P = 0.17$) [11], or the incidence of hot flashes (42 vs. 40%, respectively; $P = 0.28$) [52]. Overall, gynecologic symptoms were lower with exemestane than with tamoxifen (6 vs. 9%; $P < 0.001$) [52]; however, vaginal dryness was significantly more common among women taking exemestane than those taking tamoxifen, while vaginal discharge was significantly more common with tamoxifen [122]. Vaginal bleeding was significantly more common in the tamoxifen arm (7.1%) than in the exemestane group (4.8%; $P = 0.001$) [11].

Other adverse events

Secondary cancer

The association between tamoxifen and endometrial and uterine cancers is well-established [4] and is not observed with AIs. However, a safety analysis of the ATAC trial [42] showed a surprisingly higher incidence of head and neck cancer with anastrozole compared with tamoxifen (10/3092 vs. 3/3094, respectively). Similarly, there was an excess of lung cancer (25/3092 vs. 16/3094) and lung cancer deaths with anastrozole; however, further analyses are required to confirm these findings. Of note, a higher incidence of secondary cancer was not noted in the IES (72 events exemestane vs. 107 tamoxifen) or in the BIG 1–98 trial (69 letrozole vs. 82 tamoxifen) [8, 11].

A meta-analysis showed that tamoxifen is associated with a modest but statistically significant increase in the risk of developing gastrointestinal cancer (relative risk 1.31; 95% CI 1.01, 1.69), particularly for postmenopausal women (relative risk 1.77) [93].

Gastrointestinal health

Diarrhea was significantly more common among patients receiving the steroidal AI exemestane than in those taking tamoxifen (4.2 vs. 2.2%, respectively) [123] but is not a typical side effect of the non-steroidal AIs letrozole and anastrozole. However, an updated safety analysis of the ATAC trial showed that anastrozole was associated with an increased incidence of diarrhea compared with tamoxifen (9 vs. 7%; $P = 0.02$) [42].

Neurologic effects and visual disturbance

It has been suggested that endocrine therapy may affect cognitive function in patients with breast cancer [124]. In a study comparing patients from the ATAC trial with healthy controls, anastrozole was associated with significant impairments in a processing speed task and on a measure of immediate verbal memory [125]. Another study conducted in healthy, estrogen-treated postmenopausal women treated

with testosterone did not reveal any effects of aromatase inhibition on cognition [126].

The impact of adjuvant AI therapy on cognition and other neurologic processes is clearly an important issue that will require further studies in the future. Neurologic effects reported with exemestane, including dizziness and vertigo [127] and significantly more visual disturbances compared with tamoxifen [52], are not characteristic of non-steroidal AIs.

Dry mouth

The latest analysis of the ATAC trial demonstrated a significantly greater incidence of dry mouth in patients receiving anastrozole (4%) compared with tamoxifen (2%; $P = 0.003$) [42].

Cosmetic effects

Weight gain is common after breast cancer therapy and increases the risk of recurrence, cardiovascular disease, and diabetes [64]. A study of Japanese patients showed that more women reported weight gain in the anastrozole group than in the tamoxifen group (35.8 vs. 12.5%, respectively; $P \leq 0.0036$) [128], but no difference was seen among patients from the ATAC trial included in a QOL sub-analysis [118].

The androgen structure of exemestane may lead to androgenic side effects. Hypertrichosis, hair loss, hoarseness, and acne were reported in about 10% of patients treated with daily exemestane doses of 200 mg or more in dose-finding studies [129, 130], but have not emerged as a significant issue in phase II or phase III trials with this agent.

Anastrozole treatment was associated with a lower incidence of nail disorders (2 vs. 3%; $P = 0.002$) and fungal infection (1 vs. 1%; $p = 0.01$) compared with tamoxifen [42].

Quality of life and patient preference

Anastrozole

The QOL of patients treated in the ATAC trial was studied during a 5-year follow-up period [118, 131]. Anastrozole and tamoxifen had similar overall effects on QOL (Functional Assessment of Cancer Therapy-Breast [FACT-B] trial outcome index plus endocrine sub-scale) in the first 2 years of treatment [118], and an initial worsening of endocrine symptoms gradually improved over time [131]. The authors concluded that the benefits of anastrozole are achieved without detrimental effects on QOL. However, another study conducted in Japanese patients demonstrated that FACT-G, FACT-B, and FACT-ES scores were significantly better with tamoxifen than with anastrozole ($P = 0.012$, $P = 0.010$, and $P = 0.015$, respectively) [132].

Letrozole

The MA.17 and BIG 1–98 trials have demonstrated that adjuvant letrozole is well-tolerated compared with placebo [10] and better tolerated than tamoxifen [8]. In another study of postmenopausal women who were experiencing distressing side effects while taking adjuvant tamoxifen and were switched to letrozole, after 6 weeks 66% of patients preferred to remain on letrozole, 24% preferred to go back to tamoxifen, and 10% stopped all therapy [121].

In the placebo-controlled MA.17 trial, letrozole significantly improved outcomes and did not impair overall QOL [133] (Fig. 2). Minor differences seen in some domains (physical functioning, bodily pain, vitality, vasomotor, and sexual) were consistent with a minority of patients experiencing changes in QOL compatible with a reduction in estrogen synthesis. A sub-analysis of US subjects in MA.17 demonstrated no significant differences between letrozole and placebo in overall QOL summary scores (mental and physical) and five of eight sub-domains of SF-36 [134]. There were no differences in SF-36 mental and physical

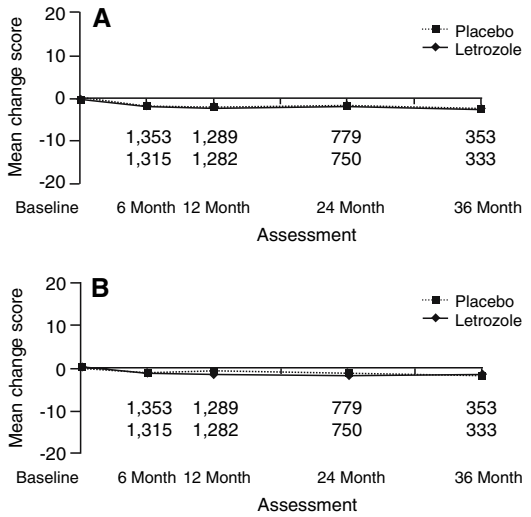

Fig. 2 Mean change score in Short Form 36-item Health Survey. A positive score indicates a favorable change in quality of life. (**A**) Physical component summary; P = not significant for all time points. (**B**) Mental component summary; P = not significant for all time points. [133]. ©2005 American Society of Clinical Oncology. Reproduced with permission

QOL scores and MENQOL (menopause symptom scale) psychosocial and physical domains [134].

Exemestane

Results from the IES QOL sub-protocol indicate that switching to exemestane from tamoxifen improves outcome without a significant detrimental impact upon QOL [135]. At entry, there was a high prevalence of severe endocrine symptoms (vasomotor complaints and sexual problems), and these persisted with exemestane and tamoxifen during the study. No significant differences between groups were seen for any endocrine symptoms apart from vaginal discharge, which was more pronounced with tamoxifen ($P < 0.001$).

Conclusions

Clinical trials show that the third-generation AIs lack the serious risks of thromboembolism and endometrial cancers associated with tamoxifen and are generally well tolerated, with the majority of adverse events occurring at mild to moderate intensity [8–11].

AIs are associated with a mild to modest increased risk of osteoporosis compared with tamoxifen, and it is therefore essential that patients have regular BMD assessments and be monitored proactively to minimize the risk of clinical fractures [20, 57]. The increased risk of fractures with an AI compared with tamoxifen needs to be balanced against the increased risk of endometrial and cerebrovascular/thromboembolic morbidity with tamoxifen [136]. Of note, the updated ATAC analysis shows that the majority of excess adverse events associated with tamoxifen occurred during the first 2.5 years of treatment; there were 142 (8%) fewer predefined adverse events in the anastrozole arm [137]. Thus, it appears that many excess gynecologic, thromboembolic, and cerebrovascular adverse effects occurring in tamoxifen-treated patients could be avoided if patients were treated initially with an AI [136].

Although AIs do not have the cholesterol-lowering and potential cardioprotective properties of tamoxifen, they do not significantly worsen total cholesterol concentrations and do not appear to increase cardiovascular risk when compared with placebo. Nevertheless, it is prudent to recommend that all patients at risk of cardiovascular effects are properly monitored and managed, and all breast cancer patients should be routinely monitored for cardiovascular disease. It is difficult to draw meaningful conclusions from comparisons of randomized trials of tamoxifen versus anastrozole, letrozole, or exemestane because of differences in assessing and reporting risk of cardiovascular disease [8, 52, 95, 138].

Current information is insufficient to determine the effects of AIs on cardiovascular disease and coronary heart disease risk [20]. Similarly, further follow-up is required to determine the late consequences of AI therapy [20]. Despite these provisos, ASCO now recommends that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an AI as initial therapy or after treatment with tamoxifen. Results from several ongoing trials, including the Femara versus Anastrozole Clinical Evaluation, MA.27, the National Surgical Adjuvant Breast and Bowel Project, LATER, and MILER, should provide more information on the long-term tolerance and the optimal duration of adjuvant AI therapy and help determine which strategy has the best ratio of efficacy to tolerance.

In conclusion, the efficacy benefits of AIs outweigh the risks when AIs are used as adjuvant therapy in postmenopausal women with early breast cancer. Safety, QOL, and patient preference must all be considered in the determination of the optimal strategy for long-term endocrine therapy, bearing in mind that patients may require treatment for 10 years or more. Every patient is unique, and endocrine therapy must be individualized according to clinical, biologic, and patient factors such as lifestyle, the presence of significant co-morbidities, and use of concomitant medications. Tolerability should no longer be an obstacle to effective, long-term endocrine therapy.

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