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EXPERT REVIEW

Exemestane in the Adjuvant Treatment of Breast Cancer in Postmenopausal Women

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Abstract: Exemestane is an irreversible inhibitor of the aromatase enzyme, which is a key component in the production of estrogen. The majority of breast cancers are sensitive to the proliferative effects of estrogen. Exemestane is approved for the adjuvant treatment of postmenopausal women with breast cancer after 2 to 3 years of tamoxifen therapy, based on a 32% improvement in disease-free survival compared with 5 years of tamoxifen alone ($P < 0.001$). Exemestane has also shown clinical benefits as an upfront therapy. The safety profile of exemestane shares some side effects with tamoxifen (hot flashes and arthralgia), but is not associated with an increased risk of endometrial cancer or thromboembolic events. This review will discuss in detail the efficacy and safety of exemestane in early breast cancer.

Keywords: aromatase inhibitor, breast cancer, exemestane, disease-free survival, tamoxifen

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Introduction

The majority of breast cancers (~61%) express the estrogen receptor,[1] which typically correlates with hormone responsiveness for growth and proliferation (Fig. 1A); therefore, treatment approaches have involved inhibition of hormone signaling using selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs).[2–4] While SERMs typically block estrogen from binding to its receptor, tamoxifen can also bind the nuclear estrogen receptor and affect the transcription of estrogen-regulated type II genes (Fig. 1B).[3] Aromatase inhibitors decrease estrogen levels by affecting a key component of the production pathway, aromatase cytochrome P450 (*CYP19*; Fig. 1C).[3,5,6] The aromatase cytochrome P450 enzyme is involved in the conversion of C19 androgens
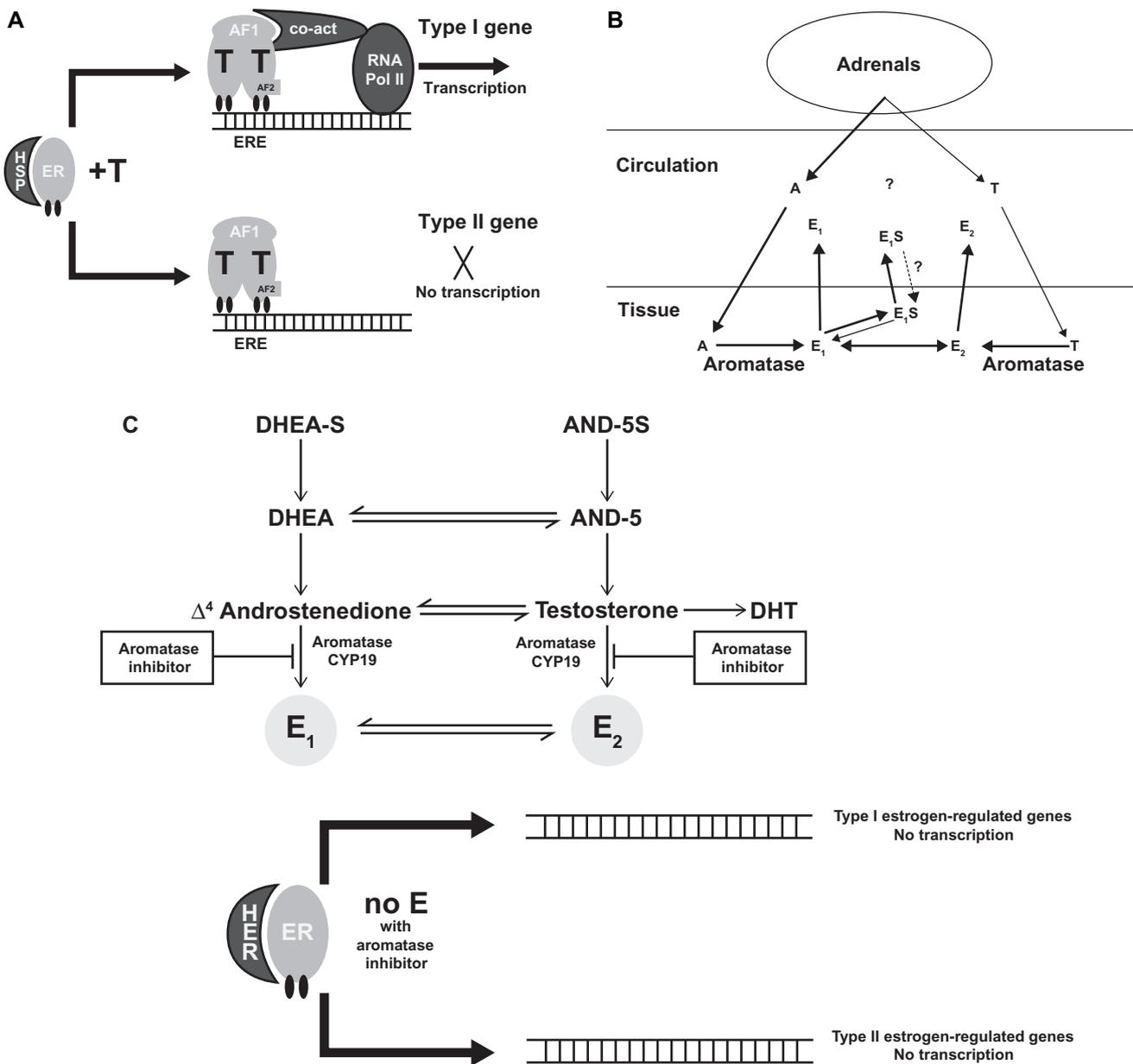
Figure 1. The hormone signaling pathway and its inhibition as therapy in breast cancer. **A**) Estrogen receptor signaling. **B**) Receptor signaling inhibited by the selective estrogen receptor modulator tamoxifen and **C**) by aromatase inhibition.
Abbreviations: A, androstenedione; AF, activating function; AND-5, androstenediol-5; AND-5S, androstenediol-5 sulfate; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; E, estrogen; E1, estrone; E2, estradiol; ER, estrogen receptor; ERE, estrogen response element; RNA Pol II, ribonucleic acid polymerase II; T, tamoxifen. Panels A and B reprinted with permission from Johnston SR 2005.[3] Panel C adapted with permission from Labrie F, Luu-The V, Lin SX, et al. *J Mol Endocrinol* 25:1–16 © Society for Endocrinology (2000).[6]

to aromatic C18 estrogens, primarily in the ovary, testis, and adrenal gland.[5] The aromatase cytochrome P450 enzyme is also active in peripheral tissues (fat, muscle, liver, and both epithelial and stromal breast cells).[5,7] Physiologic studies of the aromatase enzyme have revealed its involvement in energy balance and bone maintenance in addition to its sexual hormonal actions.[5]

Aromatase was recognized as a therapeutic target for the treatment of hormone-dependent conditions such as gynecomastia and breast cancer approximately 40 years ago.[5] Developed at the same time as tamoxifen, the first-generation AI, aminoglutethimide, was nonselective (inhibiting adrenal steroidogenesis as well as thyroid organification of iodine) and equally effective at reducing peripheral estrogen production as the standard surgical treatments for breast cancer at that time.[5] However, aminoglutethimide did not block ovarian estrogen production and was not appropriate in premenopausal women with breast cancer, possibly because of the interruption of the estradiol negative feedback and subsequent rise in luteinizing and follicle-stimulating hormones.[5,8] Compared with the antiestrogen tamoxifen, aminoglutethimide had similar clinical efficacy but a higher incidence of adverse events (AEs); therefore, tamoxifen became the standard hormonal therapy for early and metastatic hormone-receptor-positive breast cancers.[9–12]

After aminoglutethimide, more selective compounds were developed. These early selective AIs exhibited competitive, irreversible, and/or mechanism-based inhibition.[13] Mechanism-based inhibitors are highly specific for the active enzyme site and were found to produce long-lasting inhibition, with less toxicity compared with competitive inhibitors.[5,13] Further structure-function studies of mechanism-based inhibitors produced several generations of compounds, resulting in the steroidal AI exemestane and the nonsteroidal AIs letrozole and anastrozole. Initial clinical studies comparing each of the AIs (anastrozole, exemestane, and letrozole) with the standard of care, tamoxifen, demonstrated the effectiveness, and in some endpoints, superiority, of AIs in the first-line treatment setting for advanced breast cancer.[14–16] Additionally, exemestane demonstrated not only activity but also superiority to megestrol acetate (standard of care) in the second-line setting after progression with tamoxifen in patients with advanced breast cancer.[17,18]

Because suppression of estrogen levels has been associated with inhibition of the development of breast cancer in laboratory models, exemestane treatment for breast cancer prevention has recently been investigated in the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Mammary Prevention.3 trial (MAP.3).[19] Women (N = 4,560) with at least 1 of the following risk factors were randomized to treatment with exemestane or placebo: ≥60 years of age; Gail 5-year risk score >1.66%; prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; or ductal carcinoma in situ with mastectomy. After a median follow-up of 35 months, there was a 65% relative risk reduction in the annual incidence of invasive breast cancer following treatment with exemestane (0.19% vs. 0.55%; hazard ratio [HR] = 0.35; 95% confidence interval: 0.18 to 0.70; P = 0.002).[19] There were no significant differences between the exemestane and placebo groups in skeletal fractures, cardiovascular events, other cancers, treatment-related deaths, osteoporosis, or hypercholesterolemia.[19]

In the early breast cancer setting, large clinical trials evaluating adjuvant therapy showed that any 1 of the 3 AIs could improve disease-free survival (DFS) compared with tamoxifen.[20–27] However, exemestane trials were initially conducted in the metastatic breast cancer setting, and trials in the adjuvant setting have been completed recently.[7] In contrast, the anastrozole and letrozole adjuvant trials have fully matured.[28] Therefore, physicians may be unaware of the utility of exemestane in the adjuvant setting. Aromatase inhibitors, including exemestane, have been evaluated as upfront monotherapy, sequential therapy (following 2–3 years of tamoxifen), and extended therapy (following 5 years of tamoxifen). This review focuses on exemestane and its role in the adjuvant treatment of early-stage breast cancer.

## Exemestane Chemistry, Pharmacodynamics, and Pharmacokinetic Profile

Exemestane is a steroidal compound that mimics the natural substrate of aromatase, androstenedione (Fig. 2). Exemestane is a type I inhibitor (suicide), forming a tight bond with aromatase at a 2.6-fold higher affinity than androstenedione and permanently

inactivating the enzyme.[5,7,29,30] A structure-function study has suggested that exemestane binds as a substrate in the active site pocket of aromatase and is converted to reactive intermediates that bind irreversibly to aromatase.[29] Exemestane (up to 800 mg) is highly specific for aromatase, and it has no detectable effects on the adrenal synthesis of cortisol or aldosterone and no apparent effects on other endocrine parameters.[30]

In 2 small, phase I studies involving postmenopausal women with advanced breast cancer (N = 27 and N = 13), a 10-mg or 25-mg dose of exemestane maximally suppressed circulating estradiol, estrone, and estrone sulfate levels (85% to 95% from baseline) over 12 to 13 weeks of treatment.[31,32] A recent phase I study also suggested that during exemestane therapy, intratumoral androgen activity was increased in tissue from patients with breast cancer (n = 9) compared with patients without exemestane therapy (n = 7); androgen activities could include antiproliferation and may be a marker for tumor response during exemestane treatment.[33]

Exemestane is administered orally, and its pharmacokinetics have been analyzed in healthy postmenopausal

Figure 2. Chemical structures of (**A**) exemestane and (**B**) and rostenedione.

volunteers as well as patients with advanced breast cancer.[30,34] In 29 healthy postmenopausal volunteers, single doses from 0.5 mg to 800 mg demonstrated that exemestane is rapidly absorbed (peak plasma concentrations at 2 hours) and metabolized (undetectable 24 hours after highest dose).[30] Plasma concentrations of exemestane were not assayed in volunteers receiving 25 mg or less because exemestane was undetectable at 4 hours following the 50-mg dose. The mean area under the curve values from 0 to 8 hours for exemestane were 566 ng/mL (200 mg), 907 ng/mL (400 mg), and 1,081 ng/mL (800 mg), suggesting a dose-related increase up to 400 mg. Plasma levels of the primary exemestane metabolite, 17-hydroexemestane, were less than one-tenth of the corresponding exemestane concentrations. The maximum aromatase enzyme suppression was observed 3 days after the single exemestane 25-mg dose and persisted for up to 5 days with the higher doses; however, activity was detected as low as 5 mg, with 50% inhibition of baseline estrogen and urinary estrone levels. The distribution and metabolism of exemestane were investigated using radiolabeled drug.[34] Following oral administration, at least 42% of radiolabeled drug was absorbed from the gastrointestinal tract and was extensively distributed into tissues and metabolized into a primary and many secondary metabolites (<10% unchanged drug of total dose was evident in plasma during a 1-week collection). The metabolites were inactive or inhibited aromatase to a lesser extent than exemestane; however, 17-hydroexemestane bound the androgen receptor with a 100-fold increased affinity than that of exemestane. Exemestane may be metabolized through CYP3A4, CYP4A11, or CYP1A1/2 to 17-dihydroexemestane,[34–36] and was equally eliminated in the urine and feces. However, a high-fat meal can increase exemestane absorption by approximately 40%, and exposure can be increased by up to 3-fold in cases of hepatic or renal insufficiency.[34] In addition, dose modifications are recommended in patients receiving a CYP3A4 inducer.[34] Compared with healthy postmenopausal women, postmenopausal women with breast cancer absorb exemestane more rapidly (peak, 1.2 hours vs. 2.9 hours in healthy women), but have a 45% lower clearance, which corresponds to a 2-fold higher mean exposure compared with healthy women.[34]
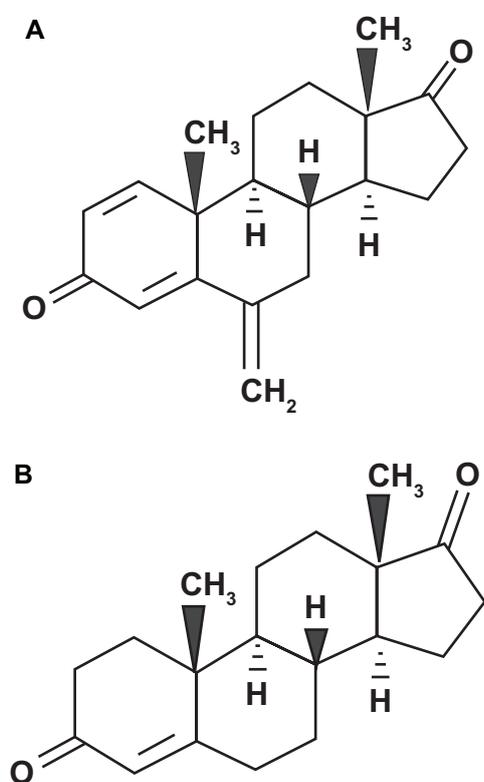
In postmenopausal women with breast cancer, orally administered exemestane inhibited plasma and urinary estrogens with a minimally effective dose of 25 mg. Exemestane concentrations quickly rose to peak levels following oral administration, and metabolism was also rapid and extensive. In these phase I studies, no serious AEs were reported, warranting further investigation of this agent.
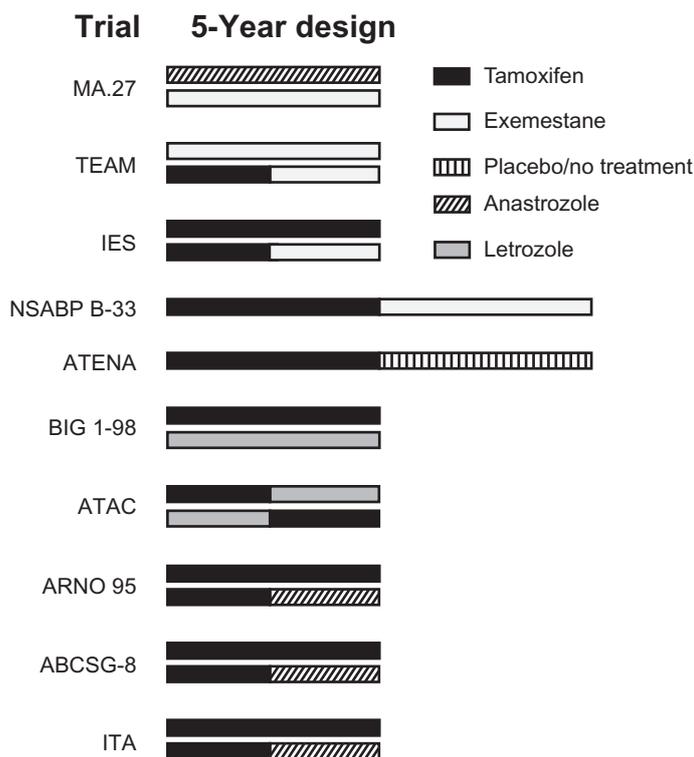
Clinical Studies using Exemestane as Adjuvant Breast Cancer Therapy

In the adjuvant setting, there have been 5 large, phase III trials of exemestane in postmenopausal women with early breast cancer, and these study designs are presented in Figure 3;[21,26,37–42] for comparison, the study designs of 5 large trials of either anastrozole or letrozole are also included. The exemestane trials have evaluated both efficacy and safety in various 5-year adjvant regimens: International Exemestane Study (IES) compared tamoxifen with exemestane following 2 to 3 years of tamoxifen;[21,38,39] Tamoxifen Exemestane Adjuvant Multicenter (TEAM) compared exemestane with a switch strategy of tamoxifen (2–3 years) to exemestane, as well as upfront exemestane with tamoxifen (2.75 years);[37,41] NCIC CTG MA.27 compared exemestane with anastrozole as upfront monotherapies (initial trial had a 2 × 2 factorial design with or without celecoxib, but this approach was discontinued because of cardiac safety concerns with COX2 inhibitors);[40] and 2 extended therapy trials with exemestane following 5 to 7 years of tamoxifen, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33,[26] and Adjuvant Post-Tamoxifen Exemestane Versus Nothing Applied (ATENA) (Table 1).[42] The efficacy of each agent will be presented, followed by their safety profiles.

Figure 3. Schematic of aromatase inhibitor therapy approaches: upfront, sequential, and extended.
Abbreviations: TEAM, Tamoxifen Exemestane Adjuvant Multicenter; IES, International Exemestane Study; NSABP B-33, National Surgical Adjuvant Breast and Bowel Project; ATENA, Adjuvant Post-Tamoxifen Exemestane Versus Nothing Applied; BIG 1–98, Breast International Group; ATAC, Arimidex, Tamoxifen, Alone or in Combination; ARNO 95, Arimidex-Nolvadex; ABCSG-8, Austrian Breast and Colorectal Cancer Study Group; ITA, Italian Tamoxifen Anastrozole.

Efficacy
IES

The objective of the large IES trial was to evaluate the efficacy of sequential therapy (tamoxifen alone versus tamoxifen followed by exemestane), with an event-driven primary endpoint (DFS) (Table 2).[21,38,39] At 30.6 months, there were 183 first events in the exemestane group and 266 in the tamoxifen group.[39] Exemestane improved DFS by 32% compared with tamoxifen (HR = 0.68; $P < 0.001$). In addition, exemestane improved both distant recurrence (HR = 0.66; $P = 0.0004$) and disease-specific survival (HR = 0.63; $P < 0.001$) to a similar extent. Overall survival at 30.6 months was similar between the 2 groups (HR = 0.88; $P = 0.37$). At 55.7 months, improvement in DFS in patients treated with exemestane compared with tamoxifen was maintained (HR = 0.76; $P = 0.0001$); similarly, time to distant recurrence (HR = 0.83; $P = 0.03$) and disease-specific survival (HR = 0.76; $P = 0.0004$) results were sustained.[21] There was a nonsignificant trend toward improvement in overall survival with exemestane compared with tamoxifen (HR = 0.85; $P = 0.08$). At 91 months, in patients with positive or unknown estrogen receptor status, improvements persisted in DFS (HR = 0.82; $P = 0.0009$), time to distant recurrence (HR = 0.83; $P = 0.01$), and disease-specific survival (HR = 0.81; $P = 0.001$) for patients treated with exemestane versus tamoxifen.[38] Moreover, overall survival in the exemestane groups achieved a significant

Table 1. Exemestane clinical trials in postmenopausal women with early breast cancer.

Study	Patients, N	Study design	Inclusion/Exclusion criteria
Intergroup Exemestane Study (IES)[21,38,39]	4,724 (T: 2,380; T/E: 2,362)	Prospective, randomized, double-blind phase III - T vs T→E (5 years)	Postmenopausal women with early hormone-sensitive BC
Tamoxifen Exemestane Adjuvant Multicenter (TEAM)[37,41]	9,779 (E: 4,875; T/E: 4,904)	Prospective, randomized, open-label, multinational phase III - Upfront T vs E (2.75 years) - Sequential T→E vs E (5 years)	Postmenopausal women with early hormone-sensitive BC
MA.27[40]	7,576 (E: 3,789; A: 3,787)	Prospective, randomized, double-blind phase III - Upfront A vs E (5 years)	Postmenopausal women with early hormone-sensitive BC
National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33[26]	1,598 (E: 799; P: 799)	Prospective, randomized, double-blind - Extended E vs P (5 years)	Postmenopausal women with hormone–receptor-positive breast cancer who had received 4.5 to 5.5 years of adjuvant tamoxifen therapy
Adjuvant post-Tamoxifen Exemestane versus Nothing Applied (ATENA)[42]	411 (E: 211; NT: 200)	Prospective, randomized, open-label, parallel-group - Extended E vs NT (5 years)	Postmenopausal women with hormone–receptor-positive breast cancer who had received 5 to 7 years of adjuvant tamoxifen therapy

Abbreviations: A, anastrozole; BC, breast cancer; E, exemestane; NT, no treatment; P, placebo; T, tamoxifen.

improvement compared with the tamoxifen group (HR = 0.86; $P = 0.04$). The IES trial demonstrated that adjuvant sequential therapy with exemestane was superior to tamoxifen alone with regard to clinical benefits in postmenopausal women with early breast cancer, including survival at long-term follow-up.

Team

The objective of the open-label TEAM trial was to evaluate 5 years of upfront exemestane versus sequential therapy (tamoxifen followed by exemestane). Postmenopausal women with hormone-sensitive early breast cancer (N = 9,779) were randomized to either 5 years of exemestane 25 mg/day (n = 4,904) or 2 to 3 years of tamoxifen 20 mg/day followed by exemestane (n = 4,875).[37,41] One of the coprimary endpoints was DFS at 2.75 years. A DFS event was defined as a locoregional or distant breast cancer recurrence, a second primary breast cancer, contralateral breast cancer, and all-cause death. The risk of a DFS

Table 2. Clinical outcomes in the ies sequential trial.

Median follow-up, months	DFS events, E vs T	DFS, HR (95% CI; *P* value)	DFS benefit, % (95% CI; *P* value)	BC-free survival, HR (95% CI; *P* value)	Distant recurrence, HR (95% CI; *P* value)	OS (ITT), HR (95% CI; *P* value)
30.6[39]	183 vs 266	0.68 (0.56–0.82; <0.001)	4.7 (2.6–6.8; <0.05)[a]	0.63 (0.51–0.77; <0.0001)	0.66 (0.52–0.83; 0.0004)	0.88 (0.67–1.16; 0.37)
55.7[21]	354 vs 455	0.76 (0.66–0.88; 0.0001)	3.4 (0.1–6.8; NR)[b]	0.76 (0.65–0.89; 0.0004)	0.83 (0.71–0.99; 0.03)	0.85 (0.71–1.02; 0.08)
91[38]	530 vs 622[c]	0.82 (0.73–0.92; 0.0009)[c]	4.4 (1.8–7.2; <0.05)[c,d]	0.81 (0.71–0.92; 0.001)[c]	0.83 (0.72–0.96; 0.01)	0.86 (0.75–0.99; 0.04)[c]

Notes: [a]3 years postrandomization; [b]5 years postrandomization; [c]In patients with estrogen-receptor-positive or unknown tumors; [d]8 years postrandomization.
Abbreviations: BC, breast cancer; CI, confidence interval; DFS, disease-free survival; E, exemestane; HR, hazard ratio; IES, Intergroup Exemestane Study; ITT, intent-to-treat; NR, not reported; OS, overall survival; T, tamoxifen.
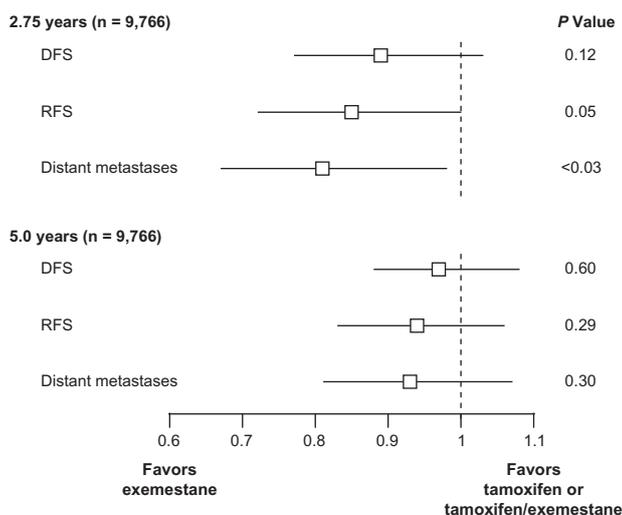
event favored exemestane but did not reach statistical significance (HR = 0.89; P = 0.12). Upfront, initial monotherapy with exemestane did improve time to distant recurrence (HR = 0.81; P < 0.03) and risk of relapse (HR = 0.85; P = 0.05) versus tamoxifen at 2.75 years in the TEAM trial (Fig. 4).[41] A limitation of this analysis is the high proportion of patients who switched from tamoxifen to exemestane before 2.75 years.

Sequential therapy with exemestane following 2 to 3 years of tamoxifen had efficacy for DFS (HR = 0.97; P = 0.60), overall survival (HR = 1.00; P > 0.99), and time to recurrence (HR = 0.94; P = 0.29) similar to tamoxifen monotherapy at 5 years in the TEAM trial (Fig. 4).[37] An exploratory analysis of the TEAM trial (n = 4,741) showed that body mass index (BMI) was not associated with the clinical outcomes at 5 years.[43] Disease relapse was 15% in all BMI groups (normal, overweight, and obese), and overall, the probability of disease-specific death and death from other causes was nearly equal. However, at 2.75 years there was an increase in DFS events among obese patients in the tamoxifen group compared with obese patients in the exemestane group (HR = 0.57; P = 0.004). Another TEAM exploratory analysis demonstrated that the release of the IES study results did not affect discontinuation rates in the sequential (tamoxifen to exemestane) therapy group.[44] The TEAM trial showed that upfront therapy with exemestane produced similar clinical benefits to that of tamoxifen followed by exemestane in postmenopausal women with early breast cancer.

MA.27

The objective of the MA.27 trial was to evaluate the efficacy of upfront exemestane versus anastrozole in postmenopausal women with early breast cancer (N = 7,576).[40] Both exemestane 25 mg/day and anastrozole 1 mg/day performed equally well in all efficacy endpoints at a median follow-up of 4.1 years: event-free survival (HR = 1.02; P = 0.85), overall survival (HR = 0.93; P = 0.64), distant recurrence (HR = 0.95; P = 0.46), and disease-specific survival (HR = 0.93; P = 0.62). A bone substudy in eligible patients with osteoporosis (n = 184) and without osteoporosis (n = 287) found no overall significant changes from baseline in bone turnover markers.[45] Among patients without osteoporosis, there was less early bone loss at the hip in the exemestane group compared with the anastrozole group (1 year, P = 0.007); however, at 2 years, the difference was no longer significant (P = 0.13). Bone loss was also less at the lumbar spine in the exemestane group compared with the anastrozole group; however, the opposite trend was observed (1 year, P = 0.32; 2 years, P = 0.08). The MA.27 trial found equivalent efficacy for clinical benefits between upfront adjuvant exemestane and anastrozole in postmenopausal women with early breast cancer.

NSABP B-33 and ATENA

The objective of the NSABP B-33 and ATENA trials was to evaluate exemestane in the extended adjuvant setting, following 5 years of tamoxifen. However, both trials were terminated after publication of a similarly designed trial of letrozole (NCIC CTG MA.17) that reported improvement in DFS compared with placebo.[23,26,46,47] The NSABP B-33 trial had enrolled approximately 50% of the planned number of patients at the time of unblinding, and patient follow-up was continued.[26] Patients in the placebo group were eligible to receive exemestane, and 44% of patients in the placebo group crossed over to exemestane. Analysis of the data by original therapy assignment showed a trend toward improvement in 4-year DFS after treatment with exemestane compared with placebo (relative risk [RR] = 0.68; P = 0.07). The time to

Figure 4. Clinical outcomes of the TEAM trial at 2.75 and 5.0 years.
Abbreviations: DFS, disease-free survival; RFS, relapse-free survival; TEAM, Tamoxifen Exemestane Adjuvant Multicenter.
Data from Jones S, et al 2009[41] and van de Velde CJ, et al 2011.[37]

distant recurrence was not improved by exemestane (RR = 0.69; $P = 0.13$), but 4-year relapse-free survival was significantly longer with exemestane than with placebo (RR = 0.44; $P = 0.004$). The ATENA trial had enrolled almost 25% of the planned number of patients at the time of study discontinuation.[42] Efficacy results from this trial have not yet been published. Although these 2 trials were terminated and extensive crossover from placebo to exemestane took place in the NSABP B-33 trial, a trend was observed for improved DFS in patients who were randomized to exemestane in NSABP B-33. This trend suggested that there might have been clinical benefit if the trial had been completed.

Taken together, these trials (IES, TEAM, MA.27, NSABP B-33) demonstrated the effectiveness of exemestane in the adjuvant setting as upfront therapy or following tamoxifen among postmenopausal women with early breast cancer. In addition to immediate clinical benefits in DFS and recurrence, patients treated with exemestane had improved long-term survival compared with tamoxifen-treated patients.

Safety and Side Effects

As determined in these large, phase III trials, the safety profile of exemestane is similar to that of other AIs, but somewhat different than that of tamoxifen (Table 3).[21,37,39–41,48] Compared with tamoxifen, patients treated with AIs have a lower incidence of endometrial cancer and venous thromboembolism, a similar incidence of cerebrovascular events, a higher incidence of fractures, and a potentially higher incidence of cardiovascular events.[49] A recent review of the effects of adjuvant endocrine therapy on cardiovascular health in postmenopausal patients with breast cancer reported that there was no evidence of increased cardiovascular risk during AI therapy based on comparisons with placebo, although there were increases in cardiovascular risk compared with tamoxifen.[50] Because hormonal therapies further lower estrogen levels in postmenopausal women, menopause-like effects are to be expected. These effects may include hot flashes, sweating, gynecologic symptoms, and musculoskeletal symptoms such as arthralgia and decreased bone mineral density (BMD).[51–53] However, the type of effects from an individual agent may relate to the specific activity of that agent. For example, AIs have no estrogenic activity, which decreases the risk for gynecologic cancers but increases the likelihood of losing BMD.[52,54]

Vasomotor symptoms

The most common vasomotor symptoms associated with hormonal therapy are hot flashes and sweating. In fact, all of the exemestane trials reporting AEs (IES, TEAM, and MA.27) listed hot flashes as 1 of the AEs most common to both exemestane and tamoxifen (Table 3).[21,37,39–41,48] Sweating was also a common AE (~18%) for both exemestane and tamoxifen in the IES trial.[21,39] In 1 analysis, among 10 specific menopause symptoms explored, the mean hot flash score was higher at 12 months after tamoxifen than after exemestane ($P = 0.03$).[48] However, the mean hot flash score peaked from baseline in both groups at 3 months (33% for tamoxifen and 7% for exemestane) and subsequently decreased. Certain individual symptoms occurred more frequently with tamoxifen (hot flashes and vaginal discharge) or exemestane (vaginal dryness, bone/muscle aches, and difficulty sleeping).

Musculoskeletal symptoms

In the IES trial at both 30.6 and 55.7 months, there was an increase in muscle cramps/disorders for tamoxifen compared with exemestane.[21,39] At 30.6 months, there was also an increase in osteoporosis and arthralgia for exemestane compared with tamoxifen.[39] At 55.7 months, osteoporosis and arthritis/arthralgia remained increased for exemestane, but there was now an increase in fractures with exemestane.[21] Further investigations into the fracture incidence included a bone substudy, which showed that BMD at both the lumbar spine and hip significantly decreased from baseline with exemestane during therapy ($P < 0.0001$ for both).[55] Changes from baseline BMD were reported, similar to those in the TEAM substudy. By a median follow-up of 58 months, a fracture had occurred in 7% of patients in the exemestane group and 5% of patients in the tamoxifen group; this translated into a 45% increased risk of fracture for the exemestane group ($P = 0.003$). However, a skeletal substudy that investigated BMD of patients 2 years after their last treatment found no difference between patients treated with tamoxifen or exemestane.[56]

Table 3. Adverse events in ≥10% of patients in phase iii clinical trials of exemestane.

Study	Adverse event	Exemestane patients, %	Tamoxifen/Anastrozole[a] patients, %	Comparative *P* value
IES (N = 4,724)[21,39]				
30.6 months	Cardiovascular disease other than myocardial infarction	42.6	39.2	0.016
	Hot flashes	42.0	39.6	0.082
	Pain or aches	33.2	29.4	0.001
	Fatigue	23.6	23.5	0.776
	Insomnia	19.5	17.4	0.151
	Sweating	18.6	17.9	0.702
	Headaches	18.6	16.2	0.035
	Dizziness	12.5	12.0	0.904
	Nausea	10.8	11.1	0.835
55.7 months	Nonischemic cardiovascular events	11.3	11.2	0.96
	Hypertension	39.1	35.9	0.03
	Arthritis	17.5	14.6	0.008
	Osteoarthritis	11.3	9.7	0.07
	Arthralgia	20.8	15.1	<0.0001
	Musculoskeletal pain	25.7	20.3	<0.0001
	Hot flashes	42.4	39.9	0.08
	Depression	11.3	9.8	0.10
	Dizziness	13.9	13.6	0.82
	Fatigue	24.5	24.1	0.75
	Headaches	19.1	17.2	0.09
	Insomnia	20.8	18.2	0.03
	Nausea	10.9	11.7	0.41
	Sweating	19.1	18.4	0.56
	Pain	13.3	14.3	0.30
TEAM (N = 9,779)[37,41,48]				
1 year	Vaginal discharge	12	32	<0.0001
	Vaginal dryness	50	42	0.0004
	Bone/muscle aches	77	70	<0.0001
	Decreased libido	58	54	0.03
	Difficulty sleeping	60	55	0.03
2.75 years	Hot flashes/flushing	28.5	33.3	≤0.001
	Arthralgia	17.9	9.2	≤0.001
5 years	Hot flashes/sweating	35.0	40.0	<0.0001
	Joint disorders	36.0	31.0	<0.0001
	Muscle disorders	11	13	0.0014
	Other MS/CT disorders	15	13	0.0023
	Osteoporosis	10	6	<0.0001
	Nervous system disorders[b]	17	14	0.0004
	Insomnia/sleep disorders	13	10	<0.0001
	Metabolism/nutrition disorders[c]	10	9	0.051
MA.27 (N = 7,576)[40]	Hot flashes	55	56	0.24
	Muscle pain	17	16	0.19
	Elevated cholesterol	15.3	17.7	0.01
	New-onset osteoporosis[d]	31	35	0.001
	Any clinical fracture at any time	10	9	0.91

Notes: [a]Anastrozole was the comparator for the MA.27 trial; [b]Excluding dizziness, headache, nerve compression, and cerebrovascular events; [c]Excluding weight increase, abnormal liver function, and hyperlipidemia; [d]Patient-reported.
Abbreviations: IES, Intergroup Exemestane Study; TEAM, Tamoxifen Exemestane Adjuvant Multicenter; MS, musculoskeletal; CT, connective tissue.

Fracture rates were also similar after the end of therapy. Therefore, ongoing assessment of BMD after exemestane may not be necessary.

In the TEAM trial at 2.75 years, differences in the AE incidence between exemestane and tamoxifen included an increase in certain musculoskeletal events for exemestane.[41] However, arthralgia was an AE common to both exemestane and tamoxifen.[41,57] At 5 years, muscle disorders became increased for tamoxifen versus exemestane, although other musculoskeletal events remained increased for exemestane.[37] As expected, a meta-analysis of data from 4 countries participating in the TEAM trial confirmed that exemestane and tamoxifen had contrasting effects on bone health during therapy.[58] At both 12 and 24 months, patients treated with tamoxifen had increased lumbar spine BMD (1.2% and 0.2%, respectively), while patients treated with exemestane had decreased BMD (2.6% and 3.5%, respectively; $P < 0.0001$ for both time points). Similar results were observed for total hip BMD.

Arthralgia, muscle pain, and fractures were common to both AIs in the MA.27 trial, although exemestane was associated with a significantly lower incidence of new-onset osteoporosis compared with anastrozole ($P \leq 0.04$ for all).[40] Analysis of tissues from the MA.27 trial indentified polymorphisms in a leukemia gene (related to interleukin-17) that correlated with musculoskeletal AEs in AI-treated women.[59] These preliminary results may lead to identification of predictive factors for musculoskeletal AEs during AI therapy and provide guidance for optimal AI therapy in individual patients. In a recent update of the MA.27 trial, women without osteoporosis had less bone loss in the hip and lumbar spine at 1 and 2 years during exemestane therapy compared with anastrozole, with a significant difference noted at 1 year in the hip ($P = 0.007$).[45] Among women with osteoporosis, bisphosphonate therapy with calcium and vitamin D increased BMD during AI therapy, without significant differences between the 2 treatment groups.

In the NSABP B-33 trial, the incidence of grade 3 toxicities was higher with exemestane than with placebo ($P = 0.03$); specifically, arthralgia was more common with exemestane (1.0% vs. 0.5%, respectively).[26] The incidence of grade 4 toxicities (1% each) was similar in the exemestane and placebo groups. The incidence of fractures at 6 months after unblinding was also similar between groups (28 exemestane-treated patients and 20 placebo-treated patients).[26]

Gynecologic symptoms

In the IES trial at both 30.6 and 55.7 months, there was an increase in gynecologic symptoms in patients treated with tamoxifen compared with those treated with exemestane.[21,39] Long-term endometrial effects were analyzed in an IES substudy.[60] Abnormal endometrial thickening ($\geq$5 mm) was significantly lower at 24 months in patients treated with exemestane than in patients treated with tamoxifen (36% vs. 62%, respectively; $P = 0.004$). Although this significant difference was observed within 6 months of starting exemestane ($P = 0.01$), the incidence was similar within 12 months of therapy cessation. In another analysis, mean endometrial thickening at 12 months was 3.36 mm less in patients treated with exemestane than in patients treated with tamoxifen ($P < 0.0006$); 17 tamoxifen-treated patients had histologically confirmed endometrial changes, whereas only 1 patient in the exemestane arm had similar changes.[61] Furthermore, no patients in the exemestane group had endometrial thickness greater than 10 mm, although 11 patients in the tamoxifen group did ($P < 0.0003$). A long-term endometrial substudy demonstrated that sequential exemestane can even reverse tamoxifen-induced endometrial effects.[60]

In the TEAM trial at 1 year, patients treated with tamoxifen had increased vaginal discharge compared with patients treated with exemestane. In the upfront exemestane arm, vaginal dryness became more common versus tamoxifen.[41,48] At 5 years, vaginal discharge remained more common in patients treated with tamoxifen (8% vs. 3% in the exemestane arm; $P < 0.0001$) and vaginal dryness remained more common in patients treated with exemestane (7% vs. 6% in the tamoxifen arm; $P = 0.038$).[37]

In the MA.27 trial, anastrozole was associated with a significantly higher incidence of vaginal bleeding compared with exemestane ($P \leq 0.04$).[40] However, vaginal bleeding occurred in less than 2% of the population (n = 7,520).

Cardiovascular symptoms

In the IES trial at both 30.6 and 55.7 months, there was an increase in thromboembolic disease in the

tamoxifen arm compared with the exemestane arm (30.6 months: 1.9% vs. 1.0%, respectively; $P = 0.005$; and 55.7 months: 3.1% vs. 1.9%, respectively; $P = 0.01$).[21,39] At 55.7 months, there was an increase in hypertension in the exemestane group (39.1% vs. 35.9% in the tamoxifen group; $P = 0.03$), which increased the incidence of overall cardiovascular events to a similar extent as that in the tamoxifen group.[21]

In the TEAM trial at 2.75 years, there was an increase in thromboembolic events in the tamoxifen arm compared with the exemestane arm (2.3% vs. 0.9%, respectively; $P \leq 0.001$) and an increase in hypertension in the exemestane arm compared with the tamoxifen arm (3.3% vs. 2.1%, respectively; $P \leq 0.001$).[41] At 5 years, the incidence of thromboembolic events and hypertension remained increased in the tamoxifen and exemestane arms, respectively.[37] However, thromboembolic events occurred in 3% or less of the study population.

In the MA.27 trial, exemestane was associated with a significantly higher incidence of atrial fibrillation compared with anastrozole ($P \leq 0.02$).[40] However, atrial fibrillation also occurred in less than 2% of the population.

Lipid parameters

At 5 years in the TEAM trial, the incidence of hyperlipidemia increased in the exemestane group versus the tamoxifen group (5% vs. 3%, respectively; $P < 0.0001$).[37] However, in the Greek substudy, exemestane had a neutral effect on the lipid profile during the first 24 months.[46] Although total cholesterol decreased from baseline in both groups, the decrease only became significantly different from that in the tamoxifen group during months 18 to 24 ($P \leq 0.02$). Similar changes from baseline were observed during months 12 to 24 in the mean low-density lipoprotein (LDL) levels of each group ($P \leq 0.03$ in the tamoxifen arm). There were no significant changes from baseline in high-density lipoprotein (HDL) in either group, although the values were higher in the tamoxifen arm compared with the exemestane arm. There were no significant trends in triglyceride levels in either group. In Japanese patients treated in the TEAM substudy, similar changes in the lipid profile were observed during the first year of treatment.[62] In this Japanese substudy, anastrozole was also included as an adjuvant treatment. Nonetheless, there were no clinically meaningful changes in the lipid profile in either the exemestane or anastrozole group. It should be noted, however, that the decrease in HDL was less pronounced in patients treated with anastrozole compared with those treated with exemestane.

In the MA.27 trial, anastrozole was associated with a significantly higher incidence of hyperlipidemia compared with exemestane ($P \leq 0.01$).[40]

In the ATENA trial, only lipid parameters were reported.[42] For the untreated and exemestane groups, total cholesterol and LDL levels increased from baseline to 24 months, and triglyceride levels decreased. Increases in LDL were sustained and significant ($P \leq 0.03$ for all), although not significantly different between the groups ($P = 0.08$). Triglyceride level decreases were sustained and significant at all time points in the exemestane group ($P \leq 0.04$ for all) and the majority of time points in the untreated group, with no significant difference between groups ($P = 0.50$). Only in the untreated group was there a sustained significant rise in total cholesterol at all time points ($P \leq 0.009$ for all); however, there was still no significant difference between groups ($P = 0.68$).

Cognitive function

In an exploratory analysis of the TEAM trial, patients treated with tamoxifen processed information more slowly than patients treated with exemestane ($P = 0.02$). In addition, cognitive functioning in the areas of verbal memory and executive function was lower among patients treated with tamoxifen compared with healthy controls ($P \leq 0.01$ for both), but this was not the case among patients treated with exemestane.[63] In fact, the cognitive functioning of patients treated with exemestane was not significantly different from that of healthy controls.

Other adverse events

At 30.6 months in the IES trial, the other common AEs across the study were fatigue, insomnia, dizziness, and nausea.[39] Patients treated with exemestane reported more pains/aches, headaches, visual disturbances, and diarrhea than patients treated with tamoxifen. At 55.7 months, fatigue and insomnia remained the most common other AEs for both groups, and diarrhea was still reported more often in the exemestane group.[21] In addition, there was an increase in insomnia,

paresthesia, and gastric ulcer in the exemestane group compared with the tamoxifen group.[21] In the MA.27 trial, exemestane was associated with a significantly higher incidence of steroid-related effects (acne, masculinization, and elevated liver enzymes) compared with anastrozole ($P \leq 0.04$ for all).[40] However, these events occurred in less than 2% of the population. In the NSABP B-33 trial, fatigue was more common in the exemestane group compared with the placebo group (0.9% vs. 0.5%, respectively).[26]

In general, exemestane has been well tolerated in clinical trials evaluating adjuvant therapy. An in-depth understanding of its safety profile and those of other AIs should guide selection of an optimal hormonal therapy in an individual patient, with early identification or proactive management of AEs.

Management of adverse events

Management of AEs thought to be related to exemestane therapy is typically symptomatic in focus. Algorithms exist for the management of arthralgias and loss of BMD.[64–69] Once an arthralgia has been identified, lifestyle changes including exercise and joint protection are recommended. Pharmacologic management of arthralgias consists primarily of pain relief from acetaminophen, non-steroidal anti-inflammatory drugs, and COX-2 inhibitors, increasing to opioid use if necessary.[64–67] For bone health, all women receiving an AI should also receive calcium and vitamin D supplementation as well as a bisphosphonate when indicated (T-score $<$ –2.0, radiologic evidence of bone destruction, or $\geq$2 risk factors in the absence of T-scores).[65,68,69] In rare cases, the AI must be discontinued.

Patient Preference and Health-Related Quality of Life Measurements

In a quality of life (QOL) report from the IES trial, the Functional Assessment of Cancer Therapy-Breast (FACT-B) scores were generally good at baseline (before randomization), and neither tamoxifen alone nor tamoxifen followed by exemestane led patients to score their QOL assessment as significantly worse.[70] An additional assessment of the endocrine subscale revealed that endocrine symptoms decreased from baseline during the trial period in both groups. Among the individual symptoms, decreases were similar between the 2 therapy groups,

except for vaginal discharge, which was lower in the tamoxifen-to-exemestane group compared with the tamoxifen monotherapy group ($P < 0.001$). A brief report from the menopause-specific QOL substudy of the terminated NSABP B-33 trial demonstrated no significant exemestane treatment effects on the 4 domains of the QOL assessment (vasomotor, psychosocial, physical, and sexual).[26] However, baseline severity was not provided.

Other studies have pointed to a lack of strong patient preference between other AIs. Two patient preference trials of letrozole and anastrozole have been conducted.[71,72] Both trials were in the adjuvant setting comparing letrozole with anastrozole in a crossover design. In 1 trial (N = 72), the letrozole group reported fewer AEs than the anastrozole group reported (43% vs. 65%, respectively; $P = 0.0028$),[72] and QOL was improved in the letrozole group compared with anastrozole ($P = 0.02$). There was a clear preference for letrozole over anastrozole (68% vs. 32%, respectively; $P < 0.01$). In the other trial (N = 181), there were no differences in the incidence of AEs, and no QOL differences were reported between the treatment groups.[71] There was also no clear patient preference for a particular AI: 31% of patients favored letrozole, 36% favored anastrozole, and 34% patients had no preference.

Patient preference may be influenced by the cost-effectiveness of therapies. Although AI therapy has become a standard of care for the treatment of postmenopausal women with early breast cancer because AIs significantly reduce the risk of disease recurrence and death, AIs do not eliminate these outcomes. Thus, physicians may need to evaluate the cost of long-term care of patients with breast cancer, including drug acquisition, follow-up, and AE management as well as QOL. Using data from the IES study, exemestane was shown to be more cost-effective than tamoxifen, producing a 0.32 increase in quality-adjusted life-years (QALYs) and a $4,400 decrease in lifetime cost of cancer care.[73] The data from IES were also used to analyze cost-effectiveness of exemestane versus tamoxifen based on the healthcare resources of different countries, and exemestane was found to be cost-effective in all instances.[74–76] Exemestane increased QALYs by 0.12 in Canadian patients and by 0.24 in German patients.[74,76] In a comparative analysis of upfront letrozole and anastrozole and sequenced

exemestane, using distant disease-free year gained, all 3 agents were considered cost-effective compared with tamoxifen.[77] Upfront letrozole had the largest gain versus tamoxifen (0.36 year). Upfront anastrozole had a gain of 0.26 year, and sequenced exemestane had a gain of 0.16 year. However, exemestane was not an upfront therapy as the comparators were, and the patient populations were different in each setting.

Adverse-event management appears to be more costly for tamoxifen, although this represents the smallest fraction of overall cost. In the ATAC and BIG 1–98 studies, the yearly cost (using conversion factor of £1 = $1.55) of managing AEs from tamoxifen ranged from £604 ($939) to £642 ($1,002), whereas those costs for anastrozole, letrozole, and exemestane were £315 ($491), £336 ($524), and £47 ($73), respectively.[78] It should be noted, however, that the impact for individual patients experiencing an AE may be much greater. For example, the cost (using conversion factor of £1 = $1.55) of managing fractures ranges from £450 ($702) for the wrist to £1,500 ($2,340) for the proximal humerus and £6,000 ($9,360) for the hip.[78] In the 68-month analysis of the ATAC trial, 11% and 7.7% of patients receiving anastrozole and tamoxifen, respectively, experienced a fracture.[79] In the 25.8-month analysis of BIG 1–98, fractures occurred in 5.7% of letrozole-treated and 4.0% of tamoxifen-treated patients.[80]

Other costs were estimated at $20,139 for the last 3 months of terminal care in IES and $47,392 for distant disease management in BIG 1–98, and appear to be the greatest financial burden.[81] In a retrospective analysis of patient charges in a large Midwestern healthcare system, it was determined that the charges incurred by patients with early-stage breast cancer were significantly lower in the 6- and 12-month periods before any recurrent event ($10,715 and $12,344, respectively) compared with a similar period after recurrence ($45,855 and $79,253; $P < 0.001$ for both).[82] Care for distant recurrence was the most costly, with mean charges of $57,642 and $104,502 in the 6- and 12-month periods, respectively, after recurrence.[82] Similarly, using data from the Henry Ford Health System, the mean monthly charges were highest for distant recurrence ($37,969), followed by locoregional ($10,934) and contralateral ($9,129) recurrence, when calculated for the year immediately

after the recurrence.[83] In the United Kingdom National Institute for Health Research analysis, other costs associated with AIs compared to tamoxifen were $8,032 (exemestane) versus $8,290, $7,491 (anastrozole) versus $7,770, and $6,781 (letrozole) versus $7,156.[81] The percentage increase in cost is largest between letrozole and tamoxifen and is possibly because of a significantly reduced risk of recurrence at distant sites.[82]

Patient preference may affect long-term adherence to therapy, as is the case with many chronic diseases.[84] The level of compliance and adherence to therapy affects clinical outcomes and is the result of many factors.[84] As expected, nonadherence is more likely if severe side effects are experienced.[85–87] Additionally, nonadherence is more likely if the perceived risks are greater than the expected benefits.[85,88] Although there are no adherence studies specific for exemestane, 1 survey reported that 30% of patients receiving any AI (N = 622) discontinued their agent during the course of therapy.[84,89] In addition, an examination of 3 healthcare databases for adherence to anastrozole therapy among pre- and postmenopausal women with early breast cancer (N = 12,391) found that nonadherence ranged from 14% to 22% in the first year and 21% to 38% in the third year.[90] Similarly, during tamoxifen therapy for pre- and postmenopausal women in adherence trials, the proportion of patients adherent to therapy decreased by 13% to 22% within the first year and further declined 31% to 50% within the 5-year course of therapy.[85,91,92] Therefore, if there is no clear evidence on which to base a medication choice (such as among the AIs), allowing patient preference for a medication may improve not only adherence but also outcomes.

Role in Disease Management

In the adjuvant setting, specific hormonal regimens have not been established in the treatment of postmenopausal women with hormone-sensitive breast cancer. A recent consensus from an expert panel favored an AI upfront, especially in patients with a high risk of relapse.[93] Recurrence of breast cancer increases mortality, especially with distant metastases (eg, bone, liver, lung).[94] As shown in the previously discussed exemestane clinical trials and in clinical trials with letrozole or anastrozole,[94] time to recurrence, risk of relapse, and time to distant metastasis are

improved with AIs compared with tamoxifen in postmenopausal women with early-stage, hormone-sensitive breast cancer. For patients with a low risk of relapse, the expert panel recommended use of the agent that would be best tolerated, in order to maximize adherence.[93] In postmenopausal women, there may be a perception that AIs are not appropriate for patients with cardiovascular disease. These concerns may result from the meta-analysis reporting a higher risk of grade 3 and 4 cardiovascular AEs with AIs compared with tamoxifen. However, these data have not been substantiated in trials comparing AIs with placebo.[50,95] Although the difference in cardiovascular events between AIs and tamoxifen was statistically significant, the absolute difference was low (would need to treat 160 to 180 patients to observe 1 cardiovascular event).[95] Therefore, the perception that AIs increase cardiovascular risk may result more from the positive cardiovascular effect of tamoxifen than from negative effects of AIs.[50]

As described, the expert panel did not recommend a particular AI from among the approved AIs.[93] In another guideline, anastrozole, exemestane, and letrozole are considered to have equal efficacy and may be used without preference.[96] However, as noted in the MA.27 trial, the safety profiles of exemestane and anastrozole are not identical. Therefore, the 3 AIs may not be exactly the same, and therapy could be optimized for individual patients.[97] Translational studies may identify prognostic markers that can improve the classification of individual risk for relapse and thereby provide guidance in selection of the optimal AI therapy for an individual patient.[98–108] These studies may also identify predictive factors for benefit from each AI and possibly determine patient subsets that preferentially benefit from a particular AI.

Exemestane is approved by the US Food and Drug Administration for use following 2 to 3 years of tamoxifen to complete 5 years of therapy in postmenopausal women with early hormone-sensitive breast cancer.[34] However, in the TEAM and BIG 1–98 studies, sequential therapy with exemestane or letrozole following tamoxifen was not superior to upfront AI therapy.[27,37] Furthermore, upfront therapy with anastrozole or exemestane had similar efficacy.[40] It is also feasible to switch from one AI to another if intolerability occurs, which may maximize the benefits from AI therapy.[109]

Physician adherence to the recommended management of treatment for postmenopausal women with early breast cancer is not optimal.[110] In general, up to 65% of women with breast cancer do not receive the recommended treatment regimens.[110] Adjuvant hormonal therapy is underutilized by approximately 30% of women with hormone-sensitive breast cancer.[110] In 1study, a primary reason that patients did not receive recommended adjuvant therapy was physician perception that the risks were greater than the expected benefits.[111] Increased physician awareness of evidence-based guidelines should improve management of breast cancer and clinical outcomes.

Conclusions

Exemestane is indicated as an adjuvant therapy following tamoxifen in postmenopausal women with hormone-sensitive breast cancer. However, the efficacy of exemestane has been evaluated versus tamoxifen as an upfront monotherapy and as an extended therapy beyond 5 years of tamoxifen. Exemestane provided clinical benefits that were equal to tamoxifen in the upfront setting and trended toward a clinical benefit in the terminated, extended-therapy trials.

The safety profile of exemestane is well established and is, in general, similar to those of other AIs. The only comparison between exemestane and another AI reported thus far has been an upfront trial with anastrozole showing that both AIs had equal efficacy and similar incidences of hot flashes and musculoskeletal events. The only differences were lower incidences of new-onset osteoporosis and hyperlipidemia in patients treated with exemestane compared with anastrozole.

Further direct comparisons of exemestane with other AIs are ongoing, and results from these trials may aid therapy selection.[112–114] Because results are not expected for another 3 to 5 years, until that time, management decisions for adjuvant therapy in breast cancer must rely on evidence-based guidelines, baseline patient characteristics, and patient preference.

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