REVIEW

Long-term efficacy and safety of exemestane in the treatment of breast cancer

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Abstract: Exemestane, a steroidal aromatase inhibitor, is licensed for postmenopausal patients with estrogen receptor (ER)-positive breast cancer as second-line therapy in metastatic disease following antiestrogen failure and as part of sequential adjuvant therapy following initial tamoxifen. This study is a systematic literature review, evaluating exemestane in different clinical settings. The Ovid Medline (1948–2012), Embase (1980–2012), and Web of Science (1899–2012) databases were searched. Forty-two relevant articles covering randomized controlled trials were reviewed for efficacy and safety, and three for adherence. With regard to efficacy in metastatic disease, exemestane is superior to megestrol acetate after progression on tamoxifen. There is evidence for noninferiority to fulvestrant (following a prior aromatase inhibitor) and to nonsteroidal aromatase inhibitors in the first-line setting. Combined use with everolimus is shown to be more efficacious than exemestane alone following previous aromatase inhibitor use. In the adjuvant setting, a switch to exemestane after 2–3 years of tamoxifen is superior to 5 years of tamoxifen. Exemestane is noninferior to 5 years of tamoxifen as upfront therapy, and may have a role as an extended adjuvant therapy. Used as neoadjuvant therapy, increased breast conservation is achievable. As chemoprevention, exemestane significantly reduces the incidence of breast cancer in "at-risk" postmenopausal women. Exemestane is associated with myalgias and arthralgias, as well as reduced bone mineral density and increased risk of fracture, which do not appear to persist at follow-up, with subsequent return to pretreatment values. Compared with tamoxifen, there is a reduced incidence of endometrial changes, thromboembolic events, and hot flashes. Limited evidence shows nonadherence in 23%–32% of patients. Evidence is growing in support of exemestane in all clinical settings. It is generally more efficacious and has a better safety profile than tamoxifen. How it compares with the nonsteroidal aromatase inhibitors remains to be established. Further studies are required on adherence to ensure that maximum benefit is obtained.

Keywords: breast cancer, exemestane, review, adherence, metastatic, adjuvant

Introduction

Exemestane is a third-generation, selective, irreversible, steroidal aromatase inhibitor and inhibits the enzyme aromatase in peripheral fat. This action reduces levels of circulating estrogen in postmenopausal women. Unlike tamoxifen, exemestane has no partial estrogen agonist activity. This study reviewed the literature systematically to evaluate the long-term clinical efficacy and safety of exemestane in the treatment of breast cancer and to identify the findings of studies, if any, related to adherence with the drug in clinical practice. An attempt will be made to contrast this compound against the "gold standard" endocrine agent, tamoxifen, as well as the nonsteroidal third-generation aromatase inhibitors.

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Literature search

A selective review of the literature in the Ovid Medline (1948–2012), Embase (1980–2012), and Web of Science (1899–2012) database using the search terms "exemestane" and "breast cancer" or "breast neoplasm" was undertaken, yielding 352 articles. The search was then limited to: humans; female; randomized controlled trial; invasive carcinoma; post-menopausal; and English language. Studies were excluded if outcomes were nonclinical, involved ductal carcinoma in situ (noninvasive), or pilot studies. The articles were first evaluated by title and abstract, yielding 62 results. After reading the full text, 42 remained (Figure 1).

A separate search was conducted for adherence. The aforementioned databases were searched using the terms "exemestane" and "adherence or nonadherence", "compliance or noncompliance", and "persistence or nonpersistence," finding 173 articles. After reading the title and abstract, 18 articles were identified for review of full text. Of these, three articles were selected by differentiating exemestane from the class of aromatase inhibitors (Figure 2).

Efficacy
Metastatic disease

Exemestane was first licensed for use in postmenopausal patients having metastatic breast cancer with estrogen receptor (ER)-positive tumors following progression on first-line antiestrogen therapy (tamoxifen). There are also emerging data to support its use in the first-line metastatic setting. Five key Phase III trials will be discussed in turn. The trials can be assigned to three groups according to the timing of intervention with exemestane (Table 1).
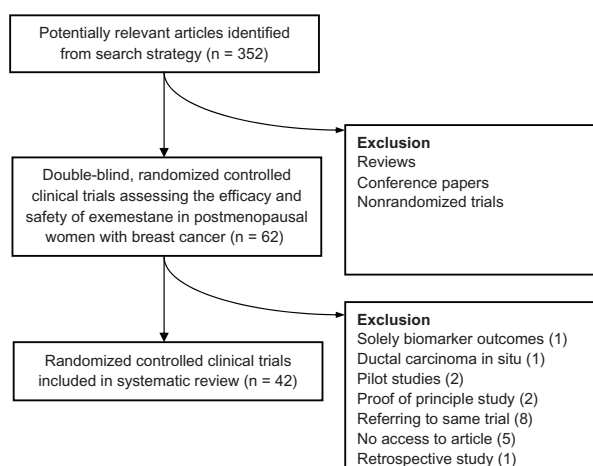

Figure 1 Process of identifying eligible studies addressing efficacy and safety of exemestane in the systematic review.
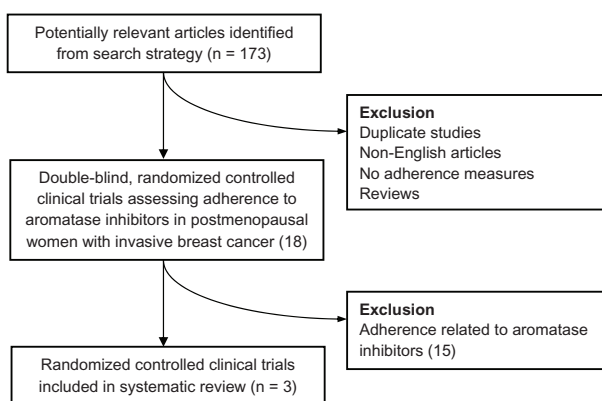

Figure 2 Process of identifying eligible studies addressing adherence with exemestane in the systematic review.

Following progression on tamoxifen

The Exemestane Study Group performed a trial assessing the efficacy of exemestane versus megestrol acetate (n = 769), following progression of metastatic breast cancer on tamoxifen.[1] The results demonstrated improved response rates (15% versus 12.4%) and better progression-free survival (20.3 versus 16.6 weeks, $P = 0.037$) with exemestane. At a median follow-up of 49 weeks, median overall survival was not reached in the exemestane arm, whilst it was reported as 123 weeks in the megestrol acetate arm ($P = 0.039$). The recommendation of the group was that exemestane should be considered more efficacious than megestrol acetate in this setting.

A Phase III GINECO (Groupe d'Investigateurs Nationaux pour L'Etude des Cancers Ovarien) trial identified in our search assessed exemestane versus exemestane and celecoxib in the setting of tamoxifen failure.[2] Celecoxib has been reported to have antitumor effects and synergistic properties when combined with an aromatase inhibitor, and has been well tolerated in Phase II studies.[3] On analysis of the 157 patients recruited, there was a trend towards improved progression-free survival in the combination arm of 9.6 versus 5.1 months. This identified a drug combination with potentially increased efficacy compared with monotherapy. However, following on from the increased cardiovascular events with rofecoxib in the APPROVe (Adenomatous Polyp PRevention On Vioxx) study, this trial was terminated before reaching accrual.[4]

Following progression on nonsteroidal aromatase inhibitors

EFECT (Evaluation of Faslodex versus Exemestane Clinical Trial) assessed the efficacy of fulvestrant, a pure estrogen antagonist (intramuscular injection every 28 days) and exemestane in 693 patients with metastatic breast

Table 1 A summary of the trials assessing the efficacy of exemestane in the metastatic, adjuvant, neoadjuvant and chemoprevention setting

	Trial	Drug in arm 1	Drug in arm 2	Ratio (95% CI)	P Value
Metastatic disease					
Kauffmann et al[1]	Exemestane study group trial	Exemestane (n = 366)	Megestrol Acetate (n = 403)		
	CR + PR, %, (95% CI)	15.0 (11.5–19.1)	12.4 (9.4–16.0)		NS
	Median TTP, weeks	20.3 (16.1–24.7)	16.6 (15.6–22.9)		0.037
Chia et al[5]	EFECT trial	Exemestane (n = 342)	Fulvestrant (n = 351)		
	CR + PR, %	6.7 (n = 270)	7.4 (n = 270)	OR 1.12 (0.58 to 2.19)	NS
	CR + PR + SD ≥ 24 weeks, %	31.5 (n = 270)	32.2 (n = 270)	OR 1.03; (0.72 to 1.49)	NS
	Median TTP, months	3.7	3.7	HR 0.96 (0.82 to 1.13)	NS
	Median duration of response (from the date of random assignment), months	9.8	13.5		
	Median duration of response (measured from date of first response), months	5.5	7.5		
Paridaens et al[8]	Phase III trial by EORTC	Exemestane (n = 182)	Tamoxifen (n = 189)		
	Median PFS, months	9.9 (8.7–11.8)	5.8 (5.3–8.1)		
	OS, %	45	43	HR 1.13 (0.85 to 1.50)	
	Median OS, months	37.2 (29.2–45.5)	43.3 (32.8–51.6)		
Llombart-Cussac et al[11]	Spanish Breast Cancer Group 2001–03 phase II randomized trial	Exemestane (n = 49)	Anastrozole (n = 51)		
	Median TTP after first line aromatase inhibitor therapy, months	6.1 (2.52–9.65)	12.1 (7.34–16.79)	HR 1.13 (0.75–1.72)	NS
	Median OS, months	48.3 (18.3–78.3)	19.9 (15.32–24.46)	HR 1.33 (0.78–2.25)	NS
	TTP after second line aromatase inhibitor therapy, months	2.0 (1.17–2.84)	4.4 (2.34 –6.47)	HR 4.01 (1.64–9.81)	0.002
Adjuvant setting					
Bliss et al[17]	Intergroup exemestane study	Tamoxifen followed by Exemestane (n = 2294)	Tamoxifen (n = 2305)		
	DFS first events, %	23.1	27	HR 0.81 (0.72–0.91)	<0.001
	OS, %	15.3	17.6	HR 0.86 (0.74–0.99)	0.04
	Time to distant recurrence, %	15	17.6	HR 0.73–0.97)	0.01
	CLBC, %	1.8	2.5	HR 0.71 (0.48–1.05)	NS
Van de Velde et al[12]	TEAM trial	Tamoxifen followed by exemestane (n = 4868)	Exemestane (n = 4898)		
	DFS at 5 years (intention to treat analysis), %	85	86	HR 0.97 (0.88–1.08)	NS
	OS at 5 years, %	91	91	HR 1.00 (0.89–1.14)	NS
	RFS events at 5 years, %	11	10	HR 0.94 (0.83–1.06)	NS
Mamounas et al[18]	NSABP B-33 trial	Exemestane (n = 783)	Placebo (n = 779)		
	4 year DFS, %	91	89	RR 0.68	0.07
	4 year RFS, %	96	94	RR 0.44	0.004
Neoadjuvant setting					
Ellis et al[22]	Z1031 trial	Exemestane (n = 124)	Letrozole (n = 127)	Anastrozole (n = 123)	
	CR, %	21.8	21.3	17.9	
	PR, %	41.1	53.5	51.2	
	NC, %	22.6	15.7	16.3	
	DP, %	6.5	4.7	7.3	
	ITT clinical response rate, (range) %	62.9 (53.8–71.4)	74.8 (66.3–82.1)	69.1 (60.1–77.1)	
Chemoprevention					
Goss et al[26]	MAP 3 trial	Exemestane (n = 2285)	Placebo (n = 2275)	Ratio	p value
	Number of cases	11	32	HR 0.35 (0.18–0.7)	0.002

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; TTP, time to progression; OR, odds ratio; HR, hazard ratio; PFS, progression free survival; DFS, disease free survival; RFS, recurrence free survival; OS, overall survival; CLBC, contralateral breast cancer; NC no change; DP, disease progression; ITT, intention to treat

cancer following progression on a nonsteroidal aromatase inhibitor.[5,6] Most patients were at third or subsequent lines of hormone therapy, due to tamoxifen preceding the nonsteroidal aromatase inhibitor. Therefore, as anticipated, overall response rates, defined as complete or partial response on RECIST (Response Evaluation Criteria In Solid Tumors) criteria, were low at 7.4% and 6.7% for fulvestrant and exemestane, respectively, yet clinical benefit (complete or partial response or stable disease at 24 weeks) was reported in one third of each of the treatment groups. Median time to progression was 3.7 months in both arms, with no difference in median duration of clinical benefit, supporting the use of either agent in this setting in metastatic disease.

A further trial investigating the addition of a drug to exemestane in the metastatic setting was identified by the search criteria. The BOLERO (Breast Cancer Trials of Oral Everolimus) 2 trial investigated the addition of everolimus, an inhibitor of mammalian target of rapamycin (mTOR), to exemestane in patients who had progressed on a nonsteroidal aromatase inhibitor.[7] Resistance to endocrine therapy has been linked to activation of the mTOR pathway, so dual inhibition was hypothesized to offset this resistance. The trial randomized 724 postmenopausal women with advanced breast cancer, 84% of whom had hormone-sensitive disease. The primary end point of the study was progression-free survival, and the results showed that exemestane alone was inferior to the combination with everolimus, with progression-free survival of 4.1 months compared with 10.6 months (hazard ratio for the combination arm 0.36; 95% confidence interval [CI] 0.27–0.47, $P < 0.001$). This pivotal study showed a definite objective clinical benefit, supporting the biological concept of crosstalk between the two signaling pathways.

First-line use
A large-scale multicenter, multinational Phase III trial was conducted by the EORTC (European Organisation for Research and Treatment of Cancer) to assess the efficacy of using exemestane or tamoxifen as first-line therapy for metastatic breast cancer (n = 371), following on from the low incidence of toxicity in the Phase II trial.[8–10] Both drugs were found to be well tolerated and participants treated with exemestane had a significantly higher response rate than those treated with tamoxifen (46% versus 31%, $P = 0.005$). Both treatments had equivalent median overall survival. There was also a significantly longer median progression-free survival with exemestane (9.9 months, 95% CI 8.7–11.8) compared with tamoxifen (5.8 months, 95% CI 5.3–8.1, $P = 0.028$) but this did not translate into a statistically significant long-term

benefit in progression-free survival at a later follow-up of 46 months. While the nonsteroidal aromatase inhibitors (anastrozole and letrozole) are now recognized as the first-line endocrine therapy of choice in the setting of metastatic breast cancer, the results of this study provide evidence that a steroidal aromatase inhibitor also works in the same setting and is more efficacious than tamoxifen.

A smaller scale Phase II trial, published in 2012, assessed the efficacy of using upfront exemestane or anastrozole (a nonsteroidal aromatase inhibitor) in first-line treatment for metastatic ER-positive breast cancer, with participants permitted to switch to the other aromatase inhibitor at progression.[11] Half of the 103 participants had previously received tamoxifen and 60% had received chemotherapy. No significant difference in clinical outcome between the two treatments was found and both drugs were well tolerated overall, with no serious adverse events reported. The authors concluded that there was insufficient evidence to support one agent as being more effective than the other or to justify a subsequent Phase III trial.

Summary
In metastatic breast cancer, exemestane has been demonstrated to be superior to megesterol acetate, following progression on tamoxifen, and also to tamoxifen, as a first-line therapy. There is also evidence to support noninferiority to nonsteroidal aromatase inhibitors and the pure antiestrogen, fulvestrant.

Adjuvant setting
Exemestane is licensed in the adjuvant setting as a sequential treatment after 2–3 years of tamoxifen in postmenopausal patients with ER-positive tumors. This section divides adjuvant treatment into three categories, based on the timing of randomization to exemestane or an alternative drug in three key Phase III trials, as follows.

Upfront therapy
The Phase III TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial randomized patients to upfront exemestane for 5 years versus a switch to exemestane after 2.5–3 years of tamoxifen.[12] Postmenopausal women (median age 64 [range 35–96] years) with ER-positive breast cancer were randomly assigned in a 1:1 ratio. At 5 years, no differences were noted in disease-free survival and overall survival between the groups, indicating that steroidal aromatase inhibitors alone are an option in adjuvant treatment. This is the only study in the adjuvant setting to assess exemestane upfront.

A prospective biomarker substudy of the same TEAM trial tested the hypothesis that patients with low progesterone

Table 2 Summary of trials assessing the safety of exemestane

Safety					
Metastatic trials					
Paridaens et al[10]	Phase III trial by EORTC	Exemestane (n = 182)		Tamoxifen (n = 189)	
		Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)
	Nonhematologic events				
	Alopecia	3.8	0	1.1	0
	Anorexia	10.4	0.5	9.5	1.1
	Anxiety	11	0	7.4	0
	Arthralgia	11.5	0	5.3	0
	Cardiac dysrhythmia	5.4	1.6	1.6	1.1
	Cardiac dysfunction	4.4	0.5	3.2	0.5
	Constipation	8.2	0	12.2	0
	Cough	14.8	0	15.9	0
	Deep vein thrombosis	1.6	0	1.6	0.5
	Depression	7.7	0.5	6.9	0.5
	Diarrhea	8.8	0	2.6	0
	Dyspnea	13.7	1.6	13.2	2.6
	Edema	9.9	1.1	10.1	1.1
	Fatigue/malaise/lethargy	35.7	1.1	35.4	1.1
	Gastrointestinal events	8.2	0	11.6	0.5
	Genitourinary events	4.9	0	5.3	0
	Hot flashes	34.6	0.5	38.1	0
	Hypertension	8.2	3.3	2.6	3.2
	Infection	15.4	1.1	12.2	0
	Insomnia	9.9	0	5.3	0
	Musculoskeletal events	4.9	0.5	0.5	1.1
	Nausea	17	0	19	0.5
	Neurologic, dizziness	11.5	0	10.1	0
	Neurologic, sensory	8.8	0.5	9.5	1.1
	Pain, bone	29.1	3.8	29.1	5.8
	Pain, other	31.9	2.7	27.5	3.2
	Phlebitis	0	0	0.5	0.5
	Skin	11	0.5	9.5	0
	Sweating	10.4	0	9	0
	Vaginal bleeding	1.1	0	3.2	0.5
	Vaginal discharge	2.2	0	6.9	0
	Vomiting	8.2	0	6.9	0
	Weight loss	16.5	0.5	14.8	1.1
	Weight gain	17.6	1.1	12.2	0.5
	Hematologic events				
	Leukopenia	17.6	0	18	0
	Neutropenia	9.9	1.1	13.8	0
	Thrombocytopenia	4.4	1.6	11.6	0.5
	Anemia	28	1.1	34.9	1.1
	Biochemical changes				
	Creatinine	7.1	1.6	4.2	0
	Bilirubin	11.5	3.3	1.1	1.6
	AST	49.5	4.9	50.8	4.8
	ALT	56.6	7.7	46	4.2
Kaufmann et al[1]		Exemestane (n = 358), %	Megestrol acetate (n = 400), %	OR (EXE/MA)	95% CI
	Any adverse event	39.1	45.8	0.76	0.576–1.02
	Hot flashes	12.6	5	2.73	1.58–4.72
	Nausea	9.2	5	1.93	1.09–3.43
	Fatigue	7.5	10.3	0.71	0.43–1.19
	Increased sweating	4.5	7.5	0.58	0.31–1.08
	Insomnia	3.6	3.3	1.12	0.51–2.45

(*Continued*)

Table 2 (*Continued*)

	Dizziness	3.4	3	1.12	0.5–2.53
	Increased appetite	2.8	5.8	0.47	0.22–1
	Abdominal pain	2.8	4.3	0.65	0.29–1.43
	Vomiting	2.8	0.8	3.8	1.04–13.93
	Rash	2	0		
	Constipation	0.8	2.5	0.33	0.09–1.21
	Dyspnea	0.3	3	0.09	0.01–0.7
	Withdrawal from study due to adverse events	1.7	5	$P = 0.011$	

Adjuvant setting

Bliss et al[17]		Tamoxifen followed by exemestane (n = 2105), %	Tamoxifen (n = 2036), %	OR	99% CI	*P* value
	All cardiovascular events (excluding hypertension and VTE)	12.3	10.4	1.21	0.94–1.57	0.049
	Ischemic cardiovascular disease	6	4.6	1.33	0.92–1.92	0.043
	Angina	5.2	3.9	1.37	0.92–2.05	0.038
	Other cardiovascular event	6.1	5.4	1.15	0.81–1.65	0.284
	Hypertension	26.7	23.3	1.2	0.99–1.45	0.011
	VTE	1	0.9	1.02	0.42–2.49	0.955
	DVT	0.8	0.9	0.91	0.35–2.33	0.788
	Fractures	6.8	5.7	1.2	0.86–1.69	0.147
	Arthritis (all types)	8.7	8.2	1.07	0.80–1.44	0.534
	Osteoarthritis	5.7	5.8	0.97	0.68–1.39	0.844
	Carpal tunnel syndrome	0.5	0.3	1.38	0.35–6.11	0.509
	Osteoporosis	5	4.7	1.07	0.73–1.57	0.632
	Muscle cramps	0.6	0.7	0.84	0.28–2.40	0.64
	Pain, musculoskeletal	15	12.8	1.2	0.95–1.52	0.041
	Pain, limb and/or foot	2.7	2.4	1.13	0.67–1.92	0.54
	Arthralgia	6.4	6.4	1	0.72–1.41	0.97
	Myalgia	0.9	0.5	1.59	0.56–4.87	0.225
	Pain, abdominal	2.3	1.5	1.51	0.81–2.86	0.075
	Pain, other	5.5	6.1	0.9	0.63–1.28	0.425
	Serious gynecologic events	1.5	1.8	0.83	0.42–1.62	0.451
	Vaginal bleeding	0.8	1.2	0.62	0.25–1.46	0.129
	Uterine polyps/fibroids and endometrial hyperplasia	0.9	1.7	0.56	0.23–1.26	0.052
	Uterine polyps/fibroids	0.8	1.6	0.53	0.21–1.24	0.043
	Endometrial hyperplasia	0.1	0.2	0.49	0.02–5.91	0.408
	Vaginal discharge	0.4	0.6	0.59	0.15–2.03	0.242
	Menopausal events	11.6	11.4	1.02	0.79–1.32	0.844
	Hot flashes	9	8.8	1.02	0.76–1.36	0.876
	Anxiety	1.7	1.3	1.29	0.65–2.63	0.313
	Depression	4.9	4.6	1.07	0.73–1.59	0.622
	Diarrhea	0.8	0.8	0.97	0.37–2.52	0.922
	Dizziness	3.2	3.9	0.83	0.53–1.29	0.259
	Fatigue	6.6	6.7	0.97	0.70–1.35	0.823
	GI ulcer	0.9	0.3	2.92	0.86–13.1	0.018
	Headaches	3.9	4.7	0.84	0.56–1.26	0.252
	Hypercholesterolemia	5.1	4.9	1.04	0.71–1.51	0.8
	Insomnia	6.3	6.2	1.01	0.72–1.42	0.913
	Nausea	1.7	1.5	1.16	0.6–2.3	0.543
	Paresthesia	0.4	0.3	1.45	0.33–7.33	0.477
	Polypectomy	0.1	0.2	0.39	0.02–3.8	0.238
	Sweating	3.7	3.8	0.95	0.62–1.47	0.769
Van de Velde et al[12]		Tamoxifen followed by exemestane (n = 4814), %	Exemestane (n = 4852), %	*P* value		

(*Continued*)

Table 2 (*Continued*)

Cardiac disorders				
Arrhythmia	3	4	0.038	
Cardiac failure	<1	1	0.009	
Myocardial ischemia or infarction	1	2	0.171	
Other cardiac disorders	2	2	0.843	
Vascular disorders				
Embolism	1	<1	0.808	
Flushes and sweats	40	35	<0.0001	
Hypertension	5	6	0.0003	
Peripheral arterial disease	<1	<1	0.038	
Venous thrombosis	2	<1	<0.0001	
Other vascular events	4	3	0.024	
Reproductive system and breast disorders				
Breast or nipple disorder	5	6	0.27	
Endometrial abnormalities	4	<1	<0.0001	
Genital or vaginal discharge	8	3	<0.0001	
Postmenopausal bleeding	5	3	<0.0001	
Vaginal dryness	6	7	0.038	
Vulvovaginal disorders	5	2	<0.0001	
Other reproductive system and breast disorders	3	2	<0.0001	
Musculoskeletal and connective tissue disorders				
Fractures	3	5	<0.0001	
Joint disorders	31	36	<0.0001	
Muscle disorders	13	11	0.0014	
Osteoporosis	6	10	<0.0001	
Other musculoskeletal and connective tissue disorders	13	15	0.0023	
Nervous system disorders				
Cerebrovascular insufficiency, infarction, or thrombosis	1	2	0.035	
Dizziness	6	5	0.051	
Headache	8	8	0.97	
Nerve compression disorders	2	3	0.008	
Other nervous system disorders	14	17	0.0004	
Psychiatric disorders				
Depression	9	9	0.583	
Reduction or loss of libido	3	4	0.061	
Sleep disorder or insomnia	10	13	<0.0001	
Other psychiatric disorders	9	8	0.736	
Laboratory investigations, and metabolism and nutrition disorders				
Abnormal liver function tests	3	4	0.038	
Hyperlipidemia	3	5	<0.0001	
Weight increased	9	7	0.005	
Other investigations	6	7	0.068	
Other metabolism and nutrition disorders	9		0.051	
Other disorders				
Endocrine disorders	2	3	0.028	
Renal and urinary disorders	5	4	0.006	
Chemoprevention				
Goss et al[26]		Exemestane (n = 2240), %	Placebo (n = 2248), %	*P* value
	Any	88	85	0.003
	Cardiac: hypertension	15	16	0.65

(*Continued*)

Table 2 (*Continued*)

Endocrine			
Hot flashes	40	32	<0.001
Fatigue	23	21	0.03
Sweating	22	19	0.046
Insomnia	10	8	0.04
Constitutional and gastrointestinal			
Diarrhea	5	3	0.002
Heartburn	15	13	0.06
Nausea	7	5	0.04
Musculoskeletal: arthritis	11	9	0.01
Neurologic			
Dizziness	8	9	0.32
Mood alteration or depression	11	10	0.96
Pain			
Back	9	10	0.45
Extremity	7	5	0.054
Joint	30	27	0.04
Muscle	7	9	0.01
Upper respiratory: cough	10	12	0.14
Sexual function: vaginal dryness	16	15	0.68
Secondary end point toxic effects			
Clinical skeletal fracture	6.7	6.4	0.72
New osteoporosis	1.7	1.3	0.39
Cardiovascular events	4.7	4.9	0.78
Other solid tumors or hematologic malignant lesions	1.9	1.7	0.58

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DVT, deep vein thrombosis; EORTC, European Organisation for Research and Treatment of Cancer; OR, odds ratio; CI, confidence interval; GI, gastrointestinal; MA, megestrol acetate; EXE, exemestane; VTE, venous thromboembolism.

receptor expression have increased clinical benefit from an aromatase inhibitor compared with tamoxifen, this being an association identified in the ATAC (Arimidex Tamoxifen Alone or in Combination) adjuvant trial.[13] A treatment benefit with exemestane was not identified in the progesterone receptor-poor patients. However, on multivariate analysis, the relative risk of relapse increased proportionally with decreasing expression of either receptor and there was a trend for increased treatment benefit in patients with ER-rich tumours.[14]

Sequential therapy

IES (the Intergroup Exemestane Study) enrolled 4742 postmenopausal patients with ER-positive or unknown receptor breast cancer, who had received 2–3 years of treatment with tamoxifen.[15,16] Participants were randomized to either continue tamoxifen treatment or to switch to exemestane to complete a 5-year treatment course, the median follow-up period being 30.6 months. The randomization method differed from that of TEAM in that this did not occur upfront, but after 2–3 years of endocrine therapy. An absolute reduction in risk of death of 4.7% was found in the switch arm, with an adjusted hazard ratio of 0.68 (95% CI 0.56–0.82; $P < 0.001$) comparing against the tamoxifen arm. There

was no significant difference in overall survival between the two treatment arms, with 93 and 106 deaths in the switch and tamoxifen arms, respectively. However, participants in the switch arm had a significantly lower incidence of the secondary end point, ie, contralateral breast cancer (9 versus 20 cases, $P = 0.04$).

A recent update at median follow-up of 7.6 years showed the persistent efficacy of the sequential arm in disease-free survival, comparing against tamoxifen.[17] The switch arm also demonstrated a modest but significant survival benefit (352 deaths) compared with the tamoxifen (405 deaths) arm (hazard ratio 0.86; 95% CI 0.75–0.99; $P = 0.04$).

Extended adjuvant therapy

The NSABP (National Surgical Adjuvant Breast and Bowel Project)-B33 trial investigated the potential value of extended adjuvant endocrine therapy using exemestane.[18] Until recently, when the long-term results of the ATLAS (Adjuvant Tamoxifen Longer Against Shorter) trial were published (showing that 10 years of tamoxifen produced superior benefits in terms of disease-free survival when compared with 5 years), it was thought that extending adjuvant tamoxifen beyond 5 years would not produce any significant impact, given that a second peak of recurrence occurs after

5 years.[19,20] In consequence, researchers started to explore the potential use of an aromatase inhibitor following 5 years of adjuvant tamoxifen. A similar National Cancer Institute of Canada study, Mammary 17 (MA17), looking into a different aromatase inhibitor, ie, letrozole, was also started around the same time.[21]

In the NASBP-B33 trial, postmenopausal patients with clinically staged T1-3 N1M0 breast cancer who were disease-free after 5 years of tamoxifen were randomly assigned to 5 years of exemestane or 5 years of placebo. However, in October 2003, the B-33 trial terminated accrual following publication of the results from MA17, which demonstrated the benefit of letrozole, a third-generation nonsteroidal aromatase inhibitor, in a similar role as for extended endocrine therapy after tamoxifen. At the time when B-33 trial terminated, a total of 1598 participants of the planned 3000 had been recruited. Despite premature closure and crossover to exemestane by a substantial proportion of patients, following unblinding of the participants, the intention-to-treat analysis of the original exemestane assignment demonstrated a trend for improvement in disease-free survival and a significant improvement in relapse-free survival of 96% versus 94% at a median follow-up of 30 months, the latter defined as time to recurrence or contralateral breast cancer.

Summary
Overall, a switch to exemestane appears to improve disease-free survival compared with tamoxifen alone. Five years of an aromatase inhibitor has not been demonstrated to be superior to sequential treatment at this time, but it appears to be non-inferior to 5 years of tamoxifen and an acceptable alternative in patients for whom tamoxifen is contraindicated. There may also be a role for extended adjuvant treatment using this class of drug following on from 5 years of tamoxifen.

Neoadjuvant setting
The Phase II ACOSOG (American College of Surgeons Oncology Group) Z1031 trial investigated the efficacy of exemestane, anastrozole, and letrozole as neoadjuvant therapy in 377 postmenopausal patients with ER-positive, stage II–III breast cancer.[22] Participants were randomized to receive one of the three aromatase inhibitors for 16–18 weeks before surgery. The results show that the overall breast conservation rate was 68%, which is comparable with that in the NSABP B18 study addressing the efficacy of neoadjuvant chemotherapy, including doxorubicin and cyclophosphamide.[23]

Of the 124 participants randomized to the exemestane arm in the Z1031 trial, 27 had a complete response, 51 had a partial response, 28 had stable disease, and eight had progressive disease. Five participants discontinued the medication and measurements were unavailable for five patients. The highest clinical response rate was found in the letrozole arm (rate 70.9%; 95% CI 62.2–78.6) followed by the anastrozole arm (rate 66.7%; 95% CI 57.6–74.9) and exemestane arm (rate 60.5%; 95% CI 51.3–69.1), but there was no significant difference between the three arms. Based on this trial, all three aromatase inhibitors could be considered for further investigation in a Phase III trial for a head-to-head comparison with chemotherapy as the neoadjuvant therapy.

Other smaller studies have also shown an objective reduction in tumor size with aromatase inhibitors, and celecoxib has again been trialed in combination with exemestane.[24] Aromatase inhibitors are likely to have an increasing role in the future in selected patients with locally advanced breast cancer.

Summary
The use of exemestane as neoadjuvant therapy is an attractive alternative to chemotherapy. Data exist showing increased breast conservation rates, but long-term outcome data, as well as a head-to-head comparison against chemotherapy, are not yet available. Whether exemestane is a superior or an inferior aromatase inhibitor in this setting remains to be established.

Chemoprevention
Most of the evidence for the efficacy of treatment in the reduction of breast cancer risk comes from the selective estrogen receptor modulators, ie, tamoxifen and raloxifene. A meta-analysis suggested an overall reduction in the risk of invasive breast cancer of 38% comparing tamoxifen against placebo, with no difference in overall survival. The number needed to treat to prevent one breast cancer at 5 years is 95 with tamoxifen.[25] However, long-term adherence to tamoxifen is poor in those individuals who are "at risk" because of concerns about the uncommon but serious adverse effects of venous thromboembolism and endometrial malignancy. The superiority of aromatase inhibitors over tamoxifen in terms of efficacy, notably in reducing contralateral cancers in the adjuvant trials as mentioned, has helped to drive exploration of their role in chemoprevention.

The large-scale, double-blind, placebo-controlled Mammary Prevention Trial 3 (MAP 3) was set up by the National Cancer Institute of Canada to assess exemestane as a chemoprevention agent.[26] A total of 4560 postmenopausal patients with at least one risk factor for future breast

cancer took part and, at a median follow-up of 3 years, there were significantly fewer breast cancer occurrences in the exemestane arm, with 11 versus 32. The number needed to treat to prevent one case of breast cancer was 94, but this was projected to decrease to 26 at 5 years.

Summary

Exemestane appears to be efficacious in the setting of chemoprevention when compared with placebo. Long-term follow-up is awaited, and its specific role when compared with other aromatase inhibitors and selective estrogen receptor modulators remains to be elucidated.

Safety

Many of the trials investigating the efficacy of exemestane in the adjuvant and metastatic settings as well as in chemoprevention included safety and quality of life as a secondary end point, and provide valuable information. The adjuvant trials have the advantage of absence of metastatic disease, which can confound the causality between treatments and outcomes. Furthermore, both adjuvant and chemoprevention trials, as opposed to metastatic studies, have an additional advantage in long-term follow-up, which is more suitable to assess safety of treatments (Table 2).

Metastatic trials

In the metastatic setting, the EORTC trial of exemestane versus tamoxifen as first-line treatment provides valuable data.[8–10] Both drugs were well tolerated and there were no treatment-related deaths. Sixty-one patients had a grade 3/4 nonhematological adverse events in the tamoxifen arm versus 41 with exemestane. With exemestane, there were reduced grade 2/3 hot flashes (6.5% versus 12.2%) and grade 1/2 vaginal discharge and bleeding (3.3% versus 10.1%), but increased grade 1/2 arthralgias (11.5% versus 5.3%), grade 1/2 cardiac dysrhythmias (5.4% versus 1.6%), and grade 1 diarrhea (8.8% versus 2.6%). Approximately one-third of patients in each arm had significant fatigue and one-fifth had nausea. There was no detrimental effect on cholesterol levels or on atherogenic indices, which are well known risk factors for coronary artery disease,[27] in patients with exemestane.

The second trial to be discussed assessed exemestane versus megestrol acetate in metastatic breast cancer.[1] This trial provides safety data in relation to a comparison with megestrol acetate, which cannot be obtained in adjuvant and chemoprevention settings when the drug is not being used. Already demonstrated to be clinically more effective in the quality of life assessment, patients treated with exemestane

showed a statistically significant improvement in physical functioning, role functioning, global health, fatigue, dyspnea, and constipation compared with patients who received megestrol acetate.

Adjuvant trials

In IES, acute effects of arthralgias and diarrhea were more common with exemestane than with tamoxifen, with fewer gynecological symptoms, muscle cramps, and thromboembolic events.[28,29]

The incidence of adverse events decreased over a longer follow-up period due to the cessation of treatment.[29] For exemestane, the incidence of musculoskeletal pain, arthritis, and osteoporosis decreased. However, there was an objective decrease in bone mineral density compared with baseline in the patients who switched to exemestane, which was more marked in the first 6 months than at 2 years. No patients developed osteoporosis, but there was a significantly increased fracture risk of 7% versus 5% (odds ratio 1.45, 95% CI 1.13–1.87, $P = 0.003$).[30] Importantly, the increased fracture incidence in the exemestane arm did not persist at follow-up, and mean bone mineral density returned to pretreatment values at one year after discontinuation. Smaller trials have addressed the incidence of reduced bone mineral density compared with tamoxifen or placebo and, similarly, an early objective loss is seen, but is not maintained in the follow-up period.[31,32]

Similarly, the increased risk of serious gynecological events with tamoxifen did not continue into the follow-up period, with some objective reversal of endometrial thickening.[33] At a median follow-up of 91 months, there was an increased incidence of carpal tunnel syndrome with exemestane at 2.8% versus 0.6% with tamoxifen (OR 5.23, 99% CI 2.39–11.49, $P < 0.0001$), warranting surgical intervention in 69% of cases.[34]

There was a trend towards increased cardiovascular events (excluding hypertension and venous thromboembolism) following sequential treatment (tamoxifen followed by exemestane) as opposed to 5 years of tamoxifen alone, at 12.3% (n = 259) versus 10.4% (n = 211), which did not reach statistical significance but which the authors felt was important to acknowledge. However, despite the reported increase in cardiovascular morbidity, this did not equate to a higher cardiovascular death rate.

Follow-up for IES found what is desirable for any adjuvant treatment, ie, a prolongation of risk reduction, without prolongation of adverse effects.

The TEAM trial, which is the largest adjuvant study of exemestane to date, found that sequential treatment (tamoxifen

for 2–3 years before exemestane) had a higher incidence of gynecological symptoms (20% versus 11%), venous thrombosis (2% versus 1%), and endometrial abnormalities (4% versus <1%) compared with 5 years of exemestane alone. Musculoskeletal adverse events, including arthralgias and myalgias (50% versus 44%), hypertension (6% versus 5%), and hyperlipidemia (5% versus 3%) were reported more frequently with exemestane alone.[12,35,36] Rather than exemestane causing an increase in lipids per se, substudies of TEAM have found exemestane to have a neutral effect on lipid profiles, compared with the beneficial effect found with tamoxifen.[37–39] Hot flashes were reported to be significantly increased with tamoxifen, with an increase of 33% from baseline compared with 7% in the exemestane arm. With exemestane treatment, musculoskeletal adverse events including arthralgias and myalgias (50% versus 44%), hypertension (6% versus 5%), and hyperlipidemia (5% versus 3%) were reported more frequently. As with the IES, there was increased bone loss in the aromatase inhibitor arm. A substudy of 161 patients found that the greatest loss in bone mineral density was within the first 6 months, but this loss stabilized after 6–12 months of treatment. Tamoxifen caused a 0.5% increase in bone mineral density at the spine at 12 months, whilst exemestane-treated patients had a 2.6% decrease at 6 months with a further 0.2% decrease at 12 months ($P = 0.0008$). Bone loss was found to stabilize after 6–12 months of treatment.[40,41]

A substudy of the TEAM trial in Dutch participants to assess possible changes in cognitive function with each endocrine therapy produced interesting results.[42,43] After one year of tamoxifen (n = 80) there was a statistically significant decrease in verbal recall and executive functioning. This was not found in the 99 exemestane patients assessed.

Chemoprevention

Exemestane is associated with increased serum bone turnover markers in healthy postmenopausal women, suggesting a specific bone formation effect related to its androgenic structure.[44,45] A nested substudy of the MAP 3 trial investigated bone health. After 2 years of treatment with exemestane, there was more age-related bone loss in postmenopausal women than in those on placebo, despite calcium and vitamin D supplementation. To date, there has been no significant difference in skeletal-related events demonstrated, but longer-term follow-up is awaited.[46] Adverse events occurred in 88% of the exemestane group versus 85% of the placebo group ($P = 0.003$) with no significant difference in cardiovascular events. There was an increased incidence of menopausal symptoms and sexual dysfunction in the exemestane group, but this did not affect overall health-related quality of life.

Summary

Both tamoxifen and aromatase inhibitors (including exemestane) have differing side effect profiles, by virtue of their mechanisms of action. Tamoxifen has partial estrogen agonist properties, which have a protective effect on bone mineral density and the cardiovascular system. This cannot be said for aromatase inhibitors, and it is this depletive action on estrogen levels that is thought to have an adverse effect on cardiac and bone health.

All patients receiving aromatase inhibitors are generally recommended to have a baseline bone densitometry scan which should be repeated as appropriate.[47] Intervention with bisphosphonates and bone-strengthening medication is only recommended if the patient has osteoporosis at baseline. Cardiac dysfunction is a less frequent adverse event, hypothesized to be secondary to the cardioprotective effect of tamoxifen in the control arm, rather than an increased risk caused by aromatase inhibitors per se.

More commonly seen adverse effects of aromatase inhibitors are arthralgias and myalgias that can lead to premature discontinuation of the drug. These agents are also associated with fewer hot flashes, weight gain, thromboembolic disease, and endometrial cancer than tamoxifen.

To date, the side effect profile of exemestane appears to be a class effect (as a member of the third-generation aromatase inhibitors) with no specific adverse effects demonstrated as a result of it being a steroidal aromatase inhibitor.

Adherence

Adherence to a prescribed course of medication can be influenced by many factors, including patient age, financial situation if self-funding, and the side effect profile. Most publications have addressed aromatase inhibitors as a whole, and there is a paucity of data related to adherence specifically with regard to exemestane. A retrospective review of 13,593 patients with postmenopausal breast cancer prescribed exemestane, with anastrozole or letrozole as adjuvant therapy, found nonadherence in 23% patients over one year, based upon medication possession ratio.[48] Using multivariate logistic regression, factors associated with nonadherence included younger age, breast-conserving surgery rather than mastectomy, and an increased Charlson Comorbidity Index. The study recommended identifying such individuals for early supervision and to support "medication-taking behaviors".

One prospective study recruited 503 patients with early breast cancer to receive letrozole or exemestane, and participants could switch to the other aromatase inhibitor following a 2–8-week washout period if side effects became intolerable (Table 3).[49] Of all the patients, 32.4% stopped their aromatase inhibitor within 2 years because of adverse effects, 24.3% of which were musculoskeletal in nature. The median time to discontinuation for adverse effects was 6 (range 0.1–21) months, and this duration was significantly shorter in the exemestane arm than in the letrozole arm (hazard ratio 1.5; 95% CI 1.1–2.2, $P = 0.02$). Younger age and prior taxane exposure increased the likelihood of discontinuation of therapy. Following a switch to the other aromatase inhibitor, more than a third of patients could continue their adjuvant treatment. This may be attributable to the myalgias and peripheral paraesthesias experienced by many patients when on taxane therapy, affecting the threshold of tolerance for further adverse effects with aromatase inhibitors.

A substudy of the TEAM trial looked specifically at age-specific nonpersistence with endocrine therapy, this being defined as discontinuation of therapy within one year of follow-up.[50] Conversely, increased age was associated with a higher proportion of nonpersistence at one year. This could be secondary to older patients having an increased likelihood of coexisting health problems requiring medication. This polypharmacy could affect compliance and therefore adherence to the proposed 5-year treatment.

Summary

There is clearly a lack of evidence in the literature concerning adherence to exemestane. The limited evidence available suggests that nonadherence could affect a significant number of patients and has been associated with both extremes of age. Clearly more qualitative research is required to help identify individuals most at risk of noncompliance, in whom closer supervision in both primary and tertiary care may improve outcomes.

Conclusion

Current licensing by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK approves the use of exemestane in postmenopausal (natural or induced) ER-positive women in two settings, ie, as part of adjuvant sequential therapy, following 2–3 years of tamoxifen, to make 5 years in total, and in metastatic breast cancer, following failure on antiestrogen therapy.

In addition to and alongside these indications, key trials of exemestane in breast cancer in a number of settings in both early and advanced breast cancer have shown Phase III evidence supporting its efficacy (with some promising results in chemoprevention), but at the expense of toxicity, predominantly affecting bone, musculoskeletal, and cardiovascular health. This emphasizes the importance of patient-centered care. When deciding upon a treatment for a patient, their past medical history, quality of life, and psychosocial needs must be addressed in turn. Of utmost importance is the involvement of the patient in the decision-making process, because there are pros and cons with any treatment being considered.

Disclosure

The authors report no conflicts of interest in this work.

Table 3 Adherence of early postmenopausal breast cancer patients to exemestane versus letrozole

Adherence Henry et al[49]		Exemestane (n = 248)	Letrozole (n = 252)	*P* value
	Treatment discontinuation due to toxicity, %	36.7	28.6	0.02
	Treatment discontinuation for reasons other than toxicity, %	10.5	6.7	
	Treatment discontinuation due to musculoskeletal symptoms, %	26.6	22.2	
	Median time to treatment discontinuation, months	5.8 (range 0.2–20.3)	8.1 (range 0.1–21.2)	

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