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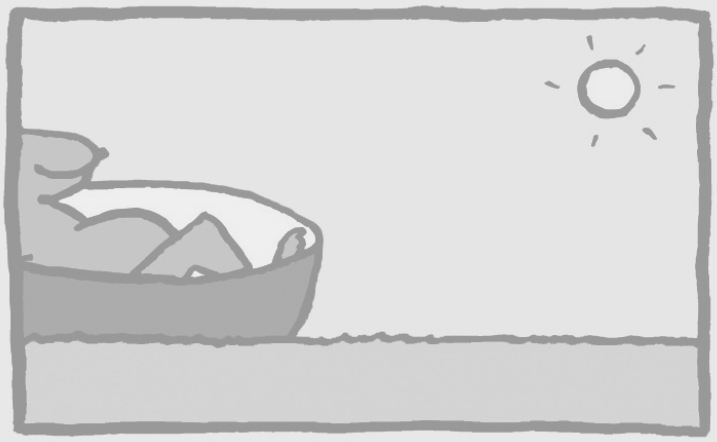
Switching from tamoxifen to aromatase inhibitors for adjuvant endocrine therapy in postmenopausal patients with early breast cancer



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Published in Cancer Treatment Reviews 2010; 36: 54-62.

Abstract

Background The third-generation aromatase inhibitors (AIs), including anastrozole, exemestane and letrozole, have demonstrated improved efficacy versus tamoxifen for the adjuvant endocrine treatment of postmenopausal patients with hormone receptor-positive breast cancer.

Methods AIs can be used in several adjuvant endocrine settings: as upfront therapy, switch to an AI after 2–3 years of tamoxifen or extended therapy following 5 years of tamoxifen. In the switch setting, two different types of study designs have been utilized. One is a late randomization design which randomizes patients who are disease-free after 2–3 years of tamoxifen to receive an AI versus continuation of tamoxifen. In contrast, an early randomization design randomizes all patients immediately after primary treatment and prior to starting tamoxifen.

Results Efficacy benefits with AIs have been shown in several trials evaluating the late randomization strategy, including the Intergroup Exemestane Study, the Italian Tamoxifen Anastrozole trial and the Anastrozole-Nolvadex 95 trial. Similarly, early randomization studies, including the Austrian Breast and Colorectal Cancer Study Group-8 and the Breast International Group (BIG) 1–98 trial, have demonstrated the effectiveness of receiving an AI after tamoxifen. Two trials are assessing an early switch strategy versus upfront AI therapy: the BIG 1–98 trial and the ongoing Tamoxifen Exemestane Adjuvant Multicentre trial are assessing switching from tamoxifen to an AI after 2–3 years versus upfront AI therapy.

Conclusion This paper reviews studies that have investigated a switch strategy with AIs and considers the implications of these data on treatment choice for postmenopausal patients with hormone receptor-positive breast cancer.

Introduction

For many years, tamoxifen has been the standard adjuvant endocrine therapy for patients with hormone receptor-positive early breast cancer, having demonstrated a long-term efficacy benefit.[1] However, the third-generation aromatase inhibitors (AIs) are now playing an increasingly important role for endocrine therapy.[2] The third-generation AIs, anastrozole and letrozole (nonsteroidal) and exemestane (steroidal), have established superior efficacy versus tamoxifen, as first-line treatment of metastatic breast cancer in postmenopausal patients.[3-5] These agents have also shown a benefit in efficacy over tamoxifen as adjuvant endocrine therapy in postmenopausal patients with hormone receptor-positive early breast cancer.[6-8] AIs can be utilized in several adjuvant settings: starting with an AI (upfront therapy), switch to an AI after 2–3 years of tamoxifen, or extended therapy with an AI following 5 years of tamoxifen.[2] All of these strategies are potentially useful dependent upon individual patient and tumour characteristics, and treatment goals.

Primary resistance to tamoxifen has been observed in some patients, and those patients who may have initially benefited from tamoxifen can develop secondary resistance.[9] It is also important to consider that although tamoxifen has been shown to have positive effects on bone and lipid metabolism, it has also been associated with an increased risk of endometrial cancer and thromboembolism.[10-13] In contrast, AIs have been associated with musculoskeletal adverse events and an increased rate of fractures and osteoporosis but have not been linked with endometrial cancer or thromboembolism.[6-8,14]

The rationale for switching from tamoxifen to an AI during adjuvant therapy is to improve efficacy, including reduction in recurrence and to improve relapse-free survival, disease-free and overall survival (OS). It has also been hypothesized that initial tamoxifen treatment would allow patients to receive some of the benefits of tamoxifen, in particular its oestrogenic effects, potentially reducing the bone loss associated with the use of AIs. Switching to an AI might then reduce the ad-

Table 1 Efficacy endpoints in trials assessing a switching or sequencing strategy.

	Primary efficacy endpoint	Other efficacy endpoints
IES[7]	Disease-free survival: Local and distant breast cancer recurrence, new primary breast cancer (ipsilateral or contralateral) and death without disease relapse (intercurrent death)	Overall survival Incidence of contralateral breast cancer Breast cancer free survival (censoring deaths of known cause) Time to distant recurrence (distant recurrence, deaths form breast cancer, deaths with unknown cause with no metastases reported)
ITA[17,18]	Disease-free survival: Locoregional and distant recurrences (except contralateral breast cancer)	Event free survival (locoregional recurrence, distant metastases, second primary tumours [including contralateral breast cancer] and breast cancer-unrelated death) Incidence of death (whatever the cause)
ARNO 95[19]	Disease-free survival: Local or distant recurrence, new contralateral breast cancer or death	Overall survival
ABCSG 8[20]	Recurrence-free survival: Local and distant recurrence, contralateral breast cancer, death without recurrence	Overall survival
ARNO 95/ABCSG 8[21]	Event-free survival: Time to relapse at any site or incidence of contralateral breast cancer	Distant recurrence-free survival
Meta-analysis of ITA, ABCSG 8 and ARNO 95[22]	Disease-free survival: Time to relapse at any site, incidence of contralateral breast cancer, death from any cause Event-free survival: Time to relapse at any site or incidence of contralateral breast cancer Distant recurrence-free survival: Time to earliest occurrence of distant recurrence Overall survival: Including deaths with or without recurrence	
TEAM[24]	Disease-free survival: Loco-regional or distant breast cancer recurrence, second primary or contra-lateral breast cancer, deaths from any cause	Overall survival Time to new primary breast cancer Relapse-free survival
BIG 1-98[26]	Disease-free survival: Recurrence at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second, non-breast cancer; or death without a prior cancer event	Overall survival Systemic disease-free survival Time to recurrence Time to distant recurrence

verse events associated with tamoxifen use, while providing greater efficacy.[7] Two different types of study designs have assessed patients receiving treatment with tamoxifen for 2–3 years, followed by an AI for 2–3 years, to complete a total of 5 years of endocrine therapy. In late randomization (switch) studies, patients are randomized after they have received tamoxifen for 2–3 years; as such, patients who have experienced a recurrence during their initial 2–3 years on tamoxifen are excluded from randomization. In early randomization (sequence) studies, patients are randomized prior to initiation of treatment with tamoxifen. These different designs may have implications for the interpretation of results of studies with AIs in the adjuvant setting.

This review provides an overview of the trials that have investigated a late randomization (switch) or an early randomization (sequencing) strategy

with AIs in postmenopausal women with early breast cancer. Furthermore, any differences between the sequenced and upfront strategies with AIs will also be considered, along with the implications for treatment choice in this patient population.

Results from late randomization studies with AIs

Aromatase inhibitors have been assessed in several late randomization trials. The use of exemestane has been assessed in a large, randomized phase III study, the Intergroup Exemestane Study (IES).[7,15] Anastrozole has been assessed in two studies, namely the Italian Tamoxifen Anastrozole (ITA) trial and the Anastrozole-Nolvadex (ARNO) 95 trial.[17-19]

The Intergroup Exemestane Study

The IES is a phase III, double-blind, randomized, international study conducted to evaluate the efficacy and safety of switching to exemestane after 2–3 years of tamoxifen, compared with continuing tamoxifen treatment.[15] A total of 4724 postmenopausal patients with unilateral, invasive, oestrogen receptor (ER)-positive or ER-unknown breast cancer who were disease-free after 2–3 years of tamoxifen use were randomized to continue tamoxifen (20 or 30mg daily) or to switch to exemestane (25mg daily) to complete 5 years of endocrine therapy.[15]

The primary endpoint of the study was disease-free survival (DFS). Secondary endpoints included OS and the incidence of contralateral breast cancer. To allow comparison with other studies, breast cancer-free survival and time to distant recurrence were also evaluated (Table 1).[7] The two treatment groups were balanced with respect to baseline patient characteristics, tumour characteristics and local and systemic treatment (Table 2).[7]

At a median follow-up of 56 months, exemestane was associated with a 24% reduction in the risk of recurrence or death (HR 0.76, 95%CI 0.66–0.88; $p = 0.0001$) compared with continued tamoxifen treatment in the intention-to-treat (ITT) population (Table 3).[7] This resulted in a 3.3% absolute benefit in DFS with exemestane relative to tamoxifen by the end of treatment (2.5 years after randomization). When the study started, receptor status was not routinely checked in all countries. In this analysis, ER status was ascertained in 381 patients who previously had unknown ER status. Of these, 122 patients were found to have ER-negative tumours. Therefore, analyses excluding these patients were also performed. Statistically significant improvement in DFS was observed in the ER-positive or ER-unknown group (HR 0.75, 95%CI 0.65–0.87; $p = 0.0001$) and in the ITT population (HR 0.76 95%CI 0.66–0.88; $p = 0.0001$).[7] Switching to exemestane also led to significant improvements in breast cancer-free survival, time to distant recurrence and time to contralateral breast cancer compared with continued tamoxifen treatment in the ITT population (Table 3).[7] In the ITT analysis, switching to exemestane was associated with a 15% reduction in death compared with tamoxifen alone; however, this improvement was not statistically significant ($p = 0.08$).[7] Importantly, when patients with ER-negative disease were excluded, a significant improvement in OS was observed with exemestane – there was a 17% relative reduction in deaths ($p = 0.05$) in patients who switched to exemestane compared with those continuing on tamoxifen (Table 3).[7] Furthermore, there were fewer non-breast cancer deaths in patients who switched to exemestane compared with those continuing tamoxifen.[7]

In an updated analysis at a median follow-up of 91 months, the benefit in DFS and OS was maintained during longer follow-up in patients who switched to exemestane after 2–3 years of tamoxifen.[16] These results confirmed the significant improvements in DFS in both the ITT population (HR 0.84, 95%CI 0.75–0.94; $p = 0.02$) and the ER+/unknown population (HR 0.82, 95%CI 0.73–0.92; $p = 0.0009$) for the switching arm compared with continuing tamoxifen. Furthermore, OS was improved with exemestane in the ITT population (HR 0.89, 95%CI 0.77–1.02; $p = 0.09$), and the risk of mortality was significantly decreased by 14% with exemestane in the ER+/unknown population (HR 0.86, 95%CI 0.75–0.99; $p = 0.04$). This resulted in a 2.4% (95%CI: 0.1–4.8) absolute benefit in OS with exemestane relative to tamoxifen at 5 years after the end of treatment. In addition, no further, unexpected adverse events were observed during longer follow-up.[16]

Table 2 Patient baseline characteristics in trials assessing a late randomisation strategy.

	IES[7]		ITA[17,18]		ARNO 95[19]	
N	4724		448		979	
Randomization strategy	Late		Late		Late	
Treatment arm	Tamoxifen	Tamoxifen → Exemestane	Tamoxifen	Tamoxifen → Anastrozole	Tamoxifen	Tamoxifen → Anastrozole
Age (years)	<60: 32.0% 60–69: 42.8%	<60: 32.4% 60–69: 42.7%	Median: 63 years	Median: 63 years	Mean: 60.9 years	Mean: 60.5 years
Surgery	Mastectomy: 51.5%	Mastectomy: 51.2%	Mastectomy: 55%	Mastectomy: 52%	BCS: 67.5% Modified radical: 32.5%	BCS: 70.0% Modified radical: 29.8%
Chemotherapy	32.4%	32.9%	67%	67%	No patients received chemotherapy	
Tumour grade						
Grade 1	16.6%	16.9%	66% (G1/2)	63% (G1/2)	13.7%	11.4%
Grade 2	42.5%	41.5%			70.1%	67.1%
Grade 3	18.0%	19.3%	19%	24%	15.5%	19.2%
Not determined/missing	22.9%	22.3%	15%	13%	0.6%	2.0%
Receptor status	ER+ and PgR+: 56% ER+ and PgR–/?: 29% ER? and PgR+/?:12% ER– and PgR+: 0.3% ER– and PgR–/?: 2.5%	ER+ and PgR+: 57% ER+ and PgR–/?: 29% ER? and PgR+/?:12% ER– and PgR+: 0.3% ER– and PgR–/?: 2.1%	ER+: 86% ER–: 0 Undetermined/ missing: 14%	ER+: 91% ER–:1% Undetermined/ missing: 8%	Confirmed positive: 97.1% Unknown: 2.9%	Confirmed positive: 96.3% Unknown: 3.7%
Nodal status	Negative: 52% 1–3 N+: 30% ≥4 N+: 14% Missing/unknown: 4%	Negative: 52% 1–3 N+: 30% ≥4 N+: 14% Missing/unknown: 4%	≤3 N+: 59% >3 N+: 40% Missing: 1%	≤3 N+: 68% >3 N+: 32% Missing: –	Negative: 74.0% 1–3 N+: 19.6% 4–9 N+: 6.3%	Negative: 73.1% 1–3 N+: 22.4% 4–9 N+: 4.5%

BCS breast conserving surgery; *ER* oestrogen receptor; *PgR* progesterone receptor.

The Italian Tamoxifen Arimidex (ITA) Trial

The ITA trial was a phase III, open-label, randomized, national trial. A total of 448 postmenopausal women with ER-positive and node-positive primary breast cancer with no evidence of recurrence after using tamoxifen for 2–3 years were randomized to switch to anastrozole (1mg daily) or to continue tamoxifen (20mg daily).[17]

The primary endpoint was DFS and the secondary endpoints included event-free survival, OS and safety (Table 1). The two treatment groups were similar with respect to age, disease status, local therapy and prior chemotherapy at baseline (Table 2).

An analysis at a median follow-up of 64 months showed that there was a significant improvement in event-free survival for patients receiving anastrozole relative to those continuing tamoxifen (HR 0.57, 95%CI 0.38–0.85; p = 0.005; Table 3).[18] Furthermore, a significant improvement in relapse-free survival (HR 0.56, 95%CI 0.35–0.89; p = 0.01) was observed in patients who switched to anastrozole compared with those continuing tamoxifen (Table 3). There was a trend towards an improvement in OS in patients who switched to anastrozole; however, the difference between the groups was not statistically significant (p = 0.1).[18]

The Arimidex-Nolvadex (ARNO) 95 trial

The activity of anastrozole in the switch setting was also evaluated in the ARNO 95 trial, a phase III, open-label, randomized, national trial.[19] A total of 979 postmenopausal women with hormone receptor-positive breast cancer who had received 2 years of tamoxifen treatment without disease recurrence were randomized to switch to anastrozole (1mg daily) or continue tamoxifen (20 or 30mg daily) to complete 5 years of endocrine therapy.[19]

The primary efficacy endpoint was DFS and secondary endpoints were OS and assessment of safety (Table 1). The demographic and baseline breast cancer characteristics of patients enrolled were similar across the treatment groups.[19] Of note, since patients with hormone-sensitive grade 3 breast cancer, considered as intermediate/high risk patients, were not eligible to receive chemotherapy in Germany at the initiation of ARNO 95, no patients received chemotherapy in this study.

At a median follow-up of 30.1 months, there was a significant improvement in DFS in patients who switched to anastrozole compared with those continuing tamoxifen (HR 0.66, 95%CI 0.44–1.00; p = 0.049; Table 3). OS was also significantly improved in the anastrozole group compared with the tamoxifen group (HR 0.53, 95%CI 0.28–0.99; p = 0.045; Table 3).[19]

Results from early randomization studies with AIs

The Austrian Breast and Colorectal Cancer Study Group trial 8 (ABCSG 8) assessed the use of anastrozole in an early randomization strategy.[20] This study has also been included in a combined analysis with a late randomization study – the ARNO 95 study.[21] A meta-analysis, including both late randomization trials with anastrozole – the ARNO 95 and ITA – and the ABCSG 8 trial has also been performed.[22]

The ABCSG 8

The ABCSG 8 trial, a phase III, randomized, open-label, national trial, enrolled postmenopausal patients with grade 1 or grade 2 hormone receptor-positive breast cancer.[20] Patients who had received prior chemotherapy were excluded. Eligible patients were randomized to receive 5 years of tamoxifen (20mg daily) or 2 years of tamoxifen followed by 3 years of anastrozole (1mg daily).[20] The primary endpoint was recurrence-free survival; secondary endpoints included OS and safety (Table 1).[20]

A total of 3714 patients were included in the analysis. Of these, 1849 patients were randomized to receive tamoxifen and 1865 were randomized to the sequence of tamoxifen followed by anastrozole. Intention-to-treat results have not been reported to date. At a median follow-up of 72 months, a censored analysis excluding non-protocolled crossover patients showed that recurrence-free survival was not significantly improved in patients in the sequence group compared with the tamoxifen alone group (HR 0.85, 95%CI 0.71–1.01; p = 0.066) and OS was significantly improved in the sequenced arm versus the tamoxifen alone group (HR 0.78, 95%CI 0.62–0.98;

Table 3 Key efficacy results in trials assessing a late randomisation strategy.

	IES[7,16] (Tamoxifen → exemestane vs. tamoxifen)	ITA[18] (Tamoxifen → anastrozole vs. tamoxifen)	ARNO 95[19] (Tamoxifen → anastrozole vs. tamoxifen)
n	4724	448	979
Randomization strategy	Late	Late	Late
Follow-up (median)	OS and DFS: 91 months Other endpoints: 55.7 months	64 months	30.1 months
Disease-free survival	HR 0.84, 95%CI 0.75–0.94; $p = 0.02$[a] HR 0.82, 95%CI 0.73–0.92; $p = 0.0009$[b]	Not reported	HR 0.66, 95%CI 0.44–1.00; $p = 0.049$
Event-free survival	Not reported	HR 0.57, 95%CI 0.38–0.85; $p = 0.005$	Not reported
Relapse-free survival	Not reported	HR 0.56, 95%CI 0.35–0.89; $p = 0.01$	Not reported
Overall survival	HR 0.89, 95%CI 0.77–1.02; $p = 0.09$[a] HR 0.86, 95%CI 0.75–0.99; $p = 0.04$[b]	HR 0.56, 95%CI 0.28–1.15; $p = 0.1$	HR 0.53, 95%CI 0.28–0.99; $p = 0.045$
Breast cancer-free survival	HR 0.76, 95%CI 0.65–0.89; $p = 0.0004$	Not reported	Not reported
Time to contrlateral breast cancer	HR 0.57, 95%CI 0.33–0.98; $p = 0.04$	Not reported	Not reported
Time to distant recurrence	HR 0.83, 95%CI 0.71–0.99; $p = 0.03$	Not reported	Not reported

[a]Intention-to-treat population
[b]Oestrogen receptor-positive or unknown populations

p = 0.032; Table 4A).[20] Furthermore, it was demonstrated that high levels of ER and progesterone (PgR) were predictive for improved recurrence-free survival and OS.[20]

Combined analysis of ARNO 95 and the ABCSG trial 8

A combined analysis of ARNO 95 and ABCSG trial 8 was performed.[21] A total of 3224 postmenopausal women with hormone-sensitive early breast cancer were included in the analysis.[21] The primary endpoint was event-free survival. Other endpoints included distant recurrence-free survival and assessment of tolerability (Table 1).[21]

At a median follow-up of 28 months there was an improvement in event-free survival in patients who switched to anastrozole compared with those who continued tamoxifen (HR 0.6, 95%CI 0.44–0.81; p = 0.0009).[21] Distant recurrence-free survival was also superior in patients receiving anastrozole (HR 0.61, 95%CI 0.42–0.87; p = 0.0067). Although OS was slightly improved in patients who switched to anastrozole, there was no statistically significant difference between the treatment groups (p = 0.16).[21]

Meta-analysis of ITA, ABCSG 8 and ARNO 95

A meta-analysis of the three anastrozole trials (including early and late randomization strategies) described above – ITA, ABCSG 8 and ARNO 95 – has also been performed.[22] The endpoints for this analysis were DFS, event-free survival, distant recurrence-free survival and OS (Table 1).[22]

A total of 4006 patients were included in the meta-analysis; 2579 patients from the ABCSG 8 trial, 979 patients from the ARNO 95 trial and 448 patients from the ITA trial.[22] After a median follow-up of 30 months, there were fewer recurrences and deaths in patients who switched to anastrozole compared with those who remained on tamoxifen: DFS was significantly improved in patients in the anastrozole group (HR 0.59, 95%CI 0.48–0.74; $p < 0.0001$).[22] The improvements in DFS observed with anastrozole were irrespective of nodal or receptor status, tumour size or previous chemotherapy.[22] There were also significant improvements in event-free survival (HR 0.55, 95%CI 0.42–0.71; $p < 0.0001$), distant recurrence-free survival (HR 0.61, 95%CI 0.45–0.83;

p = 0.0015) and OS (HR 0.71, 95%CI 0.52–0.98; p = 0.0377) in patients who switched to anastrozole compared with those continuing to receive tamoxifen.[22]

How does sequencing compare with upfront adjuvant therapy with AIs?

As well as the efficacy advantage for AIs relative to tamoxifen in the switch/sequence setting, evidence is becoming available to show that AIs can provide early disease-related and safety benefits of treatment for upfront therapy. The Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial was the first trial to demonstrate the superior efficacy of an upfront AI (anastrozole) for 5 years when compared with tamoxifen for the same period.[23] Upfront therapy with exemestane and letrozole has also been assessed in the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) and Breast International Group (BIG) 1–98 trials, respectively. Interestingly, both TEAM and BIG 1–98 are assessing an upfront strategy with an AI compared with a sequence strategy with tamoxifen followed by an AI.

Exemestane – TEAM trial

The TEAM trial was originally designed to assess the efficacy of 5 years of exemestane compared with 5 years of tamoxifen in postmenopausal patients with hormone receptor-positive breast cancer. However, following the results of the IES trial, which showed that patients receiving tamoxifen for 2–3 years who switched to exemestane had improved DFS compared with those who remained on tamoxifen, it was decided to amend the TEAM protocol to evaluate sequential therapy by switching all patients receiving tamoxifen who had by then had 2.5–3 years of tamoxifen followed by 2–2.5 years of exemestane, thus comparing that strategy with upfront exemestane for 5 years. A total of 9775 patients from nine countries have been enrolled into this open-label trial, making the TEAM trial the largest trial to date to assess the effects of adjuvant endocrine therapy in postmenopausal patients with proven hormone-sensitive breast tumours.[24] The primary endpoint was DFS; secondary endpoints included OS, relapse-free survival and time to new primary breast cancer and distant metastases (Table 1).

At 2.75 years' follow-up, upfront therapy with exemestane was associated with an improvement in DFS (HR 0.89, 95%CI 0.77–1.03; p = 0.12) compared with tamoxifen in the ITT population.[24] In total, 29.5% of patients in the tamoxifen arm and 18.9% of patients in the exemestane arm discontinued treatment before 2.75 years. An analysis of on-study drug DFS (including only patients who received allocated study drug and pre-switching) showed that exemestane was associated with a significant improvement in on-study drug DFS compared with tamoxifen (HR 0.83, 95%CI 0.71–0.97; p = 0.02).[24] Exemestane was also found to be superior to tamoxifen in terms of relapse-free survival and time to distant metastases in the ITT population. Results comparing the sequencing strategy of tamoxifen followed by exemestane with upfront exemestane may be able to provide further information on the appropriate use of these different treatment approaches.

Letrozole – BIG 1–98 trial

This trial was conducted to assess the efficacy and safety of monotherapy with letrozole or tamoxifen for 5 years following surgery. Sequential therapy with letrozole for 2 years followed by tamoxifen for three years, or tamoxifen for 2 years followed by letrozole for three years was also investigated.[25] From March 1998 to March 2000, 1835 patients were randomized to monotherapy with either letrozole (2.5mg daily) or tamoxifen (20mg daily). From April 1999 to May 2003, an additional 6193 patients were randomized to all four groups.[25] The primary endpoint was DFS; secondary endpoints included OS, systemic DFS, time to recurrence and time to distant recurrence (Table 1).

An analysis of monotherapy at a median follow-up of 51 months showed that DFS was significantly improved with letrozole versus tamoxifen (HR 0.82, 95%CI 0.71–0.95; p = 0.007).[6] When the monotherapy analysis was reported, the patients in the tamoxifen arm were unblinded and approximately 25% of patients crossed over to the letrozole monotherapy arm. In an updated analysis of monotherapy at a median follow-up of 76 months, the superiority of letrozole over tamoxifen was maintained, with significant improvements in DFS (HR 0.88, 95%CI 0.78–0.99; p = 0.03) and time to recurrence (HR 0.85, 95%CI

Table 4 Key efficacy results in trials assessing an early randomisation strategy. (A) Sequence of tamoxifen and an AI versus tamoxifen alone and (B) sequence of tamoxifen and an AI versus an AI alone.

(A)	ABCSG 8 (Tamoxifen → anastrozole vs. tamoxifen)[20]	BIG 1-98 (Tamoxifen → letrozole vs. letrozole)[26]
n	3714	4922
Randomisation strategy	Early	Early
Follow-up (median)	72 months	71 months
Disease-free survival	Not reported	HR 1.05, 99%CI 0.84–1.32
Recurrence-free survival	HR 0.85, 95%CI 0.71–1.01; $p = 0.066$[a]	Not reported
Overall survival	HR 0.78, 95%CI 0.62–0.98; $p = 0.032$[a]	HR 1.13, 99%CI 0.83–1.53
Time to distant recurrence	Not reported	HR 1.22, 99% CI 0.88–1.69

[a]Crossover censored analysis.

Table 5 Key adverse events associated with AIs in trials assessing early and late randomisation strategies.

Trial	n	Randomisation strategy	AI	Adverse event	AI (%)	Tamoxifen (%)	*p*
IES[7]	4724	Late	Exemestane	Fracture	4.3	3.1	$p = 0.03$
				Arthralgia	18.6	11.8	$p < 0.0001$
				Carpal tunnel syndrome	2.8	0.3	$p < 0.0001$
				Osteoporosis	7.3	5.5	$p = 0.01$
				Musculoskeletal pain	21.0	16.1	$p < 0.0001$
				Diarrhoea	4.2	2.2	$p = 0.0001$
				Endometrial hyperplasia	0.1	1.0	$p < 0.0001$
				Uterine polyps/fibrosis	1.2	3.2	$p < 0.0001$
ITA[18]	488	Late	Anastrozole	Fatigue	1.8	-	$p = 0.045$
				Lipis metabolism disorders	8.1	1.4	$p = 0.01$
				Musculoskeletal disorders and bone fractures	9.9	6.7	$p = 0.2$
					4.5	1.3	$p = 0.045$
				Hyperglycaemia	1.3	8.4	$p = 0.001$
				Gynaecological changes (including endometrial carcinoma)			
ARNO 95[19]	979	Late	Anastrozole	Arthralgia/bone pain	11.7	4.9	Not reported
				Osteoporosis	2.9	0.9	Not reported
				Fractures	2.2	2.2	Not reported
				Endometrial cancer	0.0	0.4	Not reported
				Endometrial hyperplasia	1.8	8.6	Not reported
ABCSG 8[20]	3714	Early	Anastrozole	Bone, joint disorders	11.4	8.2	$p < 0.001$
				Fractures	3.5	1.6	$p < 0.001$
				Gynaecological disorders	22.6	31.2	$p < 0.001$
				Uterine neoplasms	1.8	3.2	$p = 0.005$
TEAM[24]	9775	Early	Exemestane	Arthralgia	17.9	9.2	$p \leq 0.001$
				Arthritis	3.0	1.7	$p \leq 0.001$
				Reported osteoporosis	4.7	2.1	$p \leq 0.001$
				Reported fractures	2.7	2.3	NS
				Hypertension	3.3	2.1	$p \leq 0.001$
				Uterine polyp	0.1	0.5	$p \leq 0.001$
				Endometrial hyperplasia	0.0	2.0	$p \leq 0.001$
BIG 1-98[a,6]	4922	Early	Letrozole	Hypercholesterolaemia	50.6	24.6	$p < 0.001$
				Bone fractures	8.6	5.8	$p < 0.001$
				Arthralgia	20.0	13.5	$p < 0.001$
				Vaginal bleeding	3.8	8.3	$p < 0.001$

[a]Adverse events reported from the monotherapy analyses.

0.72–1.00; $p = 0.05$).[26] OS was slightly improved with letrozole compared with tamoxifen, however, this difference was not statistically significant (HR 0.87, 95%CI 0.75–1.02; $p = 0.08$).[26]

In the sequenced analysis, after a median follow-up of 71 months, sequential treatment with tamoxifen followed by letrozole did not significantly improve DFS compared with letrozole alone.[26] The HRs for tamoxifen followed by letrozole versus letrozole alone (with HRs greater than one favouring letrozole monotherapy) were 1.05 (99%CI 0.84–1.32) for DFS, 1.13 (99%CI 0.83–1.53) for OS and 1.22 (99%CI 0.88–1.69) for distant recurrence (Table 4B).

Reverse sequencing – AIs followed by tamoxifen

In the BIG 1–98 trial, one of the treatment arms assessed a reverse sequencing strategy, with patients receiving letrozole initially for 2–3 years followed by tamoxifen for 2–3 years, to complete 5 years of endocrine therapy. When this treatment arm was compared with letrozole monotherapy, there were no significant efficacy differences between treatment arms. For the comparison of letrozole followed by tamoxifen and letrozole alone, the HRs were 0.96 (99%CI 0.76–1.21) for DFS, 0.90 (99%CI 0.65–1.24) for OS and 1.05 (99%CI 0.75–1.47) for distant recurrence (HRs greater than 1 favoured letrozole monotherapy).[26]

Adverse events associated with AI therapy

In terms of safety, the adverse-event profile of the AIs is different from that observed with tamoxifen. The tolerability of tamoxifen is well defined, and tamoxifen use has been associated with gynaecological symptoms, including vaginal bleeding and endometrial cancer, and thromboembolic events.[1,27,28]

In the trials investigating AIs as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer, the AIs have been generally well tolerated; however, they have been associated with a distinct adverse-event profile, including increased musculoskeletal side effects, such as arthralgia and bone loss, relative to tamoxifen. However, unlike tamoxifen, the AIs have not been associated with endometrial cancer and thromboembolic events.[6–8]

Table 5 shows the key adverse events observed with AIs in switching trials with both early and late randomization designs. In general, AI therapy has been associated with a greater risk of musculoskeletal complications and fracture; there is also some evidence to suggest that the AIs may have an effect on lipid metabolism.[6–8] Importantly, the safety profiles of all three thirdgeneration AIs appear to be generally similar irrespective of the treatment strategy used.[6–8]

Sub-studies of trials assessing AIs have been conducted to provide further details on the effects of AIs and tamoxifen on key adverse events. Several bone sub-studies with exemestane have shown that after an initial more rapid rate of bone loss compared with tamoxifen, there is evidence of a slowing of the rate of bone loss during treatment.[29,30] A further sub-study of the TEAM trial showed that there was no significant change in BMD after 2 years of treatment with exemestane.[31] Additionally, long-term follow-up from the IES bone sub-study and the ATAC study indicate that after treatment completion the ongoing fracture rate in patients who received anastrozole or exemestane becomes similar to those who received tamoxifen.[8,32] Although, it has been suggested that AIs may have an effect on lipid metabolism, a prospectively planned sub-study of the TEAM trial demonstrated that exemestane did not appear to have an effect on the lipidaemic profiles of patients.[33] Several sub-studies have also assessed the impact of treatment on quality of life. In the switch setting, results from a sub-study of the IES indicated that there were no significant differences in quality of life between patients receiving tamoxifen or those switched to exemestane.[34] Within the TEAM trial, there were no significant differences in quality of life between treatment groups (exemestane versus tamoxifen) or over time.[35] A further sub-study of the TEAM trial showed that after one year of therapy, tamoxifen had a negative impact on cognitive function in postmenopausal women. In contrast, cognitive function was not negatively affected in patients receiving exemestane.[36]

It is also interesting to note that the safety profiles of the different endocrine therapies may have an

effect on patient adherence with treatment. Patient adherence is defined as 'the extent to which the patient's behaviour (e.g. taking medication) corresponds with agreed recommendations from a healthcare provider'.[37] With tamoxifen, one study found that 31% of patients did not complete the 5-year course.[38] Another study of patients receiving tamoxifen showed that during 5 years of follow-up, 50% discontinued therapy.[39] For patients receiving AI therapy, a study assessing adherence to anastrozole showed that during the first year, treatment adherence was approximately 82–88%. By 3 years, adherence had decreased to around 62–79%.[40] Issues with adherence have also been observed in the TEAM trial, in which 29.5% of patients randomized to receive tamoxifen and 18.9% of patients randomized to receive exemestane stopped treatment before 2.75 years.[24] In this case, adherence relates to adherence to study protocol and not only adherence to drug.

Future Perspectives

The trials assessing AIs detailed here clearly demonstrate the efficacy of AIs as endocrine treatment for hormone receptor-positive breast cancer. However, key questions regarding the optimal AI in this setting and the optimal regimen remain unanswered. There are several ongoing head-to-head trials with AIs: the Femara Anastrozole Clinical Evaluation (FACE), which is evaluating upfront letrozole compared with upfront anastrozole, and the MA.27 trial, assessing anastrozole versus exemestane in the upfront setting.[41] An Italian phase III trial (NCT00541086) is comparing sequential treatment with tamoxifen and anastrozole, letrozole or exemestane with upfront treatment with anastrozole, letrozole or exemestane.[41] Results from these trials may help to provide further information on optimal endocrine treatment with AIs for postmenopausal early breast cancer patients.

Additionally, translational research, which aims to identify prognostic and/or predictive markers of treatment benefit, is an area of increasing interest. Identification of markers which can allow the selection of patients who are more likely to respond or be resistant to specific treatments may aid clinicians in their treatment choice. A sub-analysis of the ATAC trial suggested that time to recurrence was more greatly improved with anastrazole compared with tamoxifen in patients with ER/PgR-positive and ER-positive/PgR-negative tumours than in those with ER-positive/PgR-positive tumours.[42] In the TRANS-ATAC trial, tumour blocks were collected and ER, PgR and human epidermal growth factor receptor 2 (HER2) expression was determined. In contrast with the main trial, ER, PR and HER2 expression did not have an effect on the differential benefit of anastrozole over tamoxifen.[43] Hormone receptor status was, however, predictive of outcome: low ER or PgR or HER2 overexpression was associated with a higher risk of recurrence, regardless of the treatment the patient received.[43] Consistent with this, central review of tissue from patients in the BIG 1–98 trial demonstrated that ER/PgR expression showed prognostic value, but was not predictive of treatment benefit with letrozole over tamoxifen.[44] In contrast with the TRANS-ATAC trial, all tumours were centrally assessed in this analysis of the BIG 1–98 trial. Within the TEAM trial, multiple analyses are planned to assess the effect of receptor status on treatment benefit using original tumour material. A prospectively planned sub-analysis of the TEAM trial showed the risk of relapse increasing in patients with lower ER or PgR expression.[45] PgR expression was not predictive of treatment benefit from exemestane; however, an unplanned analysis suggested that high ER expression might predict benefit from exemestane.[45] Further analysis of this finding is ongoing. A further prospectively planned analysis is assessing if the outcome of individuals with positive HER status can be improved depending on initiating treatment with an AI or tamoxifen.

Cytochrome P450 2D6 (CYP2D6) genotype may also be important to select out patients who are not likely to benefit from tamoxifen. Tamoxifen is converted to endoxifen by CYP2D6 and tamoxifen-treated patients who have impaired metabolism by CYP2D6 can have reduced plasma concentrations of endoxifen. Patients with impaired metabolism of tamoxifen have been shown to have a higher risk of recurrence during tamoxifen treatment.[46,47] An analysis of the ABCSG 8 study, which randomized patients prior to the initiation of therapy, showed that poor CYP2D6 metabolizers who received tamoxifen for 5 years had a significantly increased risk of recurrence

compared with extensive metabolizers.[48] In patients randomized to receive tamoxifen followed by anastrozole, however, there was no significant difference in risk of recurrence between extensive and poor metabolizers of CYP2D6 during years 3–5 of treatment.[48] Therefore, it may be of value to determine CYP2D6 genotype in patients receiving tamoxifen, as poor metabolizers may benefit from alternative treatment with an AI.

Conclusion

The studies described above provide strong evidence that switching to an AI after using tamoxifen for 2–3 years prolongs DFS compared with continuing tamoxifen treatment. Furthermore, in the IES study, a switching strategy from tamoxifen to exemestane was associated with a significant improvement in OS compared with continued tamoxifen.[7] An improvement in OS was also demonstrated when switching from tamoxifen to anastrozole in the ARNO 95.[19] Furthermore, a crossover censored analysis of the ABCSG 8 study showed that an early randomization design with an AI after 2–3 years of tamoxifen was associated with improved OS compared with tamoxifen alone.[19,20]

Tamoxifen may still have a role to play as endocrine therapy in some patients, as a result of its adverse-event profile. However, it is now beyond question that the use of AIs is justified as endocrine treatment for early hormone receptor-positive breast cancer patients. Moreover, their use in this setting is recommended in international guidelines, such as St. Gallen, the American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines.[2,49,50] The complete results from the TEAM trial and the head-to-head trials with AIs, may be able to answer the remaining questions regarding the optimal AI, optimal treatment strategy and the selection of patients for these therapies.

Acknowledgements

Editorial support was provided by ACUMED (Tytherington, UK), with funding from Pfizer, Inc.

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