Adjuvant Endocrine Therapy

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Abstract

The risk of subsequent development of distant metastases from early breast cancer (BC) underpins the rationale for offering treatment in the adjuvant setting. Current guidelines recommend that patients with hormone receptor-positive disease be offered adjuvant endocrine therapy (ET). Oestrogen receptor (ER)-positivity progressively increases with age, with more than 80% of BCs being ER-positive in patients aged 65 and older. As such, given that the majority of early BC cases in the elderly would be considered theoretically eligible for ET, the evidence regarding its use in the adjuvant setting is of particular interest for this cohort. Recent large randomised controlled trials and meta-analyses have provided data regarding the type, duration and sequencing of ET in postmenopausal women, which can assist clinicians in their recommendations to elderly patients. This chapter will summarise the findings of these seminal trials, and their applicability to the elderly subpopulation will be discussed.

Keywords

Adjuvant · Endocrine therapy · Elderly · Hormone receptor positive · Aromatase inhibitor · Tamoxifen · SERD

A major concern associated with early breast cancer (BC) is the subsequent development of distant metastasis. Adjuvant treatment is given with the intent to reduce the risk of eventual tumour relapse and death, with adjuvant endocrine therapy (ET)

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being offered to patients with oestrogen-receptor (ER) and/or progesterone-receptor (PgR)-positive disease. The current St Gallen guidelines recommend that adjuvant ET should be offered to patients with highly endocrine-responsive tumours (high expression of both ER and PgR in a majority of tumour cells) as well as to patients with incompletely endocrine-responsive BC (low expression of ER and/or PgR) [10]. Given that ER-positive disease progressively increases with aging, with less than 20% of BC cases being ER-negative in patients aged 65 or older, the majority of elderly patients are therefore candidates for adjuvant ET.

9.1 Tamoxifen: Efficacy and Safety Data

Tamoxifen, a selective ER modulator, has historically been the most commonly used hormonal therapy for endocrine sensitive early BC. The administration of 5 years of tamoxifen versus no treatment almost halves the annual recurrence rate (recurrence rate ratio 0.59 [SE 0·03]), and reduces BC mortality rate by a third (death rate ratio 0.69 [SE 0·04]). This translates to an absolute 15-year gain of 11.8 and 9.2% in terms of recurrence and BC mortality, respectively [16]. This benefit is observed, irrespective of patient age.

In terms of adverse events, treatment with tamoxifen is associated with an increased risk of endometrial cancer and thromboembolic events such as deep venous thrombosis, pulmonary embolism, and cerebrovascular accidents. The risk of uterine cancer is strongly correlated with age [17]. With respect to the impact of age on the risk of thromboembolic events among tamoxifen users, Ragaz et al. calculated that the relative risk of mortality for thromboembolic events was 1.5 at the age of 50, with a dramatic increase to 17.5% by the age of 80 [36]. However, in that specific age group, the risk of thromboembolic-related mortality was outweighed by a protective cardiac effect bestowed by tamoxifen. There is evidence that the risk of thromboembolic events is related to the duration of the treatment, which was shown by another group to double from 2 to 5 years [38].

9.2 Aromatase Inhibitors

The introduction of aromatase inhibitors (AIs) to clinical practice has challenged the role of tamoxifen in post-menopausal women. Adjuvant AI trials can be grouped according to the modality of introduction of an AI in the adjuvant treatment regimen, as follows: (1) Upfront therapy trials, in which there is a head-to-head comparison between tamoxifen and an AI, or direct comparison between two or more AIs; (2) switching trials, in which 5 years of therapy with tamoxifen or an AI is compared with tamoxifen for 2–3 years followed by AI for an overall duration of 5 years; (3) extended adjuvant trials, evaluating the potential benefits of various ET regimens/combinations for durations beyond 5 years. The study design and results of published trials are summarised in Table 9.1.

Table 9.1 Trials evaluating the role of aromatase inhibitors (AIs) in the adjuvant setting

Study (No. patients)	Study design		Follow-up months	Endpoints					
Up-front trials									
ATAC [11] (n = 6241)	5 y A		120	DFS	HR 0.91; $p = 0.04$	TDR	HR 0.87; $p = 0.03$	OS	HR 0.97; $p = 0.6$
	5 y T			TTR	HR 0.84; $p = 0.001$				
BIG 1–98 [37] (n = 4922)	5 y L		104	DFS	HR 0.86; $p = 0.007$	DRFI	HR 0.86; $p = 0.047$	OS	HR 0.87; $p = 0.048$
	5 y T			BCFI	HR 0.86; $p = 0.03$				
FATA-GIM3 [13] (n = 1847)	5y L		60	DFS	NS			OS	NS
	5 y A								
	5 y E								
FACE [39] (n = 4136)	5y L		65	DFS	HR 0.93; p = 0.32	TDM	HR 0.94; p = 0.99	OS	HR 0.98; p = 0.79
	5 y A								
				DDFS	HR 0.96; p = 0.62				
Switching trials comparing 5 y T versus 2–3 y T → AI									
Intergroup Exemestane Study (IES) [33] (n = 4724)	2–3y T	2–3y E	120	DFS	HR 0.85; $p = 0.002$	BCEFS	HR 0.86; p = 0.03	OS	HR 0.89; $p = 0.08$
	2–3y T	2–3y T		EFS	HR 0.81; p < 0.001				
ABCSG8/Italian tamoxifen anastrozole (ITA)/ ARN095 [27] (n = 4600)	2–3y T	2–3y A	128	DFS	HR 0.59; p < 0.0001	EFS	HR 0.55; p < 0.0001	OS	HR 0.71; $p = 0.04$
	2–3y T	2–3y T		DRFS	HR 0.61; p = 0.002				

(continued)

Table 9.1 (continued)

Study (No. patients)	Study design		Follow-up months	Endpoints					
Switching trials comparing 5 y IA versus 2–3 y T → AI									
FATA-GIM 3 [13] (n = 3697)	5 y AI	2 y T	60	DFS	HR 0.0.89; p = 0.23			OS	HR 0.72; p = 0.052
		3 y AI							
TEAM [12] (n = 6120)	5 y E	2–3 y T	118	DFS	HR 0.96; p = 0.39	DRFI	HR 0.91 p = 0.15	OS	HR 0.98 p = 0.74
		2–3 y E							
Extended adjuvant therapy									
MA 17 [19] (n = 5187)	5y T	5 y L	30	DFS	HR 0.58; $p < 0.001$	DDFS	HR 0.60; p < 0.002	OS	HR 0.82; p = 0.3
	5y T	placebo							
MA.17R [22] (n = 1918)	10y AI	5y L	75	DFS	HR 0.66; p = 0.01			OS	HR 0.97, p = 0.83
	4.5–6 yr. ET	placebo							
ABCSG 6a [26] (n = 856)	5y T ± AG	3 y A	62.3	DFS	HR 0.62; $p = 0.031$			OS	NS
	5y T ± AG	NT							
NSABP B-33 [31] (n = 1598)	5y T	5y E	30	DFS	HR 0.68; $p = 0.07$	RFS	HR 0.44; $p = 0.004$	OS	NS
	5y T	placebo							
DATA [42] (n = 1860)	2–3 y T	2–3 y T	50	DFS	HR = 0.79; p = 0.066			OS	HR 0.91, p = 0.6
	3 y A	6 y A							
IDEAL (Blok et al. 2017) (n = 1824)	ET 5y	ET 5y	79	DFS	HR = 0.96; p = 0.7			OS	HR 1.08; p = 0.59
	2.5 y L	5 y L							

NSABP-B42 [32] (n = 3966)	ET 5y	ET 5y	83	DFS	HR = 0.85; p = 0.048 (NS)			OS	HR = 1.15, p = 0.22
	L 5y	P 5y							
ABSCG −16 [23] (n = 3484)	ET 5y	ET 5y	105	DFS	HR = 1.007, p = 0.925			OS	HR 1.007, p = 0.947
	A 2y	A 5y							
SOLE (Colleoni et al., 2017) (n = 4851)	4–6 y ET	4–6y ET	60	DFS	HR = 1.08 p = 0.31	DDFS	HR 0.88p = 0.25	OS	HR = 0.85, p = 0.16
	5y L	5y IL							

AI aromatase inhibitor, *A* anastrozole, *T* tamoxifen, *L* letrozole, *IL* intermittent letrozole, *E* exemestane, *NS* not significant, *NT* no treatment, *HR* hazard ratio, *ET* endocrine therapy, *y* years, *AG* aminoglutethimide, *BCEFS* breast cancer event-free survival, *BCFI* breast cancer-free interval, *EFS* event-free survival, *DFS* disease-free survival, *DRFI* distant recurrence-free interval, *DRFS* distant recurrence-free survival, *TDR* time to distant recurrence, *OS* overall survival, *TTR* time to recurrence, *DDFS* distant disease-free survival, *TDM* time to distant metastasis, *RFS* relapse-free survival. Modified from Biganzoli et al. [1], with permission

9.2.1 Efficacy Data

9.2.1.1 Upfront Trials (Tam Versus AI Comparison)

The Arimidex & Alone or in Combination (ATAC) trial randomised a total of 9366 postmenopausal patients to receive adjuvant tamoxifen or anastrozole alone, or a combination of tamoxifen plus anastrozole for 5 years [41]. The most recent analysis, conducted after a median follow-up of 120 months, anastrozole monotherapy appeared superior to tamoxifen alone [11]. In the hormone receptor-positive subgroup, anastrozole was favoured in terms of PFS, TTR and TDR, but no OS advantage was seen.

The Breast International Group (BIG) 1–98 study was a randomised, phase 3, double-blind trial that compared 5 years of treatment with four possible adjuvant ET regimens: (1) letrozole, (2) letrozole followed by tamoxifen, (3) tamoxifen, or (4) tamoxifen followed by letrozole. A total of 4922 patients were randomised in the upfront comparison of the tamoxifen versus letrozole arms [4]. Patient median age was 61 years (range: 38–90). After a median follow-up of 8.1 years, an advantage in favour of letrozole monotherapy over tamoxifen was seen in terms of DFS, TTR and TDR, whilst also gaining an advantage in terms of OS which was not observed in earlier published analyses (HR 0.79; 95% CI 0.69–0.90) [37]. Adjusted analyses using inverse probability of censoring weighting modelling, designed to adjust for the selective crossover that occurred after initial trial results were reported, produced a statistically significant 18% reduction in the hazard of an OS event with letrozole over tamoxifen [6].

9.2.1.2 Switching Trials

In the intergroup exemestane study (IES) 4724 postmenopausal women with ER-positive or ER-unknown BC, who were disease-free on 2–3 years of tamoxifen, were randomly assigned to switch to exemestane or continue tamoxifen for the remainder of 5 years of treatment [8]. Patients' median age was 64 years. At a median follow-up of 55.7 months, patients who switched to exemestane demonstrated a DFS and TDR advantage. Adjustment for potential confounders related to baseline and treatment characteristics did not substantially affect the estimates of treatment effect (DFS adjusted 0.75 [0.65–0.86, $p = 0.0001$]). Final analysis after a median of 120 months follow up revealed a reduction in BC related events with an absolute difference between exemestane and tamoxifen of 4% (95% CI 1.2–6.7) favouring exemestane [33]. This difference persisted in multivariate analyses taking into account nodal status, prior endocrine therapy and prior chemotherapy.

Three clinical trials: the Arimidex-Nolvadex (ARNO 95), the Austrian Breast and Colorectal Cancer Study Group (ABCSG 8), and the Italian tamoxifen anastrozole (ITA) studies, randomised postmenopausal women to receive anastrozole after 2–3 years of tamoxifen or to continue to take tamoxifen up to 5 years of treatment. It should be noted that while the ITA and ARNO 95 are two classical switching trials, in ABCSG 8 patients were randomised from the outset with a pure sequencing strategy. A meta-analysis of these three clinical trials, amounting to a total of 4600 eligible patients, was published in 2006. Median patient age

was 63 years. After a median follow-up of 30 months, a significant reduction in the DFS hazard rate and in the risk of death was observed in patients treated with anastrozole [27]. The advantage in terms of OS in favour of incorporating an AI was confirmed in a separate analysis of the ARNO trial. Among 979 patients aged ≤75 years, at a median follow-up of 30.1 months, switching to anastrozole resulted in a statistically significant improvement in DFS, with a 34% reduction in the relative risk of disease recurrence or death (HR 0.66, $p = 0.049$) and in OS, with a 47% improvement (HR 0.53, $p = 0.45$), compared with patients who continued with tamoxifen [28]. After adjustment for potential prognostic factors including age, switching to adjuvant anastrozole still resulted in a statistically significant improvement in DFS and OS.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial randomised patients to receive either 5 years of exemestane monotherapy, or a sequential regimen of tamoxifen followed by exemestane for 5 years in total. This protocol was amended in 2004 after the publication of the IES trial, with all those assigned to tamoxifen being switched to exemestane after 2.5–3 years of initial tamoxifen therapy. After 5 years of median follow up, no difference was observed between the two groups in terms of DFS, OS or relapse-free survival [43]. Ten-year outcomes continued this trend overall, and planned analyses failed to identify any clinicopathological subgroup (including age) who benefited more from either treatment [12].

FATA-GIM3 assigned 3697 patients to one of six treatment strategies: anastrozole, exemestane or letrozole upfront for 5 years, or tamoxifen for 2 years, followed by a switch to one of the three aforementioned AIs for the subsequent 3 years [13]. Approximately 28% in each arm were aged 70 or more. After a median follow up of 60 months, 5 years of upfront therapy with an AI was not shown to be superior to the switch strategy, with a DFS of 89.8% (95% CI, 88.2–91.2) and 88.5% (95% CI, 86.7–90.0), respectively.

9.2.1.3 Data from EBCTCG

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has undertaken meta-analyses of randomised trials which evaluated the following strategies: (1) upfront tamoxifen versus upfront AI; (2) upfront tamoxifen versus tamoxifen followed with a switch to an AI; or (3) upfront AI versus tamoxifen followed with a switch to an AI. Reporting in 2009 [14] and again in 2015 [17], the group most recently demonstrated that when comparing 5 years of an AI against 5 years of tamoxifen, the recurrence rate ratios favoured AIs in the first 4 years of treatment, but not significantly thereafter. These rates differed little according to age, with a recurrence risk reduction rate ratio of 0.60 (CI 0.48–0.76) in patients aged 70 or more. Proportional overall recurrence rates were reduced by approximately 30% in this setting. The 10-year BC mortality rates were reduced by about 15% in favour of AI therapy. Ultimately, these analyses illustrate the overall advantage of AIs over tamoxifen, which underlines the importance of including an AI backbone in the adjuvant treatment regime at some stage (either upfront or sequentially) in postmenopausal women.

9.2.1.4 Which AI to Choose?

Three large trials have demonstrated that there are no observable differences between the AIs. MA.27 was the first trial to compare adjuvant steroidal and non-steroidal aromatase inhibitors in postmenopausal women [20]. This open-label phase 3 trial enrolled 7576 women (median age, 64 years; approximately 28% in each arm were aged 70 or above) to receive 5 years of either exemestane or anastrozole. After a median follow up of 4.1 years, neither were found to be superior in terms of BC outcomes by two-sided test. Planned multivariate analyses revealed no significant treatment-factor interactions, however, a worse event-free survival rate was observed in women aged 70 or older (HR 1.89; 95% CI, 1.35–2.66; $p < 0.001$).

The FACE study compared 5 years of letrozole versus anastrozole in a postmenopausal population with node-positive early disease [39]. Approximately 40% of enrolled patients were aged 65 or older, with a median age of 62 in each arm. Letrozole did not demonstrate superior efficacy over anastrozole in either PFS or OS. Similarly, FATA-GIM3 demonstrated no differences between the three AIs in terms of efficacy [13]. The five-year DFS was 90.0% (95% CI, 87.9–91.7) for anastrozole, 88.0% (95% CI, 85.8–89.9) for exemestane and 89.4% (95% CI, 87.3–91.1) for letrozole.

9.2.1.5 Extended Adjuvant Trials

A recent meta-analysis of 88 trials involving 62,923 women who were disease-free after receiving a total of 5 years of prescribed adjuvant ET has underlined the significance of late recurrence after cessation of treatment at the five-year mark [35]. Recurrences continued to occur throughout the study period from 5 to 20 years, correlating strongly with the original tumour and nodal stage and histological grade. In patients with T1, node negative disease, the risk of distant recurrence was 13%, rising to 20% in those with 1–3 involved nodes, and up to 34% in those with 4–9 nodes. The absolute risk of distant recurrence in those with T1 N0 low grade disease was 10%, 13% for moderate grade, and 17% for high grade status. Given this significant rate of recurrence, even in patients with small primary cancers and no nodal involvement, endocrine therapy extension beyond 5 years is of particular interest.

The NCIC CTG MA.17 study targeted women who had completed approximately 5 years of adjuvant tamoxifen [18]. A total of 5187 patients were randomised to receive (double-blind) either letrozole or placebo for 5 years. Patients median age was 62 years, with 25% aged ≥70 years. The study was interrupted and unblinded after the first interim analysis due to the clear advantage in terms of DFS with letrozole. At a median follow-up of 30 months, extended therapy with letrozole resulted in prolonged DFS and DDFS [19]. A subgroup analysis also showed an OS advantage among node-positive patients (HR 0.61; $p = 0.04$). After the unblinding, patients in the placebo arm were offered letrozole. An intention-to-treat analysis performed after a median follow up of 54 month demonstrated that patients originally randomised to receive letrozole outperformed patients originally randomised to placebo in terms of DFS (4y DFS HR = 0.64; $p = 0.00002$) and DDFS (4y DDFS HR = 0.76; $p = 0.041$), despite 73% of the patients on placebo crossed to letrozole after unblinding [24].

The National Surgical Adjuvant Breast and Bowel Project B-33 trial aimed to randomise 3000 patients who were disease-free after 5 years of tamoxifen to 5 years of exemestane or 5 years of placebo [31]. Due to the results of MA.17, the study was discontinued with 1598 randomised, at which point treatment assignment was unblinded, and exemestane was offered to patients in the placebo arm. Seventy-two percent of the patients in the exemestane group chose to continue exemestane while 44% of the patients on placebo switched to exemestane. With 30 months of median follow-up, original exemestane assignment resulted in a borderline statistically significant improvement in 4-year DFS, and a statistically significant improvement in 4-year RFS.

In the ABCSG-6a study, 456 women who had received, in the context of trial ABCSG6, either 5 years of tamoxifen or tamoxifen plus aminoglutethimide for a 2 -year period followed by 3 years of tamoxifen alone, were re-randomised to switch to anastrozole or no treatment for a further 3 years [26]. Patients' median age was 61.8 years. At a median follow-up of 60 months, significantly fewer patients in the AI group experienced disease recurrence compared with the no-treatment group.

The DATA trial assigned women to receive either 3 or 6 years of anastrozole after having previously received 2–3 years of tamoxifen therapy [42]. One thousand eight hundred sixty patients were enrolled, with a median age of 57 years for each arm. Just over 40% of patients were aged 60 or over. Overall, the 5-year DFS was 83.1% for the 6-year arm, and 79.4% in the 3-year arm (HR 0.79, 95% CI 0.62–1.02, p = 0.066). A subgroup analysis of patients aged 60 or more similarly revealed no benefit for extended therapy (HR 0.85, 95% CI 0.61–1.19, p = 0.63). IDEAL, another trial conducted by the same group, randomised patients to receive either 2.5 or 5 years of letrozole after an initial 5 years of any adjuvant endocrine therapy [2]. A total of 1824 women were enrolled, with a median follow up of 6.6 years. Just under a quarter were aged between 65–75 in each arm, with a small representation of patients over 75 (6.8% and 8.4% in the 2- and 5-year groups, respectively). Overall, no superiority was found for 5 years versus 2.5 years of extended therapy in terms of DFS, OS or distant recurrence free interval. In patients aged 65–75, PFS HR was 0.69 (95% CI 0.45–1.08), and 0.98 in patients aged more than 75 years (95% CI 0.53–1.81) (p = 0.82).

NSABP B42 randomised 3966 patients to receive either letrozole or placebo for 5 years, after having first completed 5 years of adjuvant endocrine therapy (either AI monotherapy, or tamoxifen followed by a switch to an AI) [32]. After a median follow up of 6.9 years, extended AI therapy resulted in a non-significant 15% reduction in the risk of a disease-free survival event, but did not improve OS. A statistically significant 29% reduction in the risk of BC recurrence or cancer in the contralateral breast was noted, as was a 28% reduction in the cumulative risk of disease recurrence.

Results from the ABCSG-16 trial suggest that truncation of the extension period of endocrine therapy may yield sufficient clinical benefits, whilst simultaneously avoiding associated side-effects [23]. Three thousand four hundred eighty-four women were randomised to receive either 2 or 5 years of extended adjuvant endocrine therapy (anastrozole 1 mg/day), after having completed 5 years of prior

tamoxifen or AIs. The median age was 64. After a median follow up of 105 months, 22% in each group had recorded DFS events. There was no significant difference between the two groups in terms of DFS, OS, time to secondary carcinoma or time to contralateral BC. There was, however, a greater rate of bone fractures in the five-year arm (6% versus 4%; HR, 1.405, 95% CI 1.03–1.91, p = 0.029).

One thousand nine hundred eighteen women were enrolled in MA.17R, which randomised patients to receive either placebo or letrozole for 5 years, following the completion of 4.5–6 years of initial adjuvant endocrine therapy which included an AI [22]. The majority of enrolled patients (79.3%) had received tamoxifen prior to an AI during the period of initial therapy. The median age was 65.1 years. At a median follow up of 6.3 years, the 5-year DFS rate was 95% with letrozole, versus 91% with placebo (HR 0.66; p = 0.01). However, the rate of overall survival was not higher in the letrozole arm (93% versus 94% respectively; HR 0.97; p = 0.83). It is important to note that the definition of DFS in this study did not included events of death. When all causes of death were included, there was only a 2% absolute benefit in terms of DFS (p = 0.06). In the context of elderly patients, this is of particular interest, as competing causes of death may reduce the benefit of a given treatment in an older population.

SOLE enrolled postmenopausal women with node positive early disease who had already received 4–6 years of adjuvant ET to receive either continuous or intermittent letrozole for a subsequent duration of 5 years [7]. Four thousand eight hundred fifty-one women comprised the intention-to-treat population, with a median age in both arms of 60. Intermittent dosing did not result in lower toxicity rates or improved efficacy (DFS of 85.8% for intermittent therapy, and 85.8% for continuous; HR, 1.08, 95% CI 0.93–1.26, p = 0.31). As such, continuous dosing of ET remains the standard approach.

Briefly, the above-discussed trials and metanalyses largely showed that AIs are superior to tamoxifen in reducing the risk of tumour relapse. The approach of either upfront AIs, or a switching regimen (whilst not superior to monotherapy), are both reasonable strategy choices, and can be made according to disease risk factors and patient co-morbidities, treatment tolerance and personal preference. Whilst extending the duration of ET beyond 5 years may be of benefit in preventing late recurrence, there is a paucity of evidence specifically derived from the elderly subpopulation. Furthermore, competing potential causes for mortality and morbidity and the added risk of cumulative side-effects and resultant compliance issues should be weighed up when considering an extended approach in the elderly.

9.3 From the "Postmenopausal" to the Elderly Population

Can the results from seminal trials observed in a general "postmenopausal" population be extrapolated to older women? Results from adjuvant trials that reported subgroup analyses of DFS in terms of age are presented in Table 9.2. Only for two studies detailed analyses have been conducted focused on the older population.

Table 9.2 Per age subgroup analysis for disease-free survival in adjuvant trials

Study	Follow-up	Age group	n	HR	95% CI	p
ATAC	100 months	<65	5137	0.76	0.63–0.91	NR
		65+	4229	0.77	0.63–0.93	NR
BIG 1–98	51 months	<65	3127	0.82	0.67–0.99	0.04
		65+	1795	0.82	0.67–1.01	0.06
IES	120 months	<60	1523	0.82	0.63–1.06	NR
		60–69	2021	0.70	0.56–0.87	NR
		70+	1180	0.81	0.63–1.04	NR
ABCSG8/ARN095	28 months	<60	1265	0.63	0.40–1.00	0.05
		60+	1959	0.58	0.39–0.87	0.007
MA.17	4-year outcome	<60	2152	0.46	0.30–0.70	0.0004
		60–69	1694	0.68	0.44–1.04	0.078
		70+	1323	0.67	0.41–1.11	0.12
ABCSG 6a	62.3 months	<60	147	0.60	0.21–1.72	0.336
		60+	705	0.63	0.39–1.03	0.064
NSABP B-33	4-year outcome	<60	777	0.53	NR	0.06
		60+	785	0.80	NR	0.43
TEAM	9.8 years	<50	211	1.02	0.57–1.83	NR
		50–59	1874	0.84	0.70–1.01	NR
		60–69	2373	0.95	0.81–1.11	NR
		70+	1662	1.04	0.90–1.20	NR
MA.27	4.1 years	≤59	5417	NR	NR	NR
		≥70	2159	1.89	1.35–2.66	<0.001
DATA	50 months	<60	971	0.75	0.52–1.10	NR
		≥60	689	0.85	0.61–1.19	NR

Modified from Biganzoli et al. [1], with permission
NR not reported

Crivellari et al. explored potential differences in efficacy in elderly women receiving adjuvant tamoxifen or letrozole in the BIG 1–98 trial [9]. The report included 4922 patients with a median follow-up of 40.4 months. Subpopulation treatment effect pattern plot (STEPP) analysis was used to examine the patterns of differences in DFS according to age. The authors found that letrozole was superior to tamoxifen across the age spectrum and was not significantly influenced by age (interaction of age and treatment, $p = 0.84$): leading to the assumption, as has already been shown for tamoxifen, that older patients derive the same benefit from AI as younger patients.

Regarding the extended adjuvant strategy, per age subgroup analysis data for DFS are summarised in Table 9.2. In particular, Muss and colleagues divided patients randomized in MA.17 in three age-groups: younger than 60 (<60), 61–69, and 70 years old and older (70+) [34]. There was no significant difference in DFS (4-year outcome = 92.4, 91.4, and 92.5% for women aged <60, 60–69, and 70+, respectively) and DDFS (4-year outcome = 96.0, 94.3, and 95.0% for women aged <60, 60–69, and 70+, respectively) between the three age groups. As expected, OS

was significantly different between the three age groups due to an increased risk of non-BC-related death with increasing age (4-year outcome = 97.4, 96.2, and 90.6% for women aged <60, 60–69, and 70+, respectively). The results were unchanged after adjusting for other potential prognostic factors such as letrozole or placebo treatment, duration of prior tamoxifen, nodal status, and prior chemotherapy. Significant letrozole-associated improvements in both DFS and DDFS was observed only in women younger than 60 years. However, the interaction between age and treatment was not statistically significant for neither DFS, DDFS or OS ($P = 0.36$, 0.77, and 0.98 for DFS, DDFS, and OS, respectively), indicating no evidence of a heterogeneous effect of letrozole among age groups. MA.17 showed an OS advantage for all node-positive patients. In this age-directed subset analysis, only node-positive patients aged 70+ had significant improvement in OS, which may be considered when recommending extended therapy in patients with high risk disease. Conversely, when considering extended therapy in a population with comparatively low-risk features, in the context of the findings of ABCSG-16, a shorter duration of extension may be considered in order to reduce the likelihood of associated side-effects.

9.4 Side Effects

Aging is associated with an increased incidence and prevalence of co-morbidities. The presence of co-morbidities often influences the choice between tamoxifen and AIs in an aged population, therefore an awareness of safety issues is of significant importance. The long-term safety profile of tamoxifen is well-known, with a greater association with endometrial cancer and thromboembolic events when compared to AIs. Conversely, AIs are classically associated with a higher risk of musculoskeletal disorders. Among these AI-specific side effects, osteopenia, osteoporosis, bone fracture, and cardiac events are particularly worrisome for older patients.

Therapy with AIs is generally associated with a significant increase in clinical fracture. Data from IES and BIG 1–98 suggest that there is no significant effect of age on the risk of fracture [5, 9]. The 10-year analysis of the entire ATAC population confirmed that although the incidence of fractures was greater in the anastrozole group during treatment (OR 1.33, 95% CI 1.15–1.55, p = 0.0001), following treatment completion, the incidence of fractures was similar between the two groups (OR 0.98, 95% CI 0.74–1.30, p = 0.9) [11]. Hip fractures were found to be similar in incidence between both groups throughout the study period, whereas spinal fractures were more prevalent in the anastrozole group (OR 1.49, 95% CI 1.01–2.22). A separate update on the bone mineral density (BMD) of patients from ATAC at 7 years demonstrated anastrozole-related bone loss did not persist beyond the cessation of study treatment [15]. The 10-year update of IES reported no significant difference in fracture incidence during the

post-treatment period between the exemestane and tamoxifen groups (9.3% and 8.0%, respectively; p = 0.14) [33].

On-treatment toxic bone effects were more frequent in patients receiving extended letrozole treatment compared to placebo in the MA17.R trial, an effect that did not persist beyond discontinuation of trial regimen [22]. The difference observed on treatment did not appear to be influenced by the intercurrent use of bone-protecting agents, which were utilised in similar percentages in both groups.

MA.27B, a sub-study of the MA.27 trial, recruited two groups of women: those with bone mineral density t-scores of −2.0 or more, and those with t-scores less than −2.0 [21]. Both groups received orally supplemented calcium and vitamin D, and those with t-scores of less than −2.0 also received bisphosphonate therapy. The primary endpoints were the changes in BMD in lumbar spine and hip at 2 years. In the group of women with baseline t-scores of less than −2.0, the mean change in lumbar and hip BMD after 2 years did not differ significantly between those who received exemestane, compared to those who received anastrozole, leading the authors to conclude that aromatase inhibitors may be considered in patients with t-scores less than −2.0.

The 2015 EBCTCG meta-analysis of trials comparing aromatase inhibitors to tamoxifen in early breast cancer revealed the incidence of bone fractures was increased in patients allocated to AI regimens; an effect that was observed beyond 5 years. The 5-year fracture risk for the AI group was 8.2%, versus 5.5% in the tamoxifen group (absolute excess 2.7%, 95% CI 1.7–3.7) [17].

Cardiovascular events

A higher incidence of cardiovascular events (CV) with AIs has been reported in some adjuvant trials. In the ATAC trial, apart from a statistically non-significant difference in angina, the occurrence of other ischemic CV events was similar between tamoxifen and anastrozole [40]. At 10-year follow up, 2.9% of the anastrozole group, and 3.0% of the tamoxifen group had died of cardiovascular causes. Similarly, 1.1% and 1.2% died from cerebrovascular disease, respectively [11].

Although the overall incidence of cardiac adverse events did not differ significantly between the two treatments in BIG 1–98, a trend towards higher grade (3–5) cardiac events on letrozole compared with tamoxifen was seen [4], most notably, double the incidence of cardiac deaths was reported with letrozole versus tamoxifen. Looking at the overall incidence of cardiac events, Crivellari et al. found that after adjusting for risk factors, a significant difference favouring tamoxifen was observed in the older age cohort (65–74 years), but not in the elderly cohort (≥75 years) [9]. Regarding ischemic heart events, after adjusting for risk factors, a significant difference in time to first grade 3–5 ischemic heart event favouring tamoxifen was observed in the older age cohort (65–74 years), but not in the younger (<65 years), or elderly (≥75 years) cohorts. On the basis of Cox model analysis, history of hypertension represented a statistically significant risk factor for both cardiac and ischemic heart events. Perhaps unsurprisingly, prior cardiac and

ischemic heart events were risk factors for future on-treatment cardiac and ischemic heart events, respectively.

In the IES trial, there was a trend towards a higher incidence in myocardial infarctions (MI) on exemestane, however, the effects of treatment on the risk of MI seemed largely restricted to patients with a history of hypertension. Seventy-one percent of patients on exemestane who experienced MI had hypertension at baseline, compared with 32% of the corresponding patients on tamoxifen [8].

Of particular interest are the data from MA.17, in which AI was compared with placebo. No difference in terms of CV events was reported in this trial, suggesting that the cardioprotective effect of tamoxifen may be the principal factor accounting for the difference in cardiac toxicity observed in all those adjuvant trial that compare an AI to tamoxifen. Indeed, this hypothesis appears to be validated by a recent meta-analysis of 19 randomised controlled trials (n = 62,345) concerning cardiotoxicity of AIs and tamoxifen in post-menopausal women with breast cancer [30]. Risk of cardiovascular events were increased by 19% in the setting of adjuvant AI therapy, compared to tamoxifen (relative risk, 1.19, 95% CI, 1.07–1.34). Compared to placebo in the extended adjuvant setting, AIs did not confer an analogous increased risk. Conversely, tamoxifen decreased risk by 33% when compared to placebo or no-treatment (relative risk, 0.67, 95% CI, 0.45–0.98), leading the authors to conclude that this cardioprotective effect completely accounts for the increase in risk observed in trials that compare tamoxifen to AIs.

9.5 Compliance

Adverse effects on quality of life caused by ET can lead to non-compliance and therefore a reduction in potential treatment efficacy. As such, due diligence by clinicians with regards to early detection and effective supportive treatment of treatment-associated toxicities is of paramount importance. Poor compliance and early cessation of letrozole (largely due to side effects) were both found in the BIG 1–98 trial to be associated with reduced DFS [3]. Reduced adherence was greater in patients older than 70 (HR, 1.478, 95% CI, 1.196–1.826, $p < 0.001$). One institutional retrospective analysis of ET-related side-effects reported by breast cancer patients aged over 65 years revealed 22.7% experienced hot flushes, and 16.2% had arthralgia [25]. Just over 20% discontinued treatment prematurely due to side effects, and of those, 38.6% cited arthralgia as the main cause (OR = 5.37, 95% CI, 2.33–12.39, $p = 0.0001$).

9.6 Treatment Options for Elderly Patients

A fundamental issue is whether ET is necessary in all elderly patients with hormone-receptor-positive early BC. For women with minimum risk disease, treatment decisions should be based on a risk-benefit analysis that takes into account the low relapse rate within the first 10 years, the potential reduction in both ipsi- and

contralateral BC relapse, the patient's life expectancy, and treatment-related adverse events. Older patients who have small (<1 cm) node-negative tumours, or who have serious co-morbidity with an estimated survival less than 10 years are unlikely to derive any survival benefit from tamoxifen or other endocrine treatments. No adjuvant treatment could be considered a viable option in these patients.

In elderly patients considered appropriate for adjuvant ET, it is appropriate to follow the same approach as for younger post-menopausal patients. In the absence of any absolute contraindications, an AI should be considered as a part of the five-year treatment strategy, whether upfront or as a part of a switching regimen, especially so in those patients whose disease had characteristics consistent with a high risk of relapse. A patient-profile-based approach should be considered to maximise the therapeutic index of the treatment. From the safety point of view, when ET is considered for a new patient, all risk factors for cardiovascular disease and osteoporosis should be evaluated. As such, in the setting of co-morbidities such as osteoporosis with pre-existing bone fractures or a significant cardiac history, a switching strategy may be preferred.

Data supporting extended adjuvant treatment with an AI bases its rationale on evidence of a relatively constant risk of tumour relapse for ER-positive tumours over time. Individualised estimates of the risk of relapse and death after 5 years of tamoxifen based on standard pathologic prognostic markers suggest that extended adjuvant treatment could be avoided in women at low-risk of relapse [29]. A subgroup analysis of the MA.17 trial showed that this "prolonged" approach is effective in healthy 70+ women with high-risk breast cancer [34]. In patients who receive 5 years of initial upfront AI therapy, it must be noted that extended therapy has been shown in trials to bestow arguably marginal benefits in DFS, with a paucity of data with regards to OS advantage. The overall issue of extended therapy may be less relevant in the elderly population, as many will succumb to co-morbid conditions or advanced age before any survival benefit attributable to extended therapy is reached. Relapsed or metastatic disease may be salvaged by the same ET agents as are used in the adjuvant setting. As such, the decision as to whether to extend initial ET in the adjuvant setting in order to obtain a prolonged DFS, or to offer a more conventional 5-year approach, reserving the hypothetical option of salvaging relapsed disease with ET at a later date, should be balanced according to patient preference, tolerance of treatment, and competing co-morbid conditions.

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