Aromatase Inhibitors: A New Reality for the Adjuvant Endocrine Treatment of Early-Stage Breast Cancer in Postmenopausal Women

M. Colozza[1,*], R .Califano[1], E. Minenza[1], P. Dinh[2] and E. Azambuja[2]

[1]*S.C. Oncologia Medica, Azienda Ospedaliera, San Sisto 06132, Perugia, Italy;* [2]*Medical Oncology Clinic, Jules Bordet Institute, Boulevard de Waterloo, 125, 1000 Brussels, Belgium*

Abstract: Tamoxifen, a selective estrogen receptor modulator (SERM), has been used for many decades as the "gold standard" adjuvant treatment for patients with hormone-receptor-positive early breast cancer. This drug, when administered for 5 years, reduces the risk for recurrence, contralateral breast cancer (BC) and death. The optimal duration of tamoxifen in the adjuvant setting has not been established yet, but it has been demonstrated that 5 years are better than shorter treatment while it is still unclear if a prolongation of the treatment for more than 5 years is worthwhile.

In the last few years, third generation aromatase inhibitors (AIs), either steroidal (exemestane) or non-steroidal (anastrozole, letrozole), have shown to be an effective alternative to tamoxifen in postmenopausal patients with BC regardless of its stage. These agents act by blocking the aromatase enzyme which converts androgens into estrogens.

The goal of this article was to review the results of recent randomized trials comparing AIs to tamoxifen in postmenopausal women in the adjuvant setting. Two strategies have been utilized: a direct upfront comparison in which both tamoxifen and AIs were given for 5 years or an early switch in which AIs were administered after 2-3 years of tamoxifen for 3-2 years or vice versa. Both strategies have shown a superiority of AIs over tamoxifen and a different safety profile but, the optimal treatment modality has yet to be defined.

Moreover, in an attempt to further reduce patients' risk of recurrence after the administration of tamoxifen for 5 years, three trials have evaluated the role of prolonging the adjuvant treatment with AIs for 5 more years in comparison to placebo (late switch). A significant improvement of disease-free survival and of overall survival in the subgroup of node-positive patients, at least in one trial, has been observed with AIs. Despite these important results several unanswered questions remain and the results of ongoing trials will hopefully clarify some of them.

Key Words: Aromatase inhibitors, adjuvant endocrine therapy, postmenopausal women, breast cancer.

INTRODUCTION

Breast cancer is the leading cause of cancer-related death in women despite the fact that, in the last few years, a reduction in mortality has been observed in different countries due to the extensive implementation of screening programs and the use of more effective adjuvant therapies. In postmenopausal women, hormone-responsive cancers i.e. tumours that express estrogen receptors (ER) and /or progesterone receptors (PgR) represent about two-thirds of all breast cancers. In these patients, estrogens are a potent stimulus for the proliferation and progression of tumour cells. Two different strategies have been developed to reduce the effect of estrogens on tumour growth: 1) blockade of estrogen binding with its receptor or 2) reduction of estrogen circulating levels. The anti-estrogenic drugs compete with endogenous estrogens for the binding to their receptor and tamoxifen is the most commonly used drug in the adjuvant setting both for pre- and post-menopausal patients. Tamoxifen, when administered for five years, produces a reduction of the risk of relapse and death with improvement in 10-year survival of 12.6% in node-positive patients and 5.3% in node-negative patients. Furthermore, the clinical benefits of tamoxifen persist after the completion of therapy (carry over effect) for about 15 years and are independent of patients' age, menopausal status, PgR status and the use of adjuvant chemotherapy [1]. The optimal duration of tamoxifen administration is still undefined although it is well established that 5 years of treatment are superior to shorter periods. A prolongation of the treatment for 10 years or indefinitely did not provide further benefit and was associated with a worse outcome, even if not statistically significant, in two relatively small trials [2, 3]. On the contrary, a small study that enrolled patients with node-positive disease treated also with adjuvant chemotherapy has shown a longer time to relapse (TTR) and longer time to development of contralateral tumour in patients receiving tamoxifen for 10 years [4]. Two large randomised trials, that have recently completed the accrual, are evaluating different durations of tamoxifen treatment: the ATLAS (Adjuvant Tamoxifen Longer Against Shorter) and, the aTTOm (adjuvant Tamoxifen Treatment offers more?) but, since their results are not yet available, the standard duration

*Address correspondence to this author at the S.C. Oncologia Medica, Azienda Ospedaliera, Via Dottori 1, 06132 Perugia;
E-mail: mariantonietta.colozza@tin.it

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of tamoxifen treatment remains 5 years. Fig. **1** shows the chemical structure of tamoxifen.

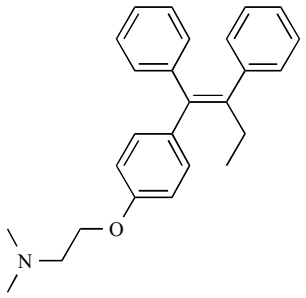

Fig. (1). Chemical structure of tamoxifen.

Tamoxifen is usually well tolerated but serious adverse events such as thromboembolic events, endometrial cancer and cerebrovascular accidents can occur because of its partial-agonist activity. The incidence of these side effects is higher in older women [5]. Furthermore, it should be noted that about 23-40% of patients, discontinue tamoxifen prematurely due to side-effects.

The third generation AIs are a new class of drugs that were initially used in postmenopausal women with hormone-receptor positive metastatic breast cancer as second-line therapy after tamoxifen failure [6-11]. Third generation AIs have been evaluated in the adjuvant setting utilizing different strategies: as direct comparison with tamoxifen (up-front), after 2-3 years of tamoxifen (early switch) or after 5 years of tamoxifen (late switch). AIs have significantly improved disease-free survival (DFS) or relapse-free survival (RFS) in all trials and, in some, also distant disease-free survival (DDFS). A statistically significant improvement overall survival (OS) has been observed in patient subgroups in only three trials but the follow-up in the majority of trials is still too short [12-14]. Tables **1** and **2** summarise the patient and tumour characteristics of these trials.

MECHANISM OF ACTION

Estradiol, which is the most potent endogenous estrogen, is biosynthesized from androgens by the cytochrome P450 enzyme complex called aromatase. The ovaries of premenopausal women, the placenta of pregnant women, and the peripheral adipose tissues of postmenopausal women and of men produce the highest levels of this enzyme [15]. In addition, the expression of aromatase is highest in or near breast tumour sites [16].

In postmenopausal women, AIs act by inhibiting the cytochrome P-450-enzyme aromatase that promotes the conversion of androstenedione and testosterone to estrone and estradiol respectively, mostly in adipose tissue, liver, muscle, brain and breast cancer tissue thereby reducing estrogen circulating levels. Figs. (**2**-**4**) show the chemical structure of letrozole, anastrozole and exemestane.

The enzyme complex is bound in the endoplasmic reticulum of the cell and is comprised of two major proteins [15]. One protein is cytochrome $P450_{arom}$, a hemoprotein that converts C_{19} steroids (androgens) into C_{18} steroids (estrogens) containing a phenolic A ring, whereas the second protein is the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH)-cytochrome P450 reductase, which is a flavoprotein and is responsible for transferring reducing equivalents from NADPH to any microsomal form of cytochrome $P450_{arom}$ [15]. For the conversion of one mole of substrate into one mole of estrogen product, three moles of NADPH and three moles of oxygen are necessary. Aromatization of androstenedione, which is the preferred substrate, proceeds *via* three successive oxidation steps, with the first two being hydroxylations of the angular C-19 methyl group. The final

Table 1. Up-front and "Early Switch" Trials: Patient and Tumour Characteristics

	ATAC [19]	BIG 1-98 [27]	IES [13]	ITA [33]	ARNO 95/ ABCSG 8 [35]
No. randomised patients	6241	8010	4742	448	3224
Median age (years)	64.1	61	64	63	62.1
Node-negative % patients	60.7	57.3	51.6	0	74
T size ≤ 2 cm % patients	63.4	62	47.7	46.5	70
Grade 3 % patients	23.5	NR	18.6	NR	5.5
Hormone-receptor positive % patients	83.5	99.7	88.1	88.5	98
Adjuvant CT % patients	21.5	25.3	32.6	67	0

Abbreviations: NR= not reported; T= tumour; CT= chemotherapy.

Table 2. "Late Switch" Trials: Patient and Tumour Characteristics

	MA.17 [42]	NSABP B-33 [47]	ABCSG 6a [46]
No. randomised patients	5187	1598	856
Median age (years)	62	*50%<60*	61.8
Node-negative % patients	50	52	67.4
T size ≤ 2 cm % patients	NR	61	62.7
Grade % patients	NR	NR	20
Hormone-receptor positive % patients	98	96	~94
Adjuvant CT % patients	45.3	55.5	NR

Abbreviations: NR= not reported; T= tumour; CT= chemotherapy.

oxidation step proceeds with the aromatization of the A ring of the steroid and loss of the C-19 carbon atom as formic acid. This last final step cleaves the C_{10}-C_{19} bond.

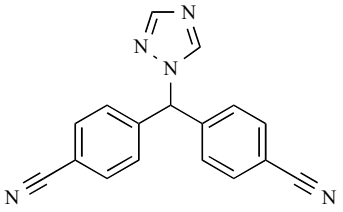

Fig. (2). Chemical structure of letrozole.

AIs may be divided into two subtypes, steroidal and non-steroidal. Steroidal inhibitors (e.g. exemestane) or enzyme inactivators are analogues of androstenedione that bind irreversibly to the substrate binding site on the aromatase molecule. The nonsteroidal compounds (e.g. anastrozole and letrozole) bind reversibly to the haem group of the enzyme. These differences in molecular structure and mechanism of action, may, indeed, underlie the differences in reducing estrogen circulating levels and in modifying lipid profiles [17] and, therefore, determine a different cardiovascular toxicity despite similar clinical activity. Trials comparing these drugs are ongoing, and their results will hopefully clarify this issue.

UP-FRONT STRATEGY

The main results of up-front Als trials are summarised in Table **3**. Two large randomised, double-blinded studies have compared tamoxifen with an AI. The ARIMIDEX, Tamoxifen Alone or in Combination (ATAC) trial randomised 9366 postmenopausal women with ER/PgR+ or unknown receptor status early-stage breast cancer to receive tamoxifen alone, anastrozole alone or tamoxifen plus anastrozole [18]. The primary endpoint was DFS, defined as the time to the earliest occurrence of local or distant recurrence, new primary breast cancer, or death from any cause. Secondary endpoints were TTR (including new contralateral tumours, but not patients who had died from non-breast-cancer causes before recurrence), incidence of new contralateral primary breast tumours, distant recurrence and OS. The tamoxifen plus anastrozole arm was prematurely stopped because the first analysis showed no superiority over tamoxifen alone. After a median follow-up of 68 months, anastrozole, in comparison to tamoxifen, significantly improved the DFS (Hazard Ratio (HR) 0.87, 95% CI 0.70-0.97, p=.01) and the TTR (402 versus 498, 0.79, 0.70-0.90, p=.0005) and this effects was greater in hormone receptor-positive patients [18]. In the first analysis of the trial [19], at a median follow-up of 33 months, no differences were seen in DFS between the two arms neither for patients with node-positive disease nor for those treated with chemotherapy. In the final analysis, all subgroup of patients had a benefit from anastrozole except those with negative or unknown hormone receptor status. In this trial, it has been shown that the reduction of the relapses increases by time even after 5 years of treatment, and that anastrozole seems to provide the same carry-over effect as tamoxifen [20]. A significant overall benefit in time-to-distant-recurrence (TTDR) in favour of anastrozole was demonstrated (324 versus 375 events, HR 0.86, 95% CI 0.74-0.99, p=.04), but there was only a trend in the subset of

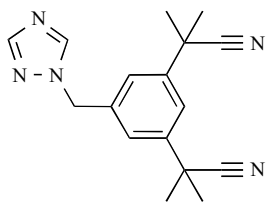

Fig. (3). Chemical structure of anastrozole.

Table 3. "Upfront and "Early Switch" Trials: Results

	ATAC [43]	BIG 1-98 [29]	IES [13]	ITA [34]	ARNO 95/ ABCSG 8 [35]
Median follow-up (months)	68	51	55.7	64	28
Patients on treatment at the moment of the analysis (%)	0	50	0	0	45
Primary end-point HR (95%CI)	DFS (not 2nd tumours) 0.87 (0.78-0.97)	DFS 0.82 (0.71-0.95)	DFS (not 2nd tumours) 0.76 (0.66-0.88)	RFS 0.56 (0.35-0.89) & EFS 0.57 (0.38-0.85)	EFS 0.60 (0.44-0.81)
Absolute benefit in DFS at 5 years (%)	2.8	2.9	3.4	NR	EFS at 3 yrs 3.1
DDFS HR (95%CI)	0.86 (0.74-0.99)	0.87 (0.75-1.01)	0.83 (0.75-0.99)	0.49 (0.22 -1.059 at 36 months	0.54 (0.37-0.80)
Overall survival HR (95%CI)	0.97 (0.85-1.12)	0.91 (0.75-1.11)	0.85 (0.71-1.02) (all pts)	0.56 (0.28-1.15)	NR

Abbreviations: NR= not reported; HR= hazard ratio; DFS=disease-free survival; DDFS=distant disease-free survival; RFS=relapse-free survival; EFS=event-free survival.

hormone receptor-positive patients (HR 0.84, 0.70-1.00, p=.06). The incidence of contralateral breast cancer was significantly reduced by anastrozole in all patients (35 versus 59, 42% reduction, 95% CI 12-62, p=.01) and in hormone receptor positive-patients (53% reduction, 95% CI 25-71, p=.001). No statistically significant difference in OS between the two treatment arms (HR 0.97, 95% CI 0.85-1.12, p=0.7) was observed even if there was a 12% reduction in deaths from breast cancer in the anastrozole group (0.88, 0.74-1.05; p=0.2). However, since the patients enrolled had a relatively good prognosis, a longer follow-up is needed to potentially observe a difference in survival.

A retrospective, unplanned subgroup analysis showed that ER+/PgR- patients had a higher clinical benefit with anastrozole [21]. These data are interesting because they raise the possibility that ER+/PgR- could be a surrogate marker of an extreme activation of growth factor receptors resulting in worse clinical benefit for tamoxifen [22]. However, a recent centralized analysis of ER, PgR and human epidermal growth factor receptor 2 (HER-2) status was undertaken in a subgroup of patients enrolled in the ATAC trial and no difference in survival among ER+/PgR- patients or HER-2-positive patients was shown between the two arms but HER-2-positive tumours tended to be less sensitive to endocrine therapy [23].

Treatment-related adverse events occurred significantly less often with anastrozole than with tamoxifen (61% versus 68%, p<.0001), as well as serious treatment-related adverse events (5% versus 9%; p<.0001) and adverse events leading to withdrawal (11% versus 14%; p=.0002). There were no significant difference in the incidence of ischemic cardiovascular events (p=0.1), the most common of which was angina (p=.07). Patients on tamoxifen had a higher incidence of endometrial cancer (p=.02), cerebrovascular events (p=.03), deep venous thromboembolic events (p=.0004), hot flushes (p<.0001), vaginal bleeding (p<.0001) and vaginal discharge (p<.0001), while patients receiving anastrozole presented a higher incidence of fractures (p<.0001) but, interestingly, the rate of hip fractures was low in both groups (1% in both arms). Hypercholesterolemia was more common in the anastrozole arm (p=.0001). Other adverse events including muscle cramps, anaemia, nail disorders, fungal infections and urinary tract infection were less common in the anastrozole arm while a higher incidence of carpal-tunnel syndrome, paresthaesia, mouth dryness, decrease of libido and dispareunia was reported with anastrozole [24]. The higher incidence of osteoporosis and osteopenia was observed mostly in the first two years of treatment with a reduction in the next three years at the lumbar spine and it is noteworthy that no patients with a baseline normal bone mineral density developed osteoporosis during the treatment [25]. Quality of life evaluation in 1091 patients enrolled in the three initial arms of the study did not show any significant difference [26].

The Breast International Group study (BIG 1-98) randomised 8010 postmenopausal patients with ER+ and/or PgR+ early breast cancer in four arms to receive: tamoxifen for five years, letrozole for five years, letrozole for two years

followed by tamoxifen for three years, or tamoxifen for two years followed by letrozole for three years. The first analysis, conducted at a median follow up of 25.8 months, evaluated tamoxifen and letrozole excluding events and follow up after 2 years of treatment in the two sequential arms [27]. The primary endpoint of the study was DFS, defined as the time from randomization to the first of one of the following events: 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. Secondary endpoints included OS (defined as the time from randomization to death from any cause) and DDFS. Patients in the letrozole arm had a significantly better DFS (HR 0.81, 95% CI, 0.70-0.93, p=.003) with a significant reduction of distant relapses (HR 0.73, 95% CI, 0.60-0.88, p=.001). Prospectively planned subgroup analyses showed greater benefits of letrozole in patients treated with chemotherapy, node-positive patients and patients who did not receive radiotherapy. DDFS was significantly greater in women treated with letrozole (HR 0.83, 95% CI, 0.72-0.97, p=.02) and, although fewer women died in the letrozole group, no statistically significant difference in OS was observed. A centralized analysis of ER, PgR and HER2 status of more than 4000 patients enrolled in this study was performed and no significant difference between the two drugs was shown in different subgroups according to hormone receptor status and HER-2 status [28]. Life-threatening or fatal protocol-specified adverse events were similar in the two arms (1.7% in both arms). In the letrozole arm, fractures were significantly more frequent than in the tamoxifen arm (P<.001), while a lower incidence of thromboembolic events (P<.001), vaginal bleeding (p<.001) and invasive endometrial cancers (p= 0.18) was observed. The overall incidence of grade 3-5 adverse cardiovascular events was similar in the two groups (3.7% in the letrozole group and 4.2% in the tamoxifen group), but more women in the letrozole group had grade 3-5 cardiac events (2.1% versus. 1.1%, p<.001) and grade 1 hypercholesterolemia. At a median follow up of 51 months, a new analysis was performed including only the 4928 women randomised to receive letrozole or tamoxifen for 5 years. A significantly longer DFS was obtained with letrozole (HR 0.82; 95% CI 0.71-0.95; p=.007), resulting in an absolute improvement of 2.9% at 5 years (84% versus 81.1%, p=.007) but only a trend for DDFS (p=.07) and no differences for OS (p=.35). Letrozole significantly prolonged the TTR (HR 0.78; 95% CI 0.65-0.92 p=.004); and the TTDR (HR 0.81; 95% CI 0.67-0.98; p=.03). Adverse events were similar to those previously reported [29].

SEQUENTIAL THERAPY AFTER 2-3 YEARS OF TAMOXIFEN (EARLY SWITCH)

The main results of the trials evaluating this strategy are summarised in Table **3**. In the Intergroup Exemestane Study (IES), a randomised, double-blinded, multi-centre trial, 4742 postmenopausal women with unknown or hormone receptor-positive breast cancer who remained free of disease after receiving adjuvant tamoxifen therapy for 2-3 years were randomised to receive tamoxifen or exemestane for other 3-2 years [30]. The primary endpoint was DFS, defined as the time from randomization to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause. Secondary endpoints included OS, the incidence of contralateral breast cancer, and long-term tolerability.

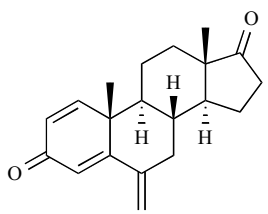

Fig. (4). Chemical structure of exemestane.

The first analysis, at a median follow-up of 30.6 months, with 90% of patients who had completed treatment, showed a longer DFS in the exemestane arm (HR 0.68%, 95% CI 0.56-0.82, p=.00005) which corresponded to an absolute benefit of 4.7% at three years, longer DDFS (HR 0.66, 95% CI 0.52-0.83, p=.0004) and a reduction of the risk of contralateral breast cancer (HR 0.44, 95% CI 0.20-0.98, p=.04). There was no statistically significant difference in OS. Patients in the exemestane arm experienced more arthralgia, diarrhoea, visual disturbances and osteoporosis than tamoxifen, but less thromboembolic events, second primary non-breast cancer, gynaecologic symptoms, vaginal bleeding, and muscle cramps. Fractures were reported more frequently in the exemestane group than in the tamoxifen group but the difference was not statistically significant.

An updated analysis was performed at a median follow up of 55.7 months with 4724 patients evaluable [13]. More than 95% of patients had at least 3 years of follow-up or had died during the corresponding period. Hormone receptor status was re-assessed in 381 patients with unknown receptor status at randomization, 122 of these resulted negative and it was decided to conduct a new analysis excluding patients with ER-negative disease. Overall, in the intention-to treat (ITT) group, a longer DFS in the exemestane group (HR 0.76, 95% CI 0.66-0.88, p=.0001) was obtained and the result were superimposable in the ER+ and ER unknown group (HR 0.75, 95% CI 0.65-0.87; p=.0001). These HR translated into a 3.4 % (0.1-6.8) and 3.5% (0.1-6.9) absolute improvement in DFS at 5 years after randomisation in the ITT group and in the ER+ and ER unknown group respectively. Breast-cancer-free survival, TTDR and time to contralateral breast cancer were all improved by switching to exemestane both in the ITT group and in the ER+ and ER unknown group. About 10% of patients had died, with 222 deaths in the exemestane group and 261 in the tamoxifen group. The unadjusted hazard ratio for OS was 0.85 (95% CI 0.71-1.02, p=.08) in the ITT group and 0.83 (95% CI 0.69-1.00, p=.05) in the ER+ and ER unknown group.

No significant difference in the incidence of grade 3-4 adverse events was observed between the two arms. Thromboembolic events and muscle cramps were more frequent in the tamoxifen arm while patients in the sequential arm experienced more diarrhoea, gastric ulcer, musculoskeletal pain, arthritis, arthralgia, carpal tunnel syndrome, paresthesia, joint stiffness, osteoporosis and fractures. The incidence of cardiovascular events was similar in the two arms, but a

higher percentage of myocardial infarction was seen in the exemestane arm. No statistically significant difference was observed between the two arms for endometrial cancer and necessity of hysterectomy, but more vaginal bleeding, uterine polyps/fibroids and endometrial hyperplasia occurred in the tamoxifen group [13].

In an ancillary study, the effects of exemestane on bone mineral density (BMD) were evaluated in 206 patients enrolled in the IES study [31]. The primary endpoint of this study was mean annual changes from baseline in lumbar spine and total hip BMD assessed by dual-energy X-ray absorptiometry (DXA) in both arms. Secondary endpoints included changes in biochemical markers of bone turnover in the two treatment groups at each time point, within-group changes in BMD and bone markers, and assessment of the links between changes in biochemical markers of bone metabolism and changes in BMD. The incidences of fractures were also assessed. A statistically significant reduction in BMD compared with baseline was seen in the exemestane group within the first six months of treatment both at the lumbar spine and at the total hip. Thereafter, the reduction in BMD progressively slowed in months 6-12 and 12-24, but continued to decline. The decline in BMD after the switch to exemestane resulted in a higher incidence of osteopenia at 24 months, and five patients, who were osteopenic at baseline, developed osteoporosis. The changes in bone markers from baseline were significantly different in patients in the exemestane arm at all time-points. Generally, there were significant negative correlations between bone-marker and BMD changes at 24 months. A significantly higher incidence of fractures occurred in the exemestane group (7% versus 5%, p=0.003) but no patients with a normal baseline BMD developed a fracture. The rate of fractures observed in 24 months was so low that it was not possible to correlate it with changes in BMD or changes in biochemical markers of bone metabolism. The quality of life assessment on 582 enrolled patients did not show any differences between the two groups [32].

Three European studies investigated five years of tamoxifen versus tamoxifen for 2-3 years followed by anastrozole for 3-2 years. The Italian Tamoxifen Anastrozole (ITA) trial randomised 448 node-positive ER+ postmenopausal women who received 2-3 years of tamoxifen to complete 5 years of treatment with tamoxifen or to receive 2-3 years of anastrozole [33]. The primary endpoint was RFS including both locoregional and distant recurrences except contralateral breast cancer. Event-free survival (EFS) included as events any of the following: locoregional recurrences, distant metastases, second primary tumours including contralateral breast cancer and breast cancer-unrelated deaths. Secondary endpoints were incidence of deaths, whatever the cause, and adverse events. All second primary tumours (except contralateral breast cancer) were included among serious adverse events. At a median follow up of 36 months, women who switched to anastrozole had a significantly longer EFS (HR 0.35; 95% CI 0.20-0.63; P=.0002) and RFS (HR 0.35; 95% CI 0.18-0.68; P =.001). Women in the anastrozole group also had significantly longer loco-regional RFS (HR 0.15; 95% CI, 0.03-0.65; P=0.003), whereas the difference in DDFS did not reach statistical significance (HR 0.49; 95% CI, 0.22-1.05; P =0.06). Overall, more patients in the anastrozole arm presented adverse events but more patients in the tamoxifen arm presented serious adverse events even if the difference was not statistically significant. These results were confirmed at a median follow-up of 64 months [34]. RFS (HR 0.56; 95% CI 0.35-0.89; P=.01) and EFS (HR 0.57, 95% CI 0.38-0.85; P=.005) were longer in the anastrozole group while the difference in OS was not statistically significant (P=0.1). Overall more patients in the anastrozole group experienced at least one adverse event (209 versus 151; P=.000) but the number of patients experiencing serious adverse events was comparable (P=0.7). However, gynaecological problems, including endometrial cancer, were significantly more frequent in the tamoxifen group (p=.006).

Two multi-centre studies with similar design, the Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG) and the ARIMIDEX/NOLVADEX (ARNO 95), randomised postmenopausal hormone receptor-positive patients, not treated with adjuvant chemotherapy, to receive anastrozole after 2 years of tamoxifen or to continue tamoxifen for overall 5 years. It is noteworthy that, in the first trial, patients were randomised before starting the adjuvant therapy while in the second trial, after completing 2 years of tamoxifen which was given at the dose of 20 mg/day in the ABCSG 8 trial and 30 mg/day in the ARNO 95 trial. A combined analysis of these two trials was performed, at a median follow-up of 28 months, with 3224 patients enrolled of whom 55% had completed the treatment [35]. Anastrozole reduced the risk of new events of 40% (HR=0.60; 95% CI 0.44-0.81; p=0.0009) with an absolute benefit at 3 years of 3.1%. This advantage was independent of nodal status, age or hormone receptor status although there was a suggestion that the benefit of anastrozole in ER+/PgR+ patients was higher. Patients in the anastrozole arm presented a decreased risk of distant metastases as first event only (HR 0.54, 95% CI 0.37-0.80; p=.0016) while there was no statistically significant difference in OS. Sequential therapy was associated with more fractures, less thrombotic events and a non-significant reduction of embolic events and endometrial cancers. Patients in the anastrozole group experienced more nausea and arthralgia.

Data from the ARNO 95 trial were analysed separately at a median follow-up of 30.1 months with 42.5% of patients who had completed the planned 5 years of treatment [14]. The primary endpoint was DFS (the time from random assignment to the occurrence of local or distant recurrence, new primary breast cancer, or death); secondary endpoints included OS, safety, and tolerability. Patients who switched to anastrozole had a statistically significant improvement in DFS (HR 0.66; 95% CI 0.44-1.00; p=.049) with an absolute difference of 4.2% at 3 years and in OS (HR=0.53; 95% CI 0.28-0.99; p=.045). After adjustment for potential prognostic factors (age, tumour size and grade, lymph node status, and type of primary surgery) these results were confirmed. The overall safety profile for anastrozole was consistent with previous reports. The incidence of serious adverse events was lower with anastrozole. It is noteworthy, the small number of any recurrence (36 *vs*. 47) and deaths (15 *vs*. 28) in the sequential arm and in the tamoxifen arm, respectively.

Table 4. "Late Switch" Trials: Results

	MA.17 [12]	NSABP B-33 [47]	ABCSG 6a [46]
Median follow-up (months)	30	30	60
Patients on treatment at the moment of the analysis (%)	>99	NR	0
Primary end-point HR (95%CI)	DFS (no BC unrelated deaths) 0.58 (0.45-0.76)	DFS RR=0.68 NS	RFS 0.64 0.41-0.99
Absolute benefit in DFS (%)	at 4 years 4.6	at 4 years 2	NR
DDFS HR (95%CI)	0.60 (0.43-0.84)	RR=0.69 NS	NR
Overall survival HR (95% CI)	0.82 (0.57-1.19)	RR=1.20	0.90 (0.59-1.34)

Abbreviations: NR= not reported; DFS=disease-free survival; RFS=relapse-free survival; DDFS= distant disease-free survival; NS= not significant

The data from the ABCSG 8 trial were also analysed separately at a median follow-up of 54.6 months. A trend for a longer EFS (HR 0.76; p=.068) and no difference in OS were observed if the data were analyzed since the randomisation. However, the EFS was significantly longer in the anastrozole arm (HR 0.63; p=.01) if the data were analysed after two years of treatment with tamoxifen [36].

A meta-analysis of the ITA, ABCSG 8 and ARNO 95 trials confirmed the results of the single trials and showed a reduction of relapses and deaths in the anastrozole arm with a significant longer DFS (HR 0.59; 0.48-0.74; p<.0001), EFS (HR 0.55; 95% CI 0.42-0.71; p<.0001), DDFS (HR 0.61; 95% CI 0.45-0.83; p=.002), and OS (HR 0.71; 95% CI 0.52-0.98; p=.04). Although these data are interesting, it is worthwhile to point out that the three trials differ in time of randomisation, primary endpoints, patient characteristics and follow-up duration [37]. The most important difference regards the time of randomisation so that the ARNO 95 and ITA trials having randomised patients after 2-3 years of tamoxifen, excluded those with early relapses and therefore less hormone-responsive disease.

SEQUENTIAL THERAPY AFTER 5 YEARS OF TAMOXIFEN (LATE SWITCH)

The main results of the trials evaluating this strategy are summarised in Table **4**. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis and some retrospective studies suggest that the risk of relapse for patients with early stage breast cancer is high and persists for many years after diagnosis [38-41]. In particular, patients with ER positive tumours who received adjuvant tamoxifen for 5 years have a risk of relapse at 10 and 15 years of 24.7% and 33.2%, respectively, and a risk of death at 10 and 15 years of 17.8% and 25.6%, respectively [1]. It appears, therefore, appropriate to prolong the hormonotherapy beyond 5 years in the attempt to reduce the risk or relapse and death. So far, tamoxifen given for more than 5 years, has not been shown to further improve survival [2, 3] and it is associated with the risk of serious adverse events and the chance of acquired resistance. Therefore, a few years ago, AIs started to be evaluated in this setting in postmenopausal women.

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17 study, a randomised double blinded placebo-controlled trial, evaluated the efficacy of letrozole in 5187 postmenopausal women with positive or unknown hormone receptor breast cancer who were disease-free after 4-6 years of therapy with tamoxifen [42]. The primary endpoint was DFS, defined as time from randomization to loco-regional recurrence, distant metastasis or a contralateral new primary breast cancer. The first interim analysis was conducted at a median follow-up of 2.4 years and based on the positive results obtained with letrozole, this trial was prematurely closed with only 14 patients having completed 5 years of treatment with letrozole. A statistically significantly longer DFS (HR 0.57, 95% CI 0.43-0.75; p=.00008) was obtained with letrozole and this advantage was evident both for node-positive (HR 0.60, p=.003) and for node-negative patients (HR 0.47; p=.005). OS was the same in both arms. In a recent update, at a median follow-up of 30 months, this advantage in DFS was confirmed (HR 0.58, 95% CI 0.45-0.76; p< .001) with an absolute reduction of the risk of relapse of 4.6% at 4 years and a longer DDFS (HR=0.60; 95% CI 0.43-0.84; p=.002) that was independent of nodal status, previous use of adjuvant chemotherapy and duration of tamoxifen treatment (≤ 5 years or ≥5 years). The incidence of contralateral breast cancer was also reduced in the letrozole arm but, the difference was not statistically significant. No difference in OS between the two arms was observed but a

pre-planned subgroup analysis showed a longer OS for node-positive patients (HR=0.61; 95% CI 0.38-0.98; p=.04). With the limits of a subgroup analysis, this was the first trial to demonstrate an advantage in OS with AIs in the adjuvant setting [12].

A retrospective analysis, based on ER and PgR status, suggested that the clinical benefits obtained with letrozole were greater in patients with ER+/PgR+ tumours which represented the largest subgroup (73%). The DFS hazard ratio for letrozole versus placebo in women with ER+/PgR+ tumours was 0.49 (95% CI, 0.36-0.67) versus 1.21 (95% CI, 0.63 to 2.34) in women with ER+/PgR- tumours. Similar results were observed for DDFS (HR 0.53; 95% CI 0.35-0.80) and OS (HR 0.58; 95% CI, 0.37-0.90) in the ER+/PgR+ subgroup. A statistically significant difference in treatment effect between ER+/PgR+ and ER+/PgR- subgroups was reported for DFS (p=.02), but not for DDFS (p=.06) or OS (p=.09). These results, which are discordant from those reported in other trials comparing AIs and tamoxifen in which subgroup analysis based on hormone receptor status, was retrospectively done, should be interpreted with caution because this was a retrospective unplanned analysis. Moreover, the determination of the hormone-receptor status was not measured centrally and all the groups except for the ER+/PgR+ subgroup had a relatively small number of patients [43].

Analyses were conducted to examine the relationships between duration of treatment and outcomes [44]. The hazard rates for DFS, DDFS and OS at 6, 12, 24, 36 and 48 months of follow-up and the hazard ratios for letrozole to placebo and associated 95% confidence intervals for DFS, DDFS and OS at these time points were estimated. Patients in the placebo arm had a continuous increase of the risk of relapse over time while in the letrozole arm this risk peaked at 2 years and then slowly decreased. These analyses suggest that, at least up to 48 months, longer duration of letrozole treatment is associated with greater benefit in the extended adjuvant therapy setting.

Hot flushes, arthralgia, muscle pain, anorexia and alopecia were significantly more frequent in the letrozole group. The higher incidence of vaginal bleeding that occurred in the placebo arm can be explained with the inhibition of endometrial proliferation due to the AIs mechanism of action. Furthermore, patients who received letrozole experienced more fractures, cardiovascular accidents and osteoporosis, although only osteoporosis reached a statistically significant difference.

When the trial was closed, after the first interim analysis, women in the placebo arm were offered to switch to letrozole. Of 2268 disease-free patients in the placebo group, 1655 accepted to start letrozole. These women were younger, with more advanced disease and most of them had received adjuvant chemotherapy. At a median follow up of 54 months from randomisation, patients who accepted the crossover had a statistically significantly longer DFS (HR 0.31; 95% CI 0.18-0.55; p<.0001), DDFS (HR0.28; 95% CI 0.13-0.62; p=.002), and OS (HR 0.53; 95% CI 0.28-1.00; p=.05) and a significant reduction of contralateral breast cancer (HR 0.23; 95% CI 0.07-0.77; p=.017). Interestingly, clinical benefits were seen even if letrozole was started more than three months after suspension of tamoxifen. More fractures and less cardiovascular events occurred in the letrozole group, without statistically significant differences while the incidence of osteoporosis was significantly higher [45].

A new randomised trial (MA.17R) is ongoing to evaluate a prolongation of letrozole treatment for ten years in patients who are disease-free after completing 5 years of letrozole (MA.17 trial or routine clinical practice) or 5 years of any other adjuvant AI.

The ABCSG 6 trial randomised 1986 postmenopausal hormone receptor-positive early breast cancer patients to receive tamoxifen for 5 years or tamoxifen plus aminoglutethimide for 2 years followed by 3 years of tamoxifen. Eight hundred fifty-six women were then enrolled in another trial (ABCSG 6a) in which they were randomised to continue hormonotherapy with anastrozole for 3 years or to receive no treatment [46]. Primary endpoint was RFS and at a median follow-up of 5 years, patients in the anastrozole arm had a longer RFS (HR=0.64; 95% CI= 0.41-0.99; p=.047) but no difference in OS was seen. So far, no toxicity data have been reported.

Another study, the National Surgical Adjuvant Breast and Bowel Project B-33 (NSABP) randomised postmenopausal, hormone-receptor positive women with stage I-II breast cancer to receive 5 years of exemestane or placebo after the standard 5 years of adjuvant tamoxifen [47]. This trial had planned to enrol 3000 patients but, was prematurely closed after the publication of the MA.17 trial's results with only 1598 patients enrolled and 1577 patients eligible. In the placebo group, 44% of patients accepted to start exemestane and 72% of patients in the exemestane group completed the treatment. The primary endpoint of the study was DFS defined as time to earliest occurrence of local or distant recurrence, new primary breast cancer, second tumour, or death without recurrence. At a median follow-up of 30 months, there were no statistically significant differences in DFS, DDFS and OS even if the number of events was reduced in the exemestane arm, but, exemestane significantly prolonged RFS (p=.004) and reduced the incidence of contralateral cancer (p=.05). A statistically significant benefit in DFS was seen in patients with node-positive disease, tumour size >2cm and who had received adjuvant chemotherapy. There were no treatment-related deaths. In the exemestane arm occurred significantly more grade 3-4 fatigue, arthralgia and muscle pain but there was no difference in the incidence of fractures.

COST-BENEFIT OF AROMATASE INHIBITORS IN EARLY BREAST CANCER

The ATAC trial was used as the model for analysing cost-effectiveness in the United Kingdom. Modelled for 25 years, anastrozole was shown to be a cost-effective alternative to generic tamoxifen in the adjuvant treatment of postmenopausal hormone-receptor positive early BC, resulting in an estimated incremental cost-effectiveness of 17 656 pounds per quality-adjusted life year (QALY) gained [48]. Also, in a cohort of 1000 postmenopausal women with HR positive early BC, another model from the United States

healthcare system, showed that anastrozole versus tamoxifen would lead to 257 QALYs gained (0.26 QALYs gained per patient), at an additional cost of $5.21 million over 25 years ($5,212 per patient) [49]. Based on the ARNO and ATAC studies, sequential tamoxifen-AI is the preferred cost-effective adjuvant strategy compared to upfront AI in postmenopausal women with hormone-receptor positive BC, whereas AI upfront appears to be the preferred cost-effective strategy for patients with ER+PgR- BC [50]. Using the two AIs upfront trials, the BIG 1-98 and ATAC trials, incremental cost per QALY gained for letrozole versus tamoxifen is $33,536 (95% CI $20,409 to $70,566) and for anastrozole versus tamoxifen is $38,967 (95% CI $23,826 to $81,904). Compared with anastrozole, letrozole is less costly ($9,647 *vs* $10,190) and gains more QALYs (0.29 *vs*. 0.26), although differences in costs (95% CI -$1,669 to $671) and QALYs (95% CI -0.16 to 0.22) are not statistically significant [51].

Comparing the ATAC, IES, and MA.17 studies, tamoxifen for 2-3 years followed by an aromatase inhibitor for 3-2 years provided the lowest cost/QALY estimates, while administration of an AI subsequent to 5 years on tamoxifen provided the highest values. The difference between strategies increased with patient age. Cost/QALY estimates were sensitive to an increase in hip fracture risk and to cost reductions due to relapse prevention [52]. A similar study performed in the United Kingdom showed that compared to 5 years of tamoxifen, adjuvant treatment of postmenopausal hormone-receptor positive women with letrozole or anastrozole for 5 years, or 2 years tamoxifen followed by exemestane for 3 years, is a cost-effective therapy. The mean results indicate that upfront use of an AI is a more cost-effective therapy than switching to an AI after 2-3 years of tamoxifen, although the difference is not significant [53]. The sequential exemestane treatment (IES study) in early BC showed that switching to an AI after 2-3 years of tamoxifen is a cost-effective option compared with tamoxifen alone in Sweden [54].

In base-case analyses using data from the MA.17 trial, extended adjuvant letrozole versus no extended adjuvant therapy results in an expected gain of 0.34 QALYs per patient (13.62 *vs*. 13.28 QALYs), at an additional lifetime cost of $9,699 per patient ($55,254 *vs*. $45,555). The incremental cost per QALY gained with letrozole is $28,728, which is within the range of other generally accepted medical interventions in the United States. Cost-effectiveness is sensitive to the assumed reduction in risk of breast cancer events with letrozole but is insensitive to the risks, costs, and quality-of-life effects of osteoporosis and hip fracture [55].

CONCLUSION

The results from the above-mentioned studies suggest that AIs are superior to tamoxifen given for 5 years both as up-front therapy (anastrozole and letrozole) and as sequential therapy (exemestane and anastrozole) after 2-3 years of treatment with tamoxifen. Mathematical models, based on the data from all these studies, have been utilized to evaluate the best strategy but, conflicting results have been obtained [56, 57]. Therefore, at the present time, it is not possible to define the optimal strategy and the results of the randomised trials comparing the two strategies (BIG-98, TEAM [Tamoxifen-Exemestane Adjuvant Multicenter study], FATA [First Adjuvant Trial on Aromatase Inhibitors]) are eagerly awaited. Recently, data from the BIG-98 study have shown that predictive factors of early relapse are node-positive disease (p<.001), ER or PgR negativity (p<.001), tumour size >2 cm (p<.001), vascular invasion (p=.02) and tamoxifen therapy (p=.002) [58].

A prolongation of adjuvant hormonotherapy with an AI for 5 years after tamoxifen given for 5 years has significantly improved DFS, DDFS in node-negative and node-positive patients and OS in node-positive patients in the MA.17 trial, DFS in ABCSG 6a trial and RFS in NSABP-B33 trial. Furthermore the benefit of letrozole seems to increase over time. The short-term toxicity of AIs is acceptable although vaginal dryness and joint pain/stiffness are not insignificant problems as well as bone loss that requires monitoring. The long-term toxicity is still largely unknown.

All these remarkable results leave, however, several unanswered questions. Among these: the necessity to identify subgroups of patients that should be approached differently according to tumour characteristics or host factors that may be predictors of efficacy and toxicity.

Pharmacogenomics and translational research could be important to better understand these differences. Recently, it has been reported in a retrospective study [59], that the levels of endoxifen, one of the most potent tamoxifen metabolites, vary with the number of mutant alleles of the cytochrome P450 2D6 (CYP2D6) enzyme and therefore, could identify good and poor tamoxifen metabolizers. Furthermore, it has been observed that polymorphisms of CYP 19, the aromatase gene, are differently distributed across ethnic groups and could be associated with a different risk-benefit profile of AIs [60, 61]. These observations need, however, to be evaluated in prospective trials.

It is also important to identify the subgroup of patients who should receive a prolonged adjuvant endocrine treatment, since in the decision-making process it is important to balance the absolute benefits with the risk of side effects and the costs of treatment.

The optimal duration of adjuvant hormonotherapy is still unknown. A treatment with AIs for 5 years has been chosen based on the results obtained with tamoxifen. Ongoing trials are evaluating different durations of AIs administration and hopefully, will help to clarify this issue. A better knowledge of the long-term adverse effects on the cardiovascular system, cognitive functions and bone metabolism of AIs is also crucial. Last but not least the different molecular structures and power of AIs could translate into different clinical efficacy and toxicity but only a direct comparison between them can give a definitive answer and there are currently studies underway.

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