Review
Update on the use of aromatase inhibitors in early-stage breast cancer

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Abstract

Aromatase inhibitors are currently included in the 'optimal' management of early-stage breast cancer. Uncertainty remains, however, as to the most appropriate treatment strategy, particularly for newly diagnosed women as they seek to trade off the cost, toxicities and efficacy of the treatment options. Recent publications provide conflicting advice on the role of aromatase inhibitors in the treatment of postmenopausal patients with early-stage hormone receptor-positive breast cancer. This review provides updates on the clinical trials of aromatase inhibitors in early breast cancer and tries to provide practical clinical guidance on their optimal use.

Introduction

Adjuvant hormonal therapy yields significant improvements in disease-free survival (DFS) and overall survival (OS) in women whose tumours express hormone receptors. Until recently, the selective oestrogen receptor (ER) modulator tamoxifen was regarded as the standard of care for women with such disease, yielding reductions in risk of relapse of 39% and reduction in risk of death of 24% attributable to the use of tamoxifen for about 5 years [1].

The superiority of the potent 'third-generation' aromatase inhibitors (AIs) in advanced-stage breast cancer (BC) underscored the need to test their efficacy in the adjuvant setting in postmenopausal women with early-stage disease [2-7]. In the past decade, several trials have been performed to compare the efficacy and toxicity of the AIs with tamoxifen. There are two types of trial: those that have randomly assigned newly diagnosed women and those that have randomly assigned women currently taking tamoxifen.

Of the trials involving newly diagnosed women, there are two main trial structures:
* 5 years of an AI versus 5 years of tamoxifen
* A planned switch (that is, sequence) involving 2 years of tamoxifen followed by 3 years of an AI versus 2 years of an AI followed by 3 years of tamoxifen versus 5 years of tamoxifen.

Of the trials involving women currently taking tamoxifen, there are two main trial structures:
* An unplanned switch from tamoxifen to an AI following 2 to 3 years of tamoxifen versus 5 years of tamoxifen
* An unplanned switch after 5 years of tamoxifen to an AI or placebo for a further 5 years.

The American Society of Clinical Oncology (ASCO) Technology Assessment of AIs states that optimal adjuvant hormonal therapy for a postmenopausal woman with hormone receptor-positive BC should include an AI [8]. The National Institute for Health and Clinical Evidence (NICE) has also recommended AIs, within their licensed indications, as options for the adjuvant treatment of early-stage ER+ invasive BC in postmenopausal women who are newly diagnosed and those women currently on tamoxifen [9]. However, due to a lack of results from directly comparative trials, neither guideline was able to recommend one particular treatment strategy over another.

Uncertainty remains as to the most appropriate treatment strategy, particularly for newly diagnosed women, as they seek to trade off the cost, toxicities and efficacy of the

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ABCSG = Austrian Breast & Colorectal Cancer Study Group; AI = aromatase inhibitor; ARNO = Arimidex-Nolvadex; ASCO = American Society of Clinical Oncology; ATAC = Arimidex, Tamoxifen, Alone or in Combination; BC = breast cancer; BIG = Breast International Group; BMD = bone mineral density; CI = confidence interval; DFS = disease-free survival; DVT = deep vein thrombosis; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; HRQoL = health-related quality of life; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Arimidex; ITT = intention to treat; MI = myocardial infarction; MRI = magnetic resonance imaging; NICE = National Institute for Health and Clinical Evidence; NSABP = National Surgical Adjuvant Breast and Bowel Project; OS = overall survival; PR = progesterone receptor; PTH = parathyroid hormone; RFS = relapse-free survival; SE = standard error; VTE = venous thromboembolic event.

treatment options. Recent publications provide conflicting advice on the role of AI in the treatment of postmenopausal patients with early-stage hormone receptor-positive BC. On one hand, Chlebowski [10] recommends up-front AI for the majority of patients, whereas Seruga and Tannock [11] suggest that tamoxifen remains the endocrine treatment of choice for most patients.

Newly diagnosed postmenopausal women with hormone receptor-positive early breast cancer
Trials comparing 5 years of an aromatase inhibitor versus 5 years of tamoxifen
The ATAC trial
The Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, involving 9,366 patients, was the first of these trials to report and remains a 'landmark' trial in the treatment of early BC. The initial report in *The Lancet*, with a median follow-up of 33.3 months, demonstrated the superiority of anastrozole compared with tamoxifen with 3-year DFS rates of 91.2% for anastrozole versus 89.3% for tamoxifen in hormone receptor-positive patients (hazard ratio [HR] 0.78, 95% confidence interval [CI] of 0.65 to 0.93, $P = 0.005$) [12]. Results with the combination were not significantly better than tamoxifen alone (HR 1.02, 95% CI of 0.87 to 1.21, $P = 0.8$). The combination arm has not been analysed subsequently, and it is unlikely that other trials of combinations of AIs and tamoxifen will be undertaken. In the latest update of this trial, with a median follow-up of 100 months, anastrozole significantly increased DFS in the hormone receptor-positive population by 74.2% versus 70.1% for tamoxifen (HR 0.85, 95% CI 0.76 to 0.94, $P = 0.003$) [13]. In anastrozole-treated patients, risk of recurrence was reduced by 24% (HR 0.76, 95% CI 0.67 to 0.87, $P = 0.0001$) compared with tamoxifen. Risk of contralateral BC was significantly reduced in the anastrozole arm by 40% (HR 0.60, 95% CI 0.42 to 0.85, $P = 0.004$) compared with tamoxifen. OS was similar with anastrozole and tamoxifen (HR 0.97, 95% CI 0.86 to 1.11, $P = 0.7$).

The BIG 1-98 Collaborative Group study
This four-arm trial compared 5 years of tamoxifen versus 5 years of letrozole, versus 2 years of tamoxifen plus 3 years of letrozole, versus 2 years of letrozole and 3 years of tamoxifen. This key study was designed to evaluate whether a planned sequence of tamoxifen and letrozole (and *vice versa*) provides benefits compared with 5 years of letrozole. A total of 8,010 women with hormone receptor-positive BC were randomly assigned. In the head-to-head comparison of letrozole versus tamoxifen for 5 years, at a median follow-up of 25.8 months, 351 events were noted in the letrozole arm and 428 with tamoxifen, with estimated 5-year DFS rates of 84.0% for letrozole and 81.4% for tamoxifen [14]. The risk of distant recurrence was also significantly reduced (HR 0.73, 95% CI of 0.60 to 0.88, $P = 0.001$).

More data from this trial were recently published [15]. This involved 4,922 patients (only those patients who continued in

the monotherapy arms following the crossover of the trial) with a median follow-up of 51 months. Three hundred fifty-two events were recorded in the letrozole arm compared with 418 with tamoxifen, with estimated 5-year DFS rates of 84.0% versus 81.1% with tamoxifen (HR 0.82, 95% CI of 0.71 to 0.95, $P = 0.007$).

The results published in 2005 in favour of letrozole led to the unblinding of the tamoxifen-alone arm, and 25.2% of the patients selectively switched to letrozole for a median duration of receiving letrozole of 18 months. As a result, the analysis recently reported with 76 months of follow-up was divided as either intention to treat (ITT) or by censoring patients who switched. In this latest update [16], there is a statistically significant difference in DFS (HR 0.88, 95% CI 0.78 to 0.99, $P = 0.03$) for both ITT and censored populations and a trend for OS benefit in the ITT population (HR 0.87, 95% CI 0.75 to 1.02, $P = 0.8$) which reached significance in the censored population (HR 0.81, 95% CI 0.69 to 0.94).

A meta-analysis of AIs versus tamoxifen in the adjuvant setting was presented by Dr Ingle at the recent San Antonio Breast Cancer Symposium [17]. The analysis was divided in two cohorts. The first was a direct comparison of mono-therapy strategies and included data from the ATAC and Breast International Group (BIG) 1-98 trials. It included 9,856 patients with 50,000 woman-years of follow-up. At 5 years, AI therapy was associated with an absolute 2.7% (standard error [SE] 0.7%) decrease in BC recurrence (10.7% versus 13.4%, relative decrease 20% [SE 5%], $P = 0.00004$). There appeared to be greater proportional decreases in isolated local recurrence (30% [SE 10%], $P = 0.003$) and in contralateral disease (38% [SE 12%], $P = 0.003$) than in distant recurrence (12% [SE 6%], $P = 0.04$). There was, however, no significant improvement in BC mortality (5.5% versus 6.5%, relative decrease 7% [SE 7%], $P = 0.28$).

Postmenopausal women with hormone receptor-positive early breast cancer currently receiving adjuvant tamoxifen
Sequencing endocrine treatments
The fundamental difference in the design of the following trials is the time point of random assignment. The switch trials randomly assign patients after 2 to 3 years of adjuvant endocrine treatment, whereas the sequencing trials randomly assign patients from the start of treatment. As a consequence, the former (switch) trial design selects a patient population who have not already relapsed and may therefore have a better prognosis and may potentially have tumours that are more endocrine-responsive.

Switching trials
The IES trial
In the Intergroup Exemestane Study (IES) trial, 4,742 patients who had received 2 to 3 years of tamoxifen were randomly assigned to receive exemestane or continue tamoxifen to a

total of 5 years of hormonal therapy. After a median follow-up of 30.6 months, the results favoured exemestane. Of a total of 449 events (local or metastatic recurrence, contralateral BC or death), 183 were in the exemestane group and 266 in the tamoxifen group [18]. The unadjusted HR in the exemestane group was 0.68 (95% CI 0.56 to 0.82, $P<0.001$), representing a 32% reduction in risk and an absolute benefit in terms of DFS of 4.7% compared with tamoxifen 3 years following random assignment. DFS rates 3 years after random assignment (following 2 to 3 years of tamoxifen treatment) were 91.5% in the exemestane group versus 86.8% in the tamoxifen group. There was no significant difference in OS, with 93 deaths in the exemestane group and 106 in the tamoxifen group. A more recent analysis was published, with a median follow-up of 55.7 months [19]. There were 354 events in patients switched to exemestane versus 455 in the tamoxifen group (ITT population, HR 0.76, 95% CI 0.66 to 0.88, $P=0.0001$). In patients with hormone receptor-positive or unknown disease, 339 events were noted in the exemestane group compared with 438 in those continuing tamoxifen (HR 0.75, 95% CI 0.65 to 0.87, $P=0.0001$). These latest IES data estimated absolute differences in 5-year DFS of 3.4% in the ITT population and 3.5% in the hormone receptor-positive and unknown group compared with tamoxifen.

This analysis also showed an improvement in OS in the group treated with exemestane versus tamoxifen. In the ITT population, the result failed to reach conventional levels of statistical significance, with 222 deaths versus 261 deaths in the exemestane and tamoxifen arms, respectively (HR 0.85, 95% CI 0.71 to 1.02, $P=0.08$). Considering the hormone receptor-positive and unknown group, the difference was barely statistically significant, with 210 deaths in the exemestane arm versus 251 with tamoxifen (HR 0.83, 95% CI 0.69 to 1.00, $P=0.05$).

The ARNO 95 trial
Analysis of the Arimidex-Nolvadex (ARNO) 95 trial at a median of 30.1 months, published in 2007, demonstrated estimated DFS rates at 3 years of 93.5% for anastrozole versus 89.3% for tamoxifen, with an absolute difference of 4.2% [20]. An OS benefit was seen in patients who switched to anastrozole versus those who continued to receive tamoxifen (HR 0.53, 95% CI 0.28 to 0.99, $P=0.045$).

Meta-analysis of the ABCSG 8, the ARNO 95 and the ITA trials
In the unplanned switching meta-analysis, including the Austrian Breast & Colorectal Cancer Study Group (ABCSG) 8, ARNO 95 and Italian Tamoxifen Arimidex (ITA) trials, involving 4,006 patients at a median follow-up of 30 months, there were significantly fewer recurrences (92 events [4.6%] versus 159 events [8.0%]) and significantly fewer deaths (66 [3.3%] versus 90 [4.5%]) in the group switched to anastrozole versus those remaining on tamoxifen [21]. A 29% reduction in risk of death in the anastrozole arm (HR 0.71,

95% CI of 0.52 to 0.98, $P=0.04$) versus the tamoxifen arm was seen. The anastrozole arm also demonstrated a 45% improvement in event-free survival (HR 0.55, 95% CI of 0.42 to 0.71, $P<0.0001$) and a 39% improvement in distant recurrence-free survival (HR 0.61, 95% CI of 0.45 to 0.83, $P=0.0015$).

Sequencing trials
The ABSCG Trial 8
The ABSCG Trial 8 explored the tamoxifen-AI sequencing strategy in postmenopausal women with hormone-responsive early BC. The ABSCG Trial 8 compared 5 years of tamoxifen versus 2 years of tamoxifen followed by 3 years of anastrozole [22]. A recent update of this trial at a median of 72 months of follow-up showed that sequencing tamoxifen to anastrozole significantly improved relapse-free survival (RFS) in the ITT population by 21% (HR 0.79, 95% CI 0.65 to 0.95, $P=0.038$). Patients treated with sequential endocrine treatment showed significantly improved OS, with a 23% reduction in the number of deaths (HR 0.77, 95% CI 0.61 to 0.97, $P=0.025$).

The BIG 1-98 trial
Results of the sequencing arms of the trial as described previously were recently presented [15], with a median follow-up of 71 months. Two pairwise comparisons were presented: letrozole versus sequencing 2 years of letrozole followed by 3 years of tamoxifen (Let x2 → Tam x3) or sequencing 2 years of tamoxifen followed by 3 years of letrozole (Tam x2 → Let x3). Although no statistically significant differences in DFS were demonstrated (5-year DFS rates of 87.9% for Let, 87.6% for Let x2 → Tam x3 and 86.2% for Tam x2 → Let x3), subset analysis revealed an increased risk of recurrence in the first 2 years of treatment in the Tam x2 → Let x3 group, especially for the node-positive population. There was no apparent benefit of the letrozole-alone versus the [Let x2 → Tam x3] strategy at this stage of follow-up.

The TEAM trial
The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial was originally designed as a monotherapy comparison of 5 years of exemestane versus tamoxifen. However, the results of the IES trial led to the amendment of the protocol and all patients on tamoxifen switched to examestane. The median time patients on the tamoxifen arm took tamoxifen was 2.75 years. At a median of 2.75 years of follow-up [23], the trial failed to reach its primary endpoint, DFS (HR 0.89, 95% CI 0.77 to 1.03, $P=0.12$), but was associated with improvements in RFS (HR 0.85, 95% CI 0.72 to 1.00, $P=0.05$) and time to distant metastases (HR 0.81, 95% CI 0.67 to 0.98, $P<0.03$).

Meta-analysis of the switch strategy
A meta-analysis reviewed the switch strategy [17] using data from the GABG (German Adjuvant Breast Study Group)/

ARNO, IES/BIG 2-97, ITA and ABCSG 8 trials. The analysis included 9,015 patients with 33,000 woman-years of follow-up. At 6 years from treatment divergence (that is, 8 to 9 years from allocation to endocrine treatment), AI therapy was associated with an absolute 3.5% (SE 1.1%) decrease in BC recurrence (12.6% versus 16.1%, relative decrease 29% [SE 6%], *P*<0.00001). There appeared to be greater proportional reductions in isolated local recurrence (40% [SE 13%], *P*=0.002) and in contralateral disease (35% [SE 16%], *P*=0.03) than in distant recurrence (24% [SE 7%], *P*=0.001). AIs yielded an absolute 1.6% (SE 0.8%) decrease in BC mortality (6.3% versus 8.0%, relative decrease 22% [SE 9%], *P*=0.02). The benefit was irrespective of progesterone receptor (PR) status, age, grade and lymph node status. Furthermore, there was no evidence of increase in overall mortality or non-BC deaths with the use of the AI, causing no concern about safety issues.

Trial comparing 5 years of 'extended' treatment with an aromatase inhibitor versus 5 years of placebo following 5 years of adjuvant treatment with tamoxifen
The MA-17 trial
Due to the early termination of the National Cancer Institute of Canada MA-17 (MA-17) trial, its aims will never be answered. The trial involved 5,187 patients who had already received tamoxifen for 5 years and then were randomly assigned to a further 5 years' therapy with either letrozole or placebo. At a median follow-up of 2.4 years, the independent data and safety monitoring committee recommended termination of the trial as a significant difference in favour of letrozole was seen. The estimated 4-year DFS rates were 93% and 87% for letrozole and placebo, respectively (*P*<0.001) [24]. More recent analysis of the MA-17 trial now indicates a survival benefit for extended adjuvant therapy with letrozole in lymph node-positive patients (HR 0.61, *P*=0.04) [25].

In the MA-17 trial, patients were randomly assigned within 3 months of stopping tamoxifen. The effect of 'delayed' extended adjuvant therapy with letrozole has been evaluated in those women who, after unblinding of the trial, opted for an unplanned switch from placebo to letrozole. Compared with the hormone receptor-positive women who chose not to do so and despite having worse prognostic features, those who switched had significantly improved DFS (HR 0.31, 95% CI 0.18 to 0.55, *P*<0.0001) [26].

Comparison of toxicity of AIs versus tamoxifen in newly diagnosed patients and those patients currently taking tamoxifen switched to an AI
Venous thromboembolic events
Trials of AIs versus tamoxifen show a lower risk of venous thromboembolic events (VTEs) with AIs. The exact mechanism that potentiates thrombotic events is unclear but possibly involves, among other mechanisms, tamoxifen-induced decrease in antithrombin III and protein C levels

[27,28]. Previous trials of tamoxifen versus placebo have shown a significant increase in the risk of VTEs, which may be related to its partial agonist oestrogenic actions. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 trial, the risk ratios for stroke (1.59), pulmonary embolism (3.01) and deep vein thrombosis (DVT) (1.60) were all raised with tamoxifen treatment compared with placebo [29].

After 68 months of follow-up in the ATAC trial, the incidence of any thromboembolic event was lower with anastrozole compared with tamoxifen (2.1% versus 3.5%, *P*=0.0006) and also for VTEs (3% versus 5%, *P*=0.0004) [30]. Similarly, in the BIG 1-98 trial, letrozole was associated with fewer thromboembolic events compared with tamoxifen (1.5% versus 3.5%, *P*<0.001). The switching trials have also shown a reduction in VTEs: The IES trial showed incidences of VTEs of 1.0% for exemestane and 1.9% for tamoxifen (*P*=0.003). The combined analysis of ABCSG 8 and ARNO 95 showed 21 VTEs with tamoxifen and only 5 with anastrozole [31]. In the MA-17 trial, VTEs were rare and not significantly different from the placebo. From the above, it is clear that patients with a previous VTE should receive an AI rather than tamoxifen, irrespectively of recurrence risk.

Gynaecological side effects
The oestrogen agonist activity of tamoxifen on endometrium can be associated with vaginal bleeding and discharge, menstrual irregularities and endometrial changes (hyperplasia, polyps, endometriosis and uterine fibroids), and an increased incidence of endometrial cancer is recognised. In the NSABP P1 prevention study, there was a 2.5-fold increase in endometrial cancer with tamoxifen treatment [29]. Most studies involving AIs in the adjuvant setting report a reduced incidence of vaginal bleeding, with a reduced need for interventions such as hysterectomy (5.1% versus 1.3%) in the 68-month follow-up ATAC data [12] and endometrial biopsy (7.2% versus 1.9%) being reported in the 25.8-month follow-up BIG 1-98 data [14]. Given the absence of agonist activity of the AIs, the incidence of vaginal discharge is usually reported as being less with this class of agents. In the two available AI quality-of-life studies carried out, decreased libido, vaginal dryness and dyspareunia were reported more frequently with anastrozole and exemestane than tamoxifen [32,33].

Hot flashes, either *de novo* or exacerbation of pre-existing symptoms, are a recognised feature of endocrine therapies, reported in up to 46% of patients [34]. They are attributed to the sudden decrease in circulating oestrogen levels, and due to their abrupt onset, they are more bothersome than the symptoms developed during natural menopause. Hot flashes are reported with slightly less frequency in the two studies in newly diagnosed women: 36% for anastrozole versus 41% for tamoxifen after 68 months of follow-up [12] and 34% for letrozole versus 38% for tamoxifen after 25.8 months of follow-up [14]. In studies exploring unplanned switching

strategies, the reported incidence of hot flashes is broadly similar to that of other studies [18,31]. Unsurprisingly, in the MA-17 study of extended adjuvant therapy, use of letrozole led to a higher frequency of hot flashes compared with placebo (47% versus 41%, respectively) [24]. Interestingly, in one study, women who reported hot flashes at baseline were less likely to develop recurrent BC than those who did not report hot flashes (12.9% versus 21%, $P = 0.01$) [35].

Bone mineral density

Trials of AIs versus tamoxifen in postmenopausal women have shown an increased risk of fractures with the use of all AIs [12,14,18]. Comparisons between AIs and tamoxifen are complicated by the fact that the effect of tamoxifen on bone mineral density (BMD) is not neutral but agonistic [36]. Previous trials of tamoxifen compared with placebo in postmenopausal women have shown an increase in BMD from tamoxifen use and a 19% reduction (nonsignificant) in the incidence of fractures [29].

In the ATAC trial at 68 months, the incidences of fractures were 11% with anastrozole versus 7.7% with tamoxifen. The 5-year bone subprotocol of the ATAC trial showed that the loss of BMD from baseline was an average of 6.1% in the lumbar spine and 7.2% in the hip with anastrozole compared with a 2.8% gain in the lumbar spine and 0.7% gain in the hip with tamoxifen ($P < 0.0001$) [37]. However, no patient with normal bone at baseline became osteoporotic after 5 years of treatment; to develop osteoporosis, a woman would need to lose 15% to 20% of normal peak bone mass. In the BIG 1-98 study, fractures were significantly more frequent in the letrozole group than in the tamoxifen group at 25.8 months (5.7% versus 4%, $P < 0.001$) [13].

In the IES trial at 55.7 months of follow-up, rates of osteoporosis (of any grade) were 7.0% with exemestane and 4.9% with tamoxifen ($P = 0.003$) [18]. In the MA-17 trial at 2.4 years, rates of osteoporosis (of any grade) were 5.8% with letrozole and 4.5% with placebo ($P = 0.07$) [24].

Although claims of superiority have been made for particular AIs with respect to bone loss [38], the LEAP (Letrozole, Exemestane, and Anastrozole Pharmacodynamics) trial involving 90 patients at 24 weeks of treatment showed that the steroidal and nonsteroidal AIs appear to have similar effects on bone biochemical measurements and presumably bone turnover. All three licensed AIs result in increases in bone turnover. With the exception of parathyroid hormone (PTH), in which there is a greater decrease in PTH with exemestane than with anastrozole ($P = 0.04$), there were no statistically significant differences between the AIs [39].

At present, it is not clear to what extent the difference in bone density seen between AIs and tamoxifen is due to their direct effect on bone or to the absence of the bone preservation effect of tamoxifen. It is reassuring that the relative incidence of fractures with anastrozole has not increased over time in the ATAC trial and appears to stabilise after 2 years [12,30,40,41]. Recent trials have provided evidence that osteopenia/osteoporosis, either present at the start of therapy with AIs or developing during treatment, can be prevented with the use of bisphosphonates [42-44]. Guidance on the management of bone loss induced by the use of AIs has recently been published (Figure 1).

Arthralgia

AIs have been associated with a broad range of musculo-skeletal adverse events (in addition to the effects on bone health described in the preceding paragraph) that have been loosely categorised under the term of AI-related arthralgias. In the trials of adjuvant AI therapy such as ATAC, IES, BIG 1-98 and MA-17, bone and joint symptoms were categorised in a variety of ways, and estimates for the incidence of musculo-skeletal problems in these trials range from 5% to 36% [45]. However, this may be an underestimate in view of the inconsistency of reporting these symptoms. Crew and colleagues [46] reported a cross-sectional survey of 200 consecutive women receiving adjuvant AI therapy, with a higher prevalence of these symptoms. Ninety-four (47%) reported having AI-related joint pains, and 88 (44%) reported joint stiffness. Patients who had received taxanes were four times more likely to report symptoms. The pathophysiology of AI-related arthralgias is not well understood, but it is thought to be related to oestrogen deprivation. Magnetic resonance imaging (MRI) studies have suggested that tenosynovial changes are seen on MRI with AIs but not with tamoxifen, and these correlate with a significant decrease in hand grip strength [47].
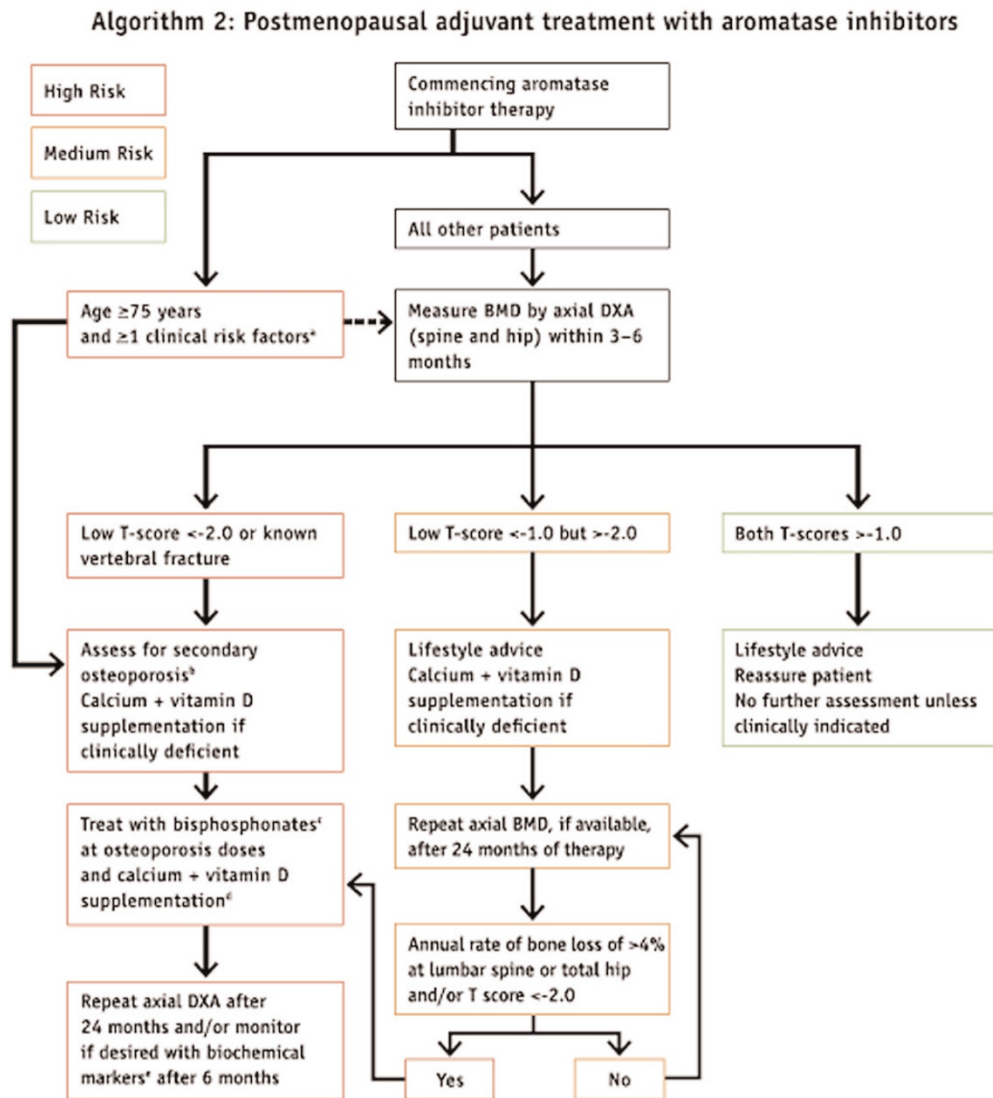
Cardiac side effects

The cardiovascular consequences of tamoxifen remain the subject of much debate. Tamoxifen has been shown to reduce lipid levels [48], coronary plaques and C-reactive protein and modulate nitric oxide production [49]. However, the clinical consequences of these changes are uncertain and trials of tamoxifen versus placebo in the preventive setting have not indicated differences in cardiac events [50].

At 28 months of follow-up, the BIG 1-98 trial reported a significant excess of cardiac (2.1% versus 1.1%, $P = 0.0003$) grade 3 to 5 events for the letrozole-containing arm [51]. However, at a median follow-up of 51 months, no significant differences in cardiovascular events in the two arms of the study were seen [15].

In the ATAC trial, no statistically significant differences in cardiac events were reported. Ischaemic cardiovascular disease occurred in 4.1% of patients receiving anastrozole versus 3.4% in the tamoxifen arm, and deaths due to ischaemic heart disease occurred in 49 and 46 patients, respectively. The ABCSG 8, ARNO 95 and ITA trials have not reported an excess of cardiovascular disease or

Figure 1

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors

Guidelines on the management of postmenopausal women treated with aromatase inhibitors. AST, aspartate aminotransferase; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; ESR, erythrocyte sedimentation rate; FBC, full blood count; GT, glutamine transpeptidase. Adapted with permission from [81].

myocardial infarctions (MIs) with anastrozole compared with tamoxifen [52].

In the most recent update of the IES trial [19], deaths from cardiac events were similar in exemestane and tamoxifen groups (22.1% versus 20.9%, $P = 0.34$). Additionally, there were no statistically significant differences in MIs (1.3 versus 0.8, $P = 0.08$), angina (7.1% versus 6.5%, $P = 0.44$) or

cerebrovascular accidents (2.5% versus 2.4%, $P = 0.89$) observed. In the extended adjuvant setting, letrozole was not associated with more cardiovascular events than placebo at a median follow-up of 2.4 years [24].

At present, it is not clear whether the early concerns with cardiac morbidity in the BIG 1-98 trial are specific to letrozole or are a class effect of AIs. Inconsistency in cardiac event

Table 1

Efficacy results of major aromatase inhibitor trials

Trial	AI versus tamoxifen	Strategy	Follow-up, months	DFS HR	DFS P value	OS HR	OS P value
ATAC	Anastrozole	Up-front	100	0.85	0.003	0.97	0.7
BIG	Letrozole	Up-front	76	0.88	0.03	0.87	0.8
BIG	Letrozole-Tamoxifen	Sequencing	71	0.96	NS		NS
BIG	Tamoxifen-Letrozole	Sequencing	71	1.05	NS		NS
TEAM	Examestane	Up-front	33	0.89	0.12		NS
IES	Examestane	Sequencing	55.7	0.76	0.0001		NS
ARNO	Anastrozole	Sequencing	30	0.66	0.049	0.53	0.045
MA-17	Letrozole	Extended	30	0.58	0.001		NS
ABCSG 6a	Anastrozole	Extended	62	0.62	0.031		NS

ABCSG, Austrian Breast & Colorectal Cancer Study Group; AI, aromatase inhibitor; ARNO, Arimidex-Nolvadex; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG, Breast International Group; DFS, disease-free survival; HR, hazard ratio; IES, Intergroup Exemestane Study; NS, not significant; OS, overall survival; TEAM, Tamoxifen Exemestane Adjuvant Multinational.

reporting in the major AI trials makes cross-trial interpretation difficult. Further follow-up of existing trials is needed, and head-to-head trials of AIs will help to answer these important questions. Current data suggest that AIs are not associated with an excess risk of cardiovascular events.

Quality-of-life evaluations

The first published results from a longitudinal follow-up of the impact of 5 years of adjuvant AI therapy on health-related quality of life (HRQoL) involved anastrozole and showed that the efficacy and tolerability benefits of anastrozole compared with tamoxifen over the full 5-year recommended adjuvant treatment period are not at the expense of HRQoL [53]. The switch from tamoxifen to exemestane did not influence endocrine symptoms present after 2 to 3 years of tamoxifen, nor did the switch lead to significant reports of new symptoms. Results indicate that the clinical benefits of exemestane over tamoxifen are achieved without significant detrimental effect on quality of life [33]. Data from the MA-17 trial indicate no overall adverse effect of letrozole in quality of life but small, though significant, worse outcomes in body pain and vasomotor symptoms [54].

Discussion

Three different third-generation AIs have been compared with tamoxifen (and in the case of letrozole versus placebo in the extended adjuvant setting) in the context of early-stage BC (Table 1). The largest studies have examined the AIs initiated at different disease time points with different patient populations involving different reporting methodologies with respect to efficacy and toxicity. Direct comparison of these AI trials is thereby problematic.

While follow-up of these studies is relatively short compared with the wealth of data on tamoxifen, the studies demonstrate that AIs significantly improve DFS, event-free survival and distant recurrence compared with tamoxifen. More recent data now show an OS benefit in patients switched to anastrozole and exemestane compared with continuation of tamoxifen [18,20,21]. Also, OS has been shown to improve in node-positive patients treated with letrozole in the extended adjuvant trial after 5 years of tamoxifen versus placebo [25].

In speculating what the longer-term benefits of AIs might be, it is important to recognise that a carryover effect of adjuvant therapies is well recognised with differences in RFS and OS increasing beyond the treatment period. For example, the difference in mortality attributable to tamoxifen at 5 years was only 3.6% compared with 9.2% at 15 years, and this for a comparison of active treatment versus none [1]. Similarly, it is interesting to consider an early Swedish trial comparing use of tamoxifen for 2 years versus 5 years [55]. No benefits of the more prolonged treatment were noted before 5 years following random assignment. With the benefit of more prolonged follow-up and the Oxford overviews, 5 years of tamoxifen has, until recently at least, been regarded as the standard of care in early-stage BC. In adjuvant endocrine therapy, prolonged follow-up to truly evaluate long-term benefits is clearly required.

AIs have also demonstrated significant improvements in tolerability compared with tamoxifen. Whilst these benefits should be balanced with the increased risk of fracture and arthralgia posed by AIs, patients considered to be low risk in terms of recurrence could benefit from the altered toxicity profile of AIs compared with tamoxifen. Overall, efficacy benefits have been established without an apparent detrimental effect on quality of life in the anastrozole and exemestane studies [32,33].

The ASCO guidelines and the NICE technology appraisal on the use of AIs concur that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive BC includes an AI, either as initial therapy or after treatment with tamoxifen [8,9]. However, the practical questions remain: *when* to initiate an AI and in *which* patients.

Tamoxifen metabolism

Tamoxifen has relatively low affinity for its target, the ER, but its metabolites 4-OH-tamoxifen and endoxifen (*N*-desmethyl-4-hydroxytamoxifen) are 10 to 100 times more potent. In the liver, tamoxifen is converted to *N*-desmethyl-tamoxifen by CYP3A4/5 and subsequently to endoxifen by CYP2D6. An alternate route of endoxifen production is mediated by CYP2D6, converting tamoxifen to 4-hydroxy-tamoxifen, which is further metabolized to endoxifen via CYP3A4/5. Serum levels of endoxifen are 5 to 10 times higher than that of 4-OH-tamoxifen and 100 times more than that of tamoxifen, and therefore endoxifen is considered the main active metabolite [56-58]. The enzyme CYP2D6 (as well as CYP3A4/5) is a member of the cytochrome P450 system and is involved in the oxidation of a wide range of substrates. Besides being involved in tamoxifen metabolism, it metabolizes codeine to morphine. About 7% of Caucasians carry null alleles, which are homozygous polymorphisms that encode for an inactive allele [59].

Interest in tamoxifen metabolites started with a report by Goetz and colleagues [60] which correlated response to tamoxifen with CYP2D6 polymorphisms. Until now, the evidence has been mixed, with the majority of the studies suggesting that patients with defective tamoxifen metabolism (as a consequence of either genetic polymorphisms or the concomitant use of drugs that inhibit CYP2D6) have an inferior clinical outcome. However, there are also clinical studies indicating the opposite, or no detrimental effect [61]. Another two clinical studies presented in ASCO 2009 reported contradictory results [62,63]. In 2006, the US Food and Drug Administration issued a label warning in the tamoxifen package, and several companies now offer genotyping tests to assess CYP2D6 status. At present, one cannot draw definite conclusions regarding the appropriateness of full-scale genotype testing, although most practitioners would avoid the concomitant use of strong pharmacologic inhibitors of CYP2D6 with tamoxifen and some may even provocatively consider that the small increase in efficacy with the modern AIs over tamoxifen would be lost [64] if poor metabolizers were excluded from the clinical trials.

Biomarkers to guide the use of adjuvant endocrine therapy

Patients with hormone-responsive disease represent a spectrum with differing degrees of clinical benefit derived from adjuvant endocrine treatments. The level of expression of ERs correlates with the degree of response to endocrine therapies [65] but does not differ between tamoxifen and AIs.

Similarly for PRs [66], the benefit correlates with the level of expression. Initially, it was suggested that ER+ PR− tumours gain even more benefit with anastrozole compared with tamoxifen than the rest of the hormone-responsive tumours [67]; however, subsequent studies failed to confirm this [66]. Preclinical studies have suggested that overexpression of human epidermal growth factor receptor 2 (HER2) in hormone receptor-positive tumours is associated with endogenous resistance to tamoxifen [68]. Retrospective clinical data indicate that HER2 overexpression in advanced BC is associated with relative resistance to treatment with tamoxifen [69] and greater benefits from the use of an AI [70]. Similar results have been shown in the neoadjuvant setting [71], but not in the adjuvant setting [66,72]. Finally, the presence of high levels of Ki-67 indicates aggressive disease and can be used as a predictive marker for choosing an AI over tamoxifen in the adjuvant setting [73], with significant benefits in DFS (HR [Let:Tam] 0.53, 95% CI 0.39 to 0.72). Current data indicate that biomarkers may define a group with some resistance to endocrine therapy but do not justify the use of these biomarkers in routine clinical practice in selecting treatment with AIs over tamoxifen.

Newly diagnosed patients

For newly diagnosed patients, those at high risk of early recurrence (including patients with nodal involvement and/or high-grade tumours, PR+ tumours or HER2+ tumours) are more likely to benefit from the introduction of an AI up front. Some patients considered to be low risk in terms of recurrence may also be considered for an up-front AI on the basis of the improved tolerability that AIs offer versus tamoxifen.

Initial reports from the ATAC trial generated the hypothesis of an increased benefit in the PR− tumours [67], but subsequent reports refuted this hypothesis [66]. To date, there are no data to support elective use of an AI in a particular endocrine-responsive subset. High expression of HER2 has been suggested to confer resistance to tamoxifen [74], and there are data from the neoadjuvant setting that letrozole is more effective than tamoxifen in women with HER2+ tumours [75]. However, there are no robust data from the major adjuvant trials to establish this practice. Despite this, women overexpressing HER2 are at higher risk of early relapse and could be candidates for an AI on this basis. Prospectively sequencing newly diagnosed patients to 2 years of tamoxifen, followed by 3 years of an AI, may be appealing with respect to toxicity, with adverse effects of each agent lessened with reduced exposure.

Patients currently on tamoxifen

For these patients, the unplanned switch approach appears appealing if reduction in risk of relapse is considered, and compared with 'up-front' comparisons, this approach appears to be associated with a survival benefit. Patients randomly assigned in these switching studies, however, were those who had not recurred already and probably represent a more

Table 2

Licensed indications of different aromatase inhibitors

Treatment	Newly diagnosed patients	Patients currently treated with tamoxifen
Anastrozole	Primary adjuvant	Unplanned switch following 2 to 3 years of tamoxifen
Exemestane	Not applicable	Unplanned switch following 2 to 3 years of tamoxifen
Letrozole	Primary adjuvant	Unplanned switch following 5 years of tamoxifen (extended adjuvant)

endocrine therapy-sensitive group. For patients who have received 2 to 3 years of tamoxifen, completion of 5 years of endocrine therapy that includes an AI should be considered.

While the optimal duration of endocrine therapy was generally regarded as being about 5 years, the results of the extended adjuvant therapy trial (MA-17) challenge this view. Patients with node-positive disease who have received 5 years of tamoxifen benefit from the introduction of an AI [24]. The optimal duration remains unclear following the early discontinuation of the study as mandated by the trial design. Recent follow-up data of the MA-17 trial suggest that benefits of an AI are seen versus placebo in patients even following its late introduction [26].

The results of trials of extended tamoxifen have been inconsistent. Reports from earlier trials [76,77] indicated that no additional advantage was obtained with extended tamoxifen therapy and actually reported a trend toward inferior survival. Only a smaller trial [78] suggested a possible benefit from increasing the length of adjuvant tamoxifen treatment. Two newer trials are trying the resolve the discrepancy. In the first, ATLAS (adjuvant tamoxifen, longer against shorter), the longer duration of tamoxifen therapy was associated with a 12% relative reduction in the risk for BC recurrence compared with 5 years of treatment alone (HR = 0.88, $P = 0.05$) [79]. In the aTTom (adjuvant Tamoxifen–To offer more?) trial, which again compared 5 versus 10 years of adjuvant tamoxifen, there was a nonstatistically significant trend in favour of the longer treatment [80]. Apart from a doubling of the incidence of endometrial tumours, there were no major safety issues raised. In terms of which AI to use, until head-to-head AI trial data comparing efficacy and tolerability are provided, AIs should be prescribed within their licensed indications as outlined below (Table 2).

Is there a role for tamoxifen alone?
For women at low risk of relapse (ER+, PR+, grade I/II, node-negative), the benefit of AIs in terms of DFS is likely to be small. None of the trials has reported the benefit for low-risk patients in absolute terms. Given the wealth of data in terms of long-term toxicity with tamoxifen, its use may be considered appropriate for such patients. However, even for these patients, AIs may be appropriate if patients have contraindications for tamoxifen (for example, DVT/pulmonary embolism) or may be intolerant to the side effects of tamoxifen (for example, hot flashes and night sweats).

Competing interests
The authors declare that they have no competing interests.

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