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Aromatase Inhibitors in Early Hormone Receptor-Positive Breast Cancer

What is the Optimal Initiation Time for the Maximum Benefit?

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Abstract

Breast cancer is common, affecting one in nine women worldwide. As stipulated by the St Gallen consensus guidelines, hormone therapy is an integral part of treatment for hormone-responsive disease. Previously, this has been with tamoxifen; however, as a result of a number of recent studies, aromatase inhibitors are now competing for use as first-line agents. In addition, there is as yet no firm consensus as to when and how these drugs should be used within the adjuvant setting. This article reviews the use of aromatase inhibitors in early stage hormone-positive breast cancer. It describes the evidence from the studies involving the aromatase inhibitors in an upfront, switch and extended setting. It further discusses the mathematical models proposed to determine the optimum timing of initiation. In light of the ongoing research into predictive biomarkers, this review then concentrates on whether future focus should be on more individualized treatment strategies than the optimum timing of aromatase inhibitors.

Breast cancer is the most common cancer affecting women worldwide. Not surprisingly, it is a heavily researched area attracting both academic and public attention. For several decades, it was recognized that hormone sensitivity opened up a new modality of treatment. In 2005, an International Consensus Panel of experts outlined new guidelines for adjuvant treatment of early breast cancer at the St Gallen consensus conference in Switzerland.[1] These recommendations emphasized the importance of endocrine responsiveness and categorized patients into three subgroups: (i) endocrine responsive; (ii) endocrine response uncertain; and (iii) endocrine nonresponsive. They recommended that patients with endocrine-responsive disease should be offered primary endocrine therapy for 5 years. In addition, those patients who were felt to be high or intermediate risk should also be offered chemotherapy. This depended upon grade, size of tumour, nodal involvement, human epidermal growth factor receptor type 2 (HER2) status and lymphovascular involvement. For all patients in the endocrine uncertain group, a combination of chemotherapy and endocrine therapy should be offered, unless deemed to be very low risk. Finally, the recommendations outlined for the group known to be hormone unresponsive was chemotherapy alone.[1]

Traditionally, the endocrine therapy of choice has been tamoxifen, a competitive estrogen receptor antagonist. However, recent studies have looked at a

new mechanism of hormonal manipulation[1-7] involving the use of aromatase inhibitors, which work by lowering the overall circulating estrogen levels.

At present, aromatase inhibitors are recommended by the UK National Institute for Health and Clinical Excellence in the adjuvant setting as an alternative primary treatment to tamoxifen, in a switch setting and also as extended therapy. Despite extensive research, the optimal use of aromatase inhibitors in early-stage breast cancer is unknown. This article reviews evidence for the use of these compounds as single agents in place of, or in combination with, tamoxifen.[1-7]

1. Tamoxifen

Over 100 years ago, Beatson[8] discovered that performing an oophorectomy in a premenopausal patient resulted in regression of her breast cancer. Since then, estrogen deprivation has become widely used, both in the adjuvant and advanced setting, and even in healthy women at high risk of developing breast cancer, within clinical trials addressing the issue of prevention.

The discovery and use of tamoxifen represented a major breakthrough and it has now been in use for >30 years. Initially thought to be valuable only in the postmenopausal setting, it acts as a selective estrogen receptor antagonist, competitively blocking receptors in breast tissue, both in the pre- and postmenopausal age groups.

The early trials confirmed that 5 years of adjuvant tamoxifen improved disease-free survival (DFS) by an impressive 47% and overall survival by 26%.[9] In 2000, the Early Breast Cancer Trialists' Collabarotive Group reported their 15-year results from a large meta-analysis of all adjuvant trials. Annual recurrence rate was reduced by 41% and the overall survival was improved by 34% in estrogen receptor-positive women, regardless of age. Importantly, the absolute benefit was even greater at 15 years than at 5 years, suggesting a 'carry-over' effect and raising the distinct possibility that 5 years' adjuvant therapy with tamoxifen might sometimes be curative, rather than simply delaying recurrence.[10]

In the US, the National Surgical Adjuvant Breast and Bowel Project (NASBP) B-14 trial randomly allocated 2818 early-stage, node-negative, estrogen receptor-positive postmenopausal women to receive tamoxifen or placebo for 5 years. Following initially encouraging results, they extended the trial to 10 years. Interestingly, this extension provided no obvious additional benefit, with both DFS and overall survival worse for the 10-year group, compared to treatment for just 5 years.[10-12] On the basis of these findings, the recommended time period for tamoxifen in the adjuvant setting has become 5 years. However, these results have not been universally replicated, leaving the field without a clear consensus.[10-12]

We still await the final results from two British-based trials, the ATTOM (Adjuvant Tamoxifen Treatment Offer More) trial and the ATLAS (Adjuvant Tamoxifen Longer And Shorter) trial, investigating extended tamoxifen therapy. The ATLAS study is a large, multicentre, randomized trial, which has now recruited 20 000 women. Half the group will continue with an additional 5 years of tamoxifen totalling 10 years, and the other group will terminate therapy at 5 years and continue with a placebo.[13] The ATTOM trial is a smaller Scottish-based study, again comparing 5 years of tamoxifen to an extended duration of 10 years. This trial is unusual in including patients who declined randomization and, in fact, some 67% of these patients preferred to continue with tamoxifen. Results from both of these trials are awaited with anticipation.[14]

In addition to trial data supporting the role of immediate adjuvant endocrine therapy, an important French study (TAM-02) was carried out by Delozier et al.[15] between 1986 and 1989, which described 'delayed' tamoxifen therapy. The study protocol administered tamoxifen to patients who had received surgery and radiotherapy (± chemotherapy) after a lag time of at least 2 years, compared with placebo. The results supported the role of tamoxifen therapy in a delayed setting. DFS was improved in the whole cohort (83% vs 75%; $p < 0.01$), and overall survival was improved in both estrogen receptor-positive (87% vs 73%; $p < 0.001$) and also

node-positive patients (80% vs 66%; $p < 0.02$). In addition, and most intriguingly, a greater delay period seemed to yield better DFS results. The group receiving tamoxifen after >5 years had a DFS of 87% compared with 80% in the <5-year group. Although this may be a chance finding, as speculated by the authors, it may have further implications with the advent of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17 extended-therapy study and its positive findings.[15]

As well as having an antagonistic effect in breast tissue, tamoxifen has partial agonistic effects in other tissues. It promotes bone mineralisation, reducing the risk of osteoporosis. It also appears to improve lipid profiles, which, in turn, may help ischaemic heart disease. However, one of its major toxicities is its estrogenic effects on the endometrium, with an increase in hyperplasia and polyp formation, and, in turn, a risk of both endometrial cancer and uterine sarcoma. The risk of endometrial cancer is known to be both time and dose dependent. Data from the Early Breast Cancer Trialists Collaborative Group show that the risk of endometrial cancer quadrupled after 5 years of tamoxifen. Although the actual numbers are small, many women will require investigation for gynaecological symptoms.[9,10,16] Tamoxifen also carries a significantly increased risk of thromboembolism, as much as 2- to 3-fold, and includes life-threatening pulmonary embolism and cerebrovascular events.[17]

A major problem with tamoxifen, relevant to the discussion regarding a switch in therapy to an aromatase inhibitor, is the development of resistance. This may have been the explanation for the disappointing NASBP B-14 results with extension of treatment to 10 years. Certainly, some women, despite having an estrogen receptor-positive tumour, have a primary resistance to tamoxifen and gain little or no benefit from the drug. Other experimental models have described secondary resistance, which can then lead to tumour recurrence.[18-20] Different hypotheses have been described for this acquired resistance, including 'estrogen hypersensitivity', in which tumour cells adapt to become more responsive to very low levels of estrogen, and growth factor signalling increases. This may then result in tamoxifen expressing more of its agonistic effect. It is in this setting that aromatase inhibitors may prove most effective, reducing circulating estrogen to an almost immeasurably low level.[20] Howell et al.[21] and Osborne et al.[22] found that ≈20% of tamoxifen-resistant patients responded to aromatase inhibitors.[20]

2. Aromatase Inhibitors

In recent years, the success of tamoxifen has been superseded by the recognition of aromatase inhibitors as a potentially superior form of treatment. These agents block the conversion of androgens to estrogens in peripheral, breast and other tissues by inhibiting the cytochrome P450 enzyme aromatase. This, therefore, lowers both the circulating estrogen level and also local estrogen production in the breast tumour.

Aminogluthimide and formestane, first- and second-generation aromatase inhibitors, respectively, have been restricted by unacceptable toxicities. Aminogluthimide lacks selectivity for the aromatase inhibitor and suppresses cortisol synthesis as well. This could induce Addisonian crises in 'stress' conditions; therefore, administration required corticosteroid and sometimes additional mineralocorticoid supplementation. It was also associated with skin reactions and drowsiness.[23] Formestane has a more tolerable adverse effect profile but is only available in parenteral form.[23] For these reasons, it is the third-generation aromatase inhibitors that have made the greatest impact, namely anastrozole, exemestane and letrozole.

Anastrozole was used as initial therapy for patients with advanced disease in Europe and North America compared with tamoxifen, in two large studies.[24-26] Anastrozole significantly improved time to progression in hormone receptor-positive patients and overall was at least as effective as tamoxifen, without the added risks of endometrial cancer and thromboembolism.

The ATAC (Arimidex, Tamoxifen Alone or in Combination) trial investigated the role of aromatase inhibitors in the adjuvant setting. To date, it

is the largest international, multicentre, endocrine therapy trial performed, accruing 9366 women during the 4-year period between 1996 and 2000, comparing anastrozole, tamoxifen and the combination in postmenopausal women with early-stage estrogen receptor-positive (or unknown) breast cancer. The first analysis (33-month exposure to trial drug) showed improved DFS with anastrozole compared with tamoxifen (89.4% vs 87.4%; p = 0.013), with a relative risk reduction of 17%. There was a 19% (p = 0.0006) improvement with anastrozole compared with the combination group, but no significant difference with tamoxifen compared with the combination. When the patients were censored at the time of death, the time to recurrence was also significantly improved in the anastrozole alone arm by 21% (p = 0.0008) compared with tamoxifen and 25% (p = 0.0007) compared with the combination arm. Again, no significant difference was noted between the tamoxifen group and the combination. The difference in recurrence rates between the tamoxifen and the anastrozole group only convincingly emerged by the second and third year, a reflection of the good overall prognosis of this large cohort of patients.[27] In the anastrozole group, there was also a remarkable reduction in primary contralateral breast cancers as a first event, with an odds reduction of 58% (p = 0.007) [figure 1].[27]

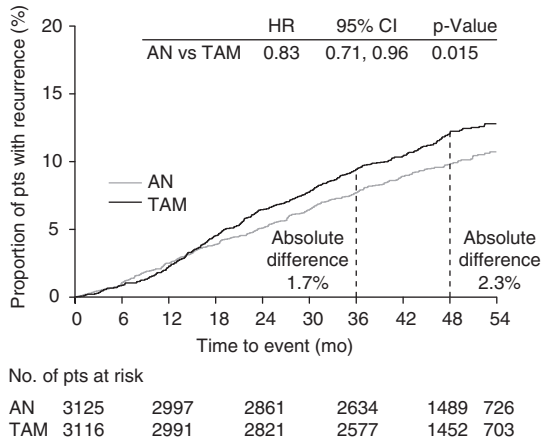


Fig. 1. The probability of recurrence of breast cancer in the overall population. Non-breast cancer deaths were censored before recurrence. Results from the ATAC (Arimidex, Tamoxifen Alone or in Combination) study. Censoring non-breast cancer deaths before recurrence (reprinted from the Lancet, Vol. 359, Baum et al.,[27] ATAC Trialists' Group Anastrozole alone or in combination with tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial, pages 2131-9, Copyright 2002, with permission from Elsevier. Available from URL: http://www.sciencedirect.com/science/journal/01406736). **AN** = anastrozole; **HR** = hazard ratio; **pts** = patients; **TAM** = tamoxifen.

Aromatase inhibitors have their own adverse effect profile, the most significant being osteoporosis. A comparison of the adverse effect profiles in the ATAC study confirmed that the anastrozole group had a lower rate of hot flushes, vaginal bleeding, thromboembolic events and endometrial cancer. Endometrial cancer developed in 0.2% versus 0.8% of the anastrozole and tamoxifen groups, respectively, (p = 0.02). In contrast, there were fewer fractures and musculoskeletal disorders, such as joint pain or arthralgia, in the tamoxifen group (7.7% vs 11% fractures [p < 0.0001]). The increased fracture incidence was predominantly due to spinal fractures, with no increase in hip fracture. An important finding was that fewer women withdrew from the anastrozole arm than the tamoxifen arm, 11.1% compared with 14.3% (p = 0.0002), as a result of drug-related adverse events. Equal numbers of life-threatening or serious events were noted in the two monotherapy groups.[27]

In a 2005 update,[28] anastrozole maintained its clear superiority over tamoxifen for both DFS and time to recurrence, 13% (p = 0.01) and 21% (p = 0.0005), respectively. There was a 42% (95% CI 12, 62; p = 0.01) reduction in the incidence of new contralateral breast cancers in the anastrozole group compared with the tamoxifen group. Time to distant recurrence was also prolonged in the anastrozole group, with a relative reduction of 14% (p = 0.04). Again, there were more adverse events noted in the tamoxifen group, leading to more patients discontinuing treatment. In summary, the results supported 'upfront' anastrozole in place of tamoxifen, although an increase in overall survival has not yet been demonstrated despite a trend in favour of anastrozole for cause-specific mortality.[28-30]

Anastrozole became licensed in the UK in June 2005 as primary adjuvant treatment for receptor-positive disease in postmenopausal women.

The Breast International Group (BIG) 1-98 is a large, double-blind, phase III, randomized trial comparing the efficacy of letrozole with tamoxifen in the adjuvant setting. This is a slightly unusual study in that it compares both single agents for 5 years upfront and also different variations of switches. There are four arms, as follows: (i) letrozole for 5 years; (ii) tamoxifen for 5 years; (iii) letrozole for 2 years followed by tamoxifen for 3 years; and (iv) tamoxifen for 2 years followed by letrozole for 3 years. 8010 postmenopausal women were recruited with positive estrogen or progesterone (or both) receptor status between March 1998 and May 2003. The primary analysis compared the two groups initially receiving letrozole and the two initially receiving tamoxifen.[31]

The results supported the case for adjuvant letrozole in place of tamoxifen. At a median follow-up of 25.8 months, there were 351 events in the letrozole group and 428 in the tamoxifen group. At 5 years, estimated DFSs were 84.0% and 81.4% for letrozole and tamoxifen, respectively. Distant recurrence was also reduced by 27% in the letrozole group ($p = 0.001$ vs baseline). Planned subgroup analyses of DFS showed letrozole as more effective with patients who had prior chemotherapy, did not receive radiotherapy and had positive lymph nodes. This suggests that letrozole was possibly more effective in patients with more advanced or aggressive disease, although the data were not statistically significant and many would question the wisdom of subgroup analysis (figure 2).[31]

Interestingly, there was no difference between the two agents in node-negative disease. Despite fewer deaths in the letrozole group, overall survival was not significantly different between the two groups. With respect to adverse events, there was no difference in serious or life-threatening events, but an increase was noted in reportable events in the letrozole arm. As expected, there were more fractures, 1.7% in the letrozole arm ($p < 0.001$) and approximately twice the number of thromboembolic events, vaginal bleeding and invasive endometrial cancers in the tamoxifen group. Not noted in the ATAC trial, there was a significant increase in hypercholesterolaemia, and adverse cardiovascular and cerebrovascular events, in the letrozole arm. Some interpret this data as tamoxifen having a possible cardio-protective role. These potential risks may not necessarily be associated with all aromatase

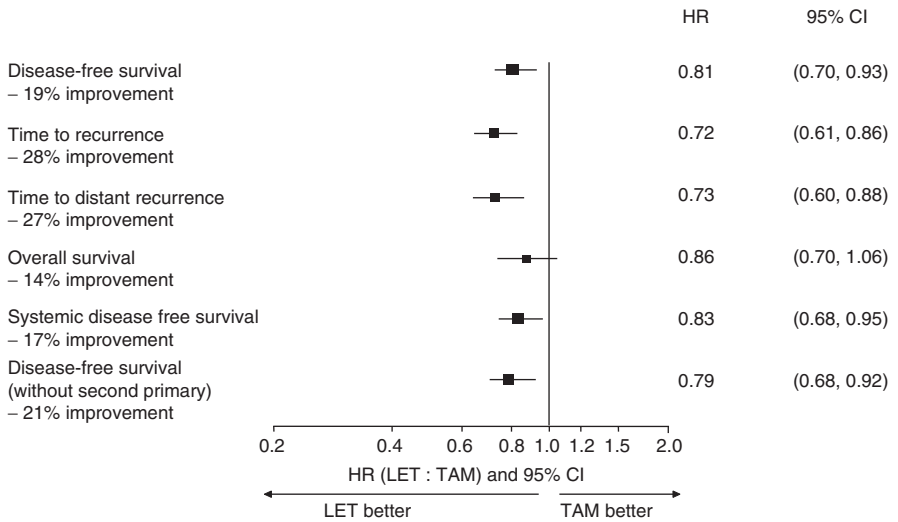


Fig. 2. Efficacy analysis from the Breast International Group (BIG) 1-98 trial.[31] **HR** = hazard ratio; **LET** = letrozole; **TAM** = tamoxifen.

inhibitors, as the adverse effect profile of anastrozole appears somewhat different.[31]

The trial is still ongoing and, as yet, there are no data on the efficacy of the switch regimens. However, based on this trial, letrozole was licensed for upfront adjuvant therapy in postmenopausal women with early-stage breast cancer by the US FDA in 2005.

Exemestane, a third-generation steroidal aromatase inhibitor, is also being compared with tamoxifen as initial therapy for 5 years. The TEAM (Tamoxifen and Exemestane Adjuvant Multicentre) trial has now closed recruitment, having accrued 4400 postmenopausal women. This trial was planned on the background of the promising results of the IES (Intergroup Exemestane Study), which is discussed in section 3.

3. Switching

Bearing in mind the large number of women currently receiving tamoxifen and the high cost of recently introduced aromatase inhibitors, several large study groups have now addressed the issue of a possible switch partway through the 5-year adjuvant tamoxifen programme. The ATAC trial proved that a combination of tamoxifen and an aromatase inhibitor was not advantageous. Each drug has its own risks and benefits. With the knowledge of tamoxifen resistance and confirmation that endometrial cancer and other risks increase with time and dose, many groups have now investigated the idea of switching drug treatment after a designated period of time.

The ITA (Italian Tamoxifen Anastrozole) trial by Boccardo et al.[32] was a phase III, randomized, multicentre trial to evaluate the efficacy of switching to anastrozole after 2–3 years of tamoxifen. 448 patients with node-positive, estrogen receptor-positive breast cancer were enrolled between March 1998 and December 2002. Patients were randomly assigned to either continue taking tamoxifen or switch to anastrozole after 2–3 years. All patients were scheduled to complete 5 years of adjuvant hormone therapy. At a median follow-up of 36 months after the switch, the results were encouraging for the anastrozole group, with 45 events reported in the tamoxifen group and 17 in the anastrozole group ($p = 0.0002$). Disease-free and local recurrence-free survival were also improved in the anastrozole arm, with a hazard ratio (HR) of 0.35 and 0.15, respectively, both statistically significant. Although there were more adverse events recorded in the anastrozole group (203 vs 150), those in the tamoxifen group were of a more serious nature and more of the events required hospitalisation. Interestingly, there was no statistically significant difference in the number of musculoskeletal disorders or fractures.[32]

One of the main problems with this trial was its size. The initial intention was to have twice the number of patients, but because of other trials at the time, there was difficulty with recruitment. Nonetheless, unlike several other studies, this group was universally node-positive, i.e. the patients were at far higher risk of recurrence. The generation of statistical recurrence events is high and the study 'punches above its weight'. Despite this shortcoming, the authors claim to have reached a statistical power of 81%. The results are extremely encouraging and statistically significant.[32]

In a larger study published in 2005,[33] the ABCSG8/ARNO-95 (Austrian Breast Cancer Study Group trial 8 and Arimidex – Nolvadex) group have also published supportive findings. Both were multicentre, randomized, open-label trials that recruited 3224 postmenopausal receptor-positive women to either continue with tamoxifen or switch to anastrozole after 2 years of tamoxifen. Both were well constructed, with slightly different inclusion and exclusion criteria. Both had a definite switch time period, namely 2 years after tamoxifen. At a median follow-up of 28 months, a statistically significant 40% decrease was noted in the number of events in the anastrozole group compared with tamoxifen ($p = 0.0009$). The absolute benefit at 3 years for event-free survival was 3.1%. Most impressively, there was also a 39% improvement in the number of distant metastases in the anastrozole group. However, the overall survival at 3 years was not significantly different and showed a 1% improvement in the anastrozole group. Both treatments were well

tolerated, incurring the expected increase in fractures in the anastrozole group, and thromboses and endometrial cancer in the tamoxifen group (figure 3).[33,34]

Both trials claimed that most of the women enrolled had a good prognosis. Approximately 75% were node negative and, thus, they interpreted the small absolute benefits as surprising and relevant.[33,34]

Results from these three trials,[32-34] taken together, were sufficient to initiate the Medicines Healthcare Products Regulatory Agency to licence anastrozole for the use after 2–3 years of tamoxifen in the UK.

The lack of supportive overall survival data encouraged Jonat and colleagues[35] to carry out a recently published meta-analysis of these three trials. In all these trials, patients initially received 2–3 years of tamoxifen and then were randomly allocated to either continue or switch to anastrozole. The ABSCG8 trial[33] differed from the other two in that patients were randomized at diagnosis rather than after completing the initial tamoxifen period. Patient characteristics differed slightly between trials; the ITA[32] patient population were mostly node positive in comparison with a majority node negative in the other two. In addition, the ITA patients were treated more aggressively with mastectomies and chemotherapy. However, the authors justify the irrelevance of these differences on the basis that the analysis used individual patient data.[35]

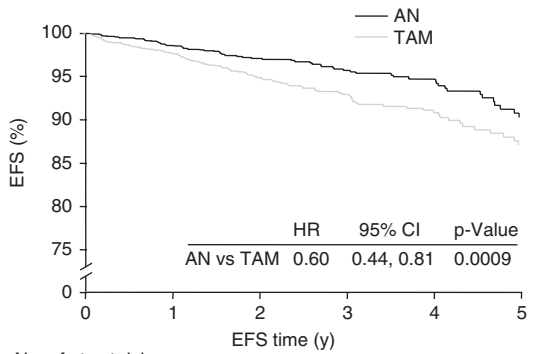


Fig. 3. Combined event-free survival (EFS) results from the ABCSG8)/ARNO-95 (Austrian Breast Cancer Study Group trial 8 and Arimidex – Nolvadex) trials. Zero point is 2 years after surgery.[33] **AN** = anastrozole; **HR** = hazard ratio; **pts** = patients; **TAM** = tamoxifen.

A total of 4006 patients were included: 2579 from ABSCG 8, 979 from ARNO 95 and 448 from the ITA. The collated results reported fewer recurrences (92 [5%] vs 159 [8%]) and deaths (66 [3%] vs 90 [5%]) in those who were switched to anastrozole. This correlated to an HR of 0.59 (95% CI 0.48, 0.74; $p < 0.0001$). There were also statistically significant improvements in event-free survival (HR 0.55, 95% CI 0.42, 0.71; $p < 0.0001$) and distant recurrence-free survival (HR 0.61, 95% CI 0.45, 0.83; $p = 0.0015$). But, the most exciting result was an improvement in overall survival with an HR of 0.71 (95% CI 0.52, 0.98; $p = 0.0377$).[35]

Clearly, the results are encouraging and unique, particularly the reported overall survival benefit. However, this does not deflect from the need for overall survival advantage from well constructed individual prospective switch trials.[35]

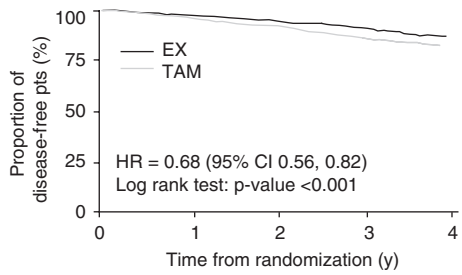
The IES was a multicentre, international, phase III, double-blind trial comparing 5 years of tamoxifen therapy with switching to exemestane after 2–3 years of tamoxifen. 4742 postmenopausal receptor-positive patients were recruited and after a median follow-up of 30.6 months, DFS was improved in the exemestane group by 4.7%, with 266 first events in the tamoxifen group compared with 183 for exemestane. This resulted in an unadjusted HR of 0.68 ($p = 0.00005$). Both recurrence (or a new primary) in the contralateral breast and distant sites were also reduced in the exemestane group. However, as with many of the trials, overall survival at this first analysis was not significantly different. The main adverse events reported in the exemestane group were musculoskeletal and diarrhoea, with an increased fracture rate and osteoporosis, although the difference was not statistically significant. Again, although very low, there were over twice as many myocardial infarctions in the exemestane group, 1% versus 0.4%. As expected, the predictable

gynaecological and thromboembolic events were increased in the tamoxifen group (figure 4).[36]

Interestingly, there appeared to be a higher withdrawal rate amongst the exemestane group. 138 patients discontinued the drug as a result of adverse events and a further 164 patients refused to continue therapy, compared with 121 and 116 patients, respectively, in the tamoxifen group. No detailed reasons were given for these withdrawals from treatment.[36]

In addition, there was an unusual eligibility policy, accepting women who had received different doses of tamoxifen. Some had received a nonconventional higher dose of 30 mg once a day, whereas others had received the conventional 20 mg dose. It is unclear as to whether this would have any impact on the findings; however, it would clearly have been a cleaner trial if all the patients included had been treated similarly.[36]

The obvious uncertainty, as with much of the data on aromatase inhibitors, is the lack of data on overall survival, together with the long-term risks. At the recent 58-month follow-up, DFS was improved by 24% in all the patients in the exemestane arm (p = 0.0001) and 25% in the estrogen receptor-positive group (p = 0.0001). Time to distant recurrence and development of a contralateral primary were improved in the exemestane arm. Overall survival was also reported to be improved, with an HR of 0.85 (95% CI 0.71, 1.02; p = 0.08) in all patients and 0.83 (95% CI 0.69, 1.00; p = 0.04) in estrogen receptor-positive patients. However, with closer analysis, this is of doubtful statistical significance, considering both the p-value and the upper limit of the confidence interval. The adverse effect profile was much the same, with a greater incidence of fractures but fewer thromboembolic and gynaecological events in the exemestane arm. We await further detailed long term assessment results.[37]



No. of events/pts at risk

EX	0/2362	52/2168	60/1696	44/757	20+6*/201
TAM	0/2380	78/2173	90/1682	76/730	18+4*/185

Fig. 4. Disease-free survival results from the Intergroup Exemestane Study (IES) [reproduced from Coombes et al.,[37] with permissions]. Copyright © [2004] Massachusetts Medical Society. All rights reserved. **EX** = exemestane; **HR** = hazard ratio; **pts** = patients; **TAM** = tamoxifen. * indicates events occurring >4 years after randomization.

4. Extended therapy

The Canadian-based MA.17 study was of a very different design. This investigated whether there is a possible advantage of following 5 years of tamoxifen therapy with a further 5 years of an aromatase inhibitor, namely letrozole. This phase III, double-blind, placebo-controlled trial recruited 5147 postmenopausal women between August 1998 and September 2002. At the first interim analysis, with a rather short median follow-up of 2.4 years, 207 events had occurred, 75 in the letrozole group and 132 in the placebo. This gave the letrozole group an estimated 4-year DFS rate of 93% compared with 87% for placebo (p < 0.001). The letrozole group exceeded the placebo group by 2% for the 'estimated' 4-year overall survival rate, although this was not statistically significant. With unplanned subgroup analysis, the HR for recurrence or development of a new contralateral primary cancer in the node-negative compared with the node-positive group was 0.47 (p = 0.005) and 0.60 (p = 0.003), respectively.[38]

None of the tolerance data reached statistical significance. However, as expected, new diagnoses of osteoporosis were diagnosed in 1.5% of the letrozole group and fractures in 0.7%.[38]

In a somewhat contentious decision that was later criticized, the study was unblinded after the first analysis because of the apparently dramatic results. This posed the serious problem that of a lack of robust long-term data for the optimum duration of treatment, treatment-related toxicities and, of course, overall survival. Furthermore, it is probable that a survival advantage will never be documented.

The ongoing follow-up will be confounded by crossover, as all the patients receiving placebo were then invited to switch to letrozole. In addition, there is not enough evidence to advise on duration of extended letrozole treatment. The median follow-up was 30 months and just 1% of patients had reached 4 years' duration of therapy.[38-44]

Despite this, MA.17 is clearly a seminal study that has both influenced clinical practice and added to the controversy, introducing the idea of sequencing rather than switching.

Ingle et al.[45] presented the intention-to-treat analysis at the American Society of Clinical Oncology (ASCO) meeting in 2006. Of the original 2268 patients receiving placebo, 1655 swapped to letrozole after the study was unblinded. At a median follow-up of 54 months, 363 recurrences had occurred, 144 in the letrozole group and 219 in the placebo. 118 compared with 176 patients had recurrent disease in the letrozole group and placebo group, respectively, and 26 compared with 43 had contralateral breast cancer. There was a 4-year DFS of 94.3% for the letrozole group and 91.4% for placebo (HR 0.64, 95% CI 0.52, 0.79; p = 0.00002). There was no statistical significant improvement in overall survival. They concluded that despite the crossover after the trial was unblinded, those patients who received letrozole from the start did better than the placebo group, so once again the data strongly supported extended therapy with letrozole.[45]

Other trials are underway, directly comparing different aromatase inhibitors with each other. The NCIC CTG MA.27 trial is a large, multicentre, phase III trial comparing exemestane with anastrozole 'upfront' and the Femara versus Anastrozole Clinical Evaluation (FACE) trial is a similar trial comparing letrozole with anastrozole. This may eventually help to guide clinicians as to which agent to use, and which might be better on a patient-specific basis according to the adverse effect profiles and the individual risk. Table I provides a summary of the results of the major trials discussed in this review.

5. Cost

Well established, generically produced agents, such as tamoxifen, are always vastly less expensive to prescribe than newer agents, for which the drug development costs can only be offset by drug sales during the limited period of patent. Tamoxifen carries an annual cost of approximately £38 and a 5-year cost of £190, which is only one-fifth of the cost of a years' worth of anastrozole (2006 values). Anastrozole carries an annual cost of £891, and exemestane and letrozole are slightly more expensive at a price of £1081 (2006 values). This does not include bone density scanning, bisphosphonates and calcium supplements that are additional costs incurred with aromatase inhibitors, although not all would insist that annual bone density assessment, for example, is necessary.[46,47]

Nevertheless, a full economic evaluation needs to consider the costs saved in investigation and treatment of the increased recurrences and gynaecological adverse effects with 5 years of tamoxifen treatment. Such assessments have been attempted

Table I. A summary of results from the major trials of aromatase inhibitors in breast cancer

Trial name	Median follow-up (mo)	Disease-free survival: HR (95% CI) [p-value]	Distant recurrence: HR (95% CI) [p-value]	Overall survival: HR (95% CI) [p-value]
ATAC	68	0.87 (0.78, 0.97) [0.01]	0.86 (0.74, 0.99) [0.04]	0.97 (0.85, 1.12) [0.7]
BIG 1-98	51	0.82 (0.71, 0.95) [0.007]	0.81 (0.67, 0.98) [0.03]	0.91 (0.75, 1.11) [0.35]
IES	55.7	0.76 (0.66, 0.88) [0.0001]	0.83 (0.70, 0.98) [0.03]	0.85 (0.71, 1.02) [0.08]
ITA	64	0.42 (0.26, 0.66) [0.0001]	0.57 (0.32, 1.02) [0.06]	0.56 (0.28, 1.15) [0.1]
ABCSG8-ARNO	28	0.60 (0.44, 0.81) [0.0009]	0.61 (0.42, 0.87) [0.0067]	Not reported
MA.17	30	0.58 (0.45, 0.76) [<0.001]	0.60 (0.43, 0.84) [0.002]	0.82 (0.57, 1.19) [0.3]

ABCSG8/ARNO = Austrian Breast Cancer Study Group trial 8 and Arimidex – Nolvadex; **ATAC** = Arimidex, Tamoxifen Alone or in Combination; **BIG 1-98** = Breast International Group 1-98; **HR** = hazard ratio; **IES** = Intergroup Exemestane Study; **ITA** = Italian Tamoxifen Anastrozole; **MA.17** = National Cancer Institute of Canada Clinical Trials Group study MA.17.

both for European and North American scenarios.[48,49]

6. Discussion and Conclusion

Despite the overwhelming trial data on activity and tolerance, it is not yet possible to define when and for how long aromatase inhibitors should be initiated. There remains a degree of uncertainty regarding the role of aromatase inhibitors in the upfront, 'switch' and extended-therapy settings. In addition, we still need to clarify which group of patients should receive adjuvant therapy beyond 5 years. The eagerly awaited ATTOM and ATLAS trials may well shed some light on this.

It is difficult to ignore the impressive DFS results that are so consistently observed throughout all the trials involving the adjuvant use of aromatase inhibitors. The ATAC trial is probably the most robust of all those described, with the greatest maturity and largest enrolment, and lends itself to the argument for upfront anastrozole. Certainly, there appeared to be less 'reported' cardiotoxicity than for the other two aromatase inhibitors, although these differences may eventually prove to be no more than a result of ascertainment bias. The final analysis of the BIG 1-98 trial will help us consider the need for switching, as this compared monotherapy with two alternative switches.

After 5 years of hormone therapy, there remains a 1.5–2% annual risk of recurrence during the 5- to 15-year period after diagnosis and treatment. Historically, with the knowledge that the risk of endometrial cancer is both dose and time dependent, and the knowledge of acquired tamoxifen resistance, we have capped treatment at 5 years. Most of the current trial data would support this view. Aromatase inhibitors are clearly efficacious, but also have potential long-term adverse effects. The optimal treatment regimen should attempt to gain the maximum benefit from both, without incurring the associated risks of extending each alone. Tamoxifen first, followed by an aromatase inhibitor, may be sensible to strengthen bones prior to the osteoporotic effects of the aromatase inhibitors. Unfortunately, despite initial promising results from the MA.17 study, we have no long-term data because it was unblinded so early. There is clearly a real need for further extended-therapy trials, with different variations of sequencing.

It is important to assess (and stress) the safety profiles of these drug regimens and these considerations must be integral to treatment decisions. We must not lose sight of the fact that the group of patients in question are often women with good prognosis disease. As clinicians, the aim should always be to balance the therapeutic index: maximal benefit with minimal risk.

Adverse effects of tamoxifen include a number of life-threatening conditions including pulmonary embolism, stroke and endometrial neoplasia (both carcinoma and rarely sarcomatous change). On the whole, aromatase inhibitors carry a less hazardous toxicity profile. The risk of osteoporosis can be monitored with regular dual energy x-ray absorptiometry scans, with preventative treatment where necessary using bisphosphonates and calcium supplements. The adverse events data appeared more robust in the ATAC trial, by comparison with the MA.17 and IES studies. Both the latter trials cast an uncomfortable shadow regarding cardiotoxicity for unknown reasons, resulting in a moderately 'increased' withdrawal rate compared with tamoxifen.[36] However, it is important to consider that tamoxifen at a similar stage in early studies was thought to be have a relatively innocuous adverse event profile. We have little data on the long-term toxicities of aromatase inhibitors, although the most recent report from the ATAC group (toxicity analysis of the mature post-treatment data) was undoubtedly reassuring.[50]

In addition, although the aromatase inhibitors have been shown to improve DFS, this has not yet been the case regarding overall survival. The IES trial has claimed an improvement in overall survival, although with closer analysis of the data, the upper limit of the HR raised a question over the statistical significance.[38] There is also the supportive recent meta-analysis by Jonat et al.[35] regarding switching to anastrozole, which was statistically significant. On the other hand, all confirmed major

studies in the past have shown an eventual advantage in terms of overall survival, following an earlier convincing demonstration of improvement in DFS.

Following the maturation of the results of these different studies, there have been several statistical models proposed to resolve the optimum timing for aromatase inhibitor initiation.

Punglia et al.[51] in 2005, proposed a Markov mathematical model based on DFS and recurrence rates. They used data from the three different settings, namely: (i) the 'upfront' from both the ATAC study and the Early Breast Cancer Trialists' Collaborative Group; (ii) the 'switch' from the IES trial, introducing an aromatase inhibitor after 2–3 years of tamoxifen; and (iii) the 'extended' setting from the MA.17 trial, initiating an aromatase inhibitor after 5 years of tamoxifen.

They found that the switch scenario was the most beneficial, securing an approximate 6% reduction in 10-year recurrence rate over the aromatase inhibitors in the upfront setting. They described an increased DFS from 82.6% to 83.7% in the node-negative patients and from 65.5% to 67.6% in the node-positive patients. The extended setting did not add further advantages.[51]

They also carried out sensitivity analyses to quantify the carry over effect of aromatase inhibitors in all three settings. Again, the switch setting was found to be the superior scenario.[51]

However, the model was heavily criticized, namely by Buzdar and Cuzick.[52] They argued the validity of using different endpoints, both DFS and recurrence rates, and the importance of the model predating the final results of many of the trials, including the ATAC study.[52] The authors themselves highlight that their calculations do not include the ABCSG8/ARNO-95 and the BIG 1-98 studies. However, on further calculation, they found these results added strength to their hypothesis that initiating aromatase inhibitors in the switch setting is optimum.

The authors also emphasize the assumptions made in calculating the model and that they may not hold true with more long-term results. They assumed that the different aromatase inhibitors yield similar benefits and did not take into account the different adverse effect profiles, patient preferences or contraindications. In addition, they did not investigate the subgroup differences between estrogen- and progesterone-receptor positivity.

They propose that those patients in the switch setting may gain the maximum benefit from aromatase inhibitors because they are clearly hormone sensitive. They have had planned switches rather than those that are switched as a result of a relapse.[51]

Following this, Buzdar and Cuzick[52] presented an alternative statistical model in 2006 that recommended initiating an aromatase inhibitor 'upfront' as the superior option rather than switching to an aromatase inhibitor after ≥2 years of tamoxifen.

Initially, HRs for recurrence for each treatment in an 'upfront setting' were derived from published data including ATAC and the Early Breast Cancer Trialists' Collaborative Group overview.[10] The data was then extrapolated to the 10-year follow-up point and compared head to head. The results clearly depicted anastrozole's superiority. Time to recurrence rates in hormone-sensitive disease were markedly reduced in the anastrozole group. In addition, the absolute difference between tamoxifen and anastrozole results increased with time and beyond treatment cessation; 1.7% at 2 years and 3.7% at 6 years. The two curves start together but by the second year start to diverge and continue to do so.[52]

The authors then analyzed the HRs from the 'upfront' trials ATAC, BIG 1-98 and the extended-therapy MA.17 trial, and the 'switch' trials ABCSG8/ARNO-95 and IES, and converted them to percentages of time lost to recurrence. For the switch trials, the point of analysis was the introduction of the aromatase inhibitor. The data was for known estrogen receptor-positive disease. At 10 years follow-up, there was a 12.1% of years lost with 5 years of tamoxifen and 10.9% of years lost with 5 years of tamoxifen followed by 5 years of aromatase inhibitor. Further benefit was accrued with 2 years of tamoxifen then 3 years of aromatase inhibitor with 9.6% of years lost. However, an aromatase inhibitor for 5 years upfront gives the best

result with 9.0% of years lost to recurrence. Furthermore, this advantage was illustrated at all timepoints up to the 10 years. Therefore, based on this statistical model, the authors concluded that the optimum timing for initiation of aromatase inhibitors is as primary adjuvant treatment.[52]

For similar reasons, this model can also be criticized. There is no head-to-head comparison of all the three settings with the same agent. In addition, this model was calculated prior to the final analysis of the IES and ABCSG8/ARNO-95 studies. As illustrated in section 3, the IES is the only trial to claim a statistically significant overall survival benefit. With the support of the recent meta-analysis from the ABCSG8/ARNO-95 trials, it could be reargued that introducing aromatase inhibitors in a switch setting is more beneficial.

The upfront argument gains further support from the compelling descriptions of the smoothed HR plots from the ATAC study as described by Howell.[53] He comments that the HR for tamoxifen increases at a steeper rate and peaks sharply in the first 2 years in comparison with anastrazole.[53] Others have argued the role of switching at this peak. This would combine both the cost effectiveness and prevention of long-term adverse effects associated with tamoxifen without compromising overall survival (figure 5).[53]

Most importantly, one cannot ignore that these conclusions are based on mathematical models rather than robust first-hand collected data. It is difficult to compare data from different trials using different agents and different trial protocols. Statistical models are important and have a role in estimating outcomes or effects, as well as supporting evidence; however, care should be taken in relying on them to change clinical practice.

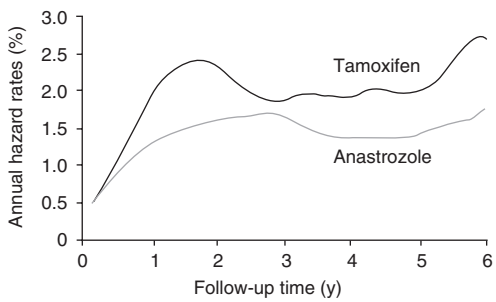


Fig. 5. Smooth hazard rates (hazard ratio plots) for recurrence of breast cancer for anastrozole vs tamoxifen. Results from the ATAC (Arimedix, Tamoxifen Alone or in Combination trial) [reprinted from the Lancet, Vol. 365, Howell,[53] ATAC trial update, 1225, Copyright 2005, with permission from Elsevier. Available from URL: http://www.sciencedirect.com/science/journal/01406736].

A further area of controversy surrounding the initiation of aromatase inhibitors is predicting which subgroups of patients are tamoxifen resistant yet aromatase inhibitor sensitive. Many studies have been designed to tease out combinations of predictive markers.

Both the ATAC trial and the IES study found that estrogen receptor-positive/progesterone receptor-negative patients responded preferentially to upfront aromatase inhibitors. Furthermore, this subgroup did not respond so favourably in the switch setting. In the ATAC trial, patients with estrogen receptor-positive/progesterone receptor-negative disease had an HR of 0.48 with anastrozole compared with tamoxifen upfront, indicating twice the number of relapses with adjuvant tamoxifen. However, the BIG 1-98 trial refuted this association.

On the back of these clinical studies, Tovey et al.[54] analysed tissue from 402 estrogen receptor-positive tamoxifen-treated patients and found supportive evidence for a predictable estrogen receptor-positive/progesterone receptor-negative resistance to tamoxifen ($p = 0.017$). Again, this was not the case after 3 years of tamoxifen in the switch setting and, therefore, they supported the conclusion that this subgroup of patients would benefit from initiating aromatase inhibitors upfront.

Additional support can be gained from the studies by Arpino et al.[55] They found that estrogen receptor-positive/progesterone receptor-negative patients had more aggressive disease, were more likely to be HER1 and HER2 positive, and thus displayed increased relapse rates.

Further predictive experimental work has been reported by Dowsett et al.[56] Tissue was taken from 813 tamoxifen-treated patients and the primary endpoint was relapse-free survival. Unsurprisingly, the estrogen receptor-positive patients benefited with a

relative risk of 0.77 (95% CI 0.63, 0.93). However, they contested the differential progesterone receptor-negative importance. The response to tamoxifen was not influenced by the progesterone receptor status with a relative risk of 0.81 (95% CI 0.65, 1.02) for receptor positivity and 0.70 (95% CI 0.49, 0.99) for receptor negativity.

In addition, Dowsett et al.[56] found that estrogen receptor-negative patients also responded to tamoxifen with a relative risk of 0.73 (95% CI 0.52, 1.02), the majority of which were progesterone receptor positive. Despite this not being statistically significant, it is nevertheless intriguing. Should these women receive adjuvant hormone therapy?

It has been well established that progesterone receptor status may predict the functional integrity of the estrogen receptor and, in turn, the likelihood of response to tamoxifen. The estrogen receptor-negative/progesterone receptor-positive phenomenon has been reported but remains difficult to explain. Theories postulated range from an active estrogen receptor variant lacking the ligand-binding domain to false negativity of the estrogen receptor status.[56]

Despite the controversy of the influence of progesterone receptor negativity, it can be concluded that it is an important marker that needs to be addressed in conjunction with estrogen receptor status.

There has also been confirmation of an association between HER2-positive tumours and response to anastrozole.[57] The Immediate Preoperative Anastrozole, Tamoxifen (IMPACT) trial suggested an objective response of 58% of patients with HER2-positive tumours given anastrozole compared with 22% for tamoxifen. However, this was not statistically significant and investigates the role of neoadjuvant hormone therapy.[57]

Dowsett et al.[56] also found that patients positive for HER2 did not benefit from tamoxifen with a relative risk of 1.14 (95% CI 0.75, 1.73). Although this again was not statistically significant because of the small numbers investigated.

Most recently, the preliminary findings of the TransATAC study were presented by Professor Dowsett at the San Antonio Symposium in December 2006.[58] This is a translational study, investigating the role of hormone receptor status and HER2 status as predictive biomarkers for differential responses to aromatase inhibitor and tamoxifen. Disappointingly, there was no statistical evidence that receptor positivity or HER2 status showed preferential response to aromatase inhibitors.

In conclusion, it is clear that further work is necessary to delineate robust predictive markers. The answer to the optimum timing of aromatase inhibitors in early-stage breast cancer almost seems obsolete. There is good evidence that aromatase inhibitors are fundamental to adjuvant treatment. The future emphasis needs to be on designing therapy for specific patients and assuming a more accurate individualized treatment strategy.

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