

Review

A Practical Overview of Aromatase Inhibitors

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Abstract. *Tamoxifen has been the standard adjuvant therapy for patients with breast cancer for several decades. Various recently completed adjuvant trials using aromatase inhibitors have shown the superiority of these agents over Tamoxifen or placebo, when used in post-menopausal women. The results from these trials present a challenging situation for practicing oncologists with regards to the choice, duration, sequence of therapy, follow-up and side-effects of aromatase inhibitors. Various management issues from a practical angle for oncologists are discussed for the effective use of these agents, with an evidence-based approach.*

The relationship between estrogen and breast cancer has been extensively investigated and hormonal manipulation against estrogen has been used for several decades. Such interventions have included Tamoxifen and, more recently, aromatase inhibitors/inactivators (AIs). Tamoxifen has remained a time-tested hormonal therapy for estrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer. The efficacy of Tamoxifen is clearly reflected through meta-analysis by the Early Breast Cancer Trialists' Cooperative Group (EBCTCG). This meta-analysis showed that adjuvant Tamoxifen reduces the relative risk of breast cancer recurrence by 47% and mortality by 26% (1). Both pre- and post-menopausal women, with or without the involvement of axillary lymph nodes, benefit from the use of adjuvant Tamoxifen. The benefits are additive when Tamoxifen is used after completing adjuvant chemotherapy. At present, five years

of Tamoxifen is recommended as adjuvant therapy in patients with breast cancer.

Aromatase inhibitors (Anastrozole and Letrozole) and inactivators (Exemestane) are third generation compounds, currently indicated for post-menopausal women with breast cancer in metastatic and in adjuvant settings. These hormonal agents have replaced earlier drugs such as aminoglutethimide. In post-menopausal women, estrogen is produced by peripheral conversion of androgens mediated through the enzyme aromatase. Inhibition of this enzyme either reversibly (Anastrozole and Letrozole) or irreversibly (Exemestane) leads to extremely low levels of estrogen, which, in turn, is responsible for the anti-tumor effects. These agents differ in their pharmacokinetic properties and with respect to their overall effect on various systems and tissues (2).

In metastatic breast cancer patients, aromatase inhibitors/inactivators (AIs) are superior to Tamoxifen as first- or second-line hormonal therapy (3-8). A similar effect has emerged for these agents as adjuvant therapy for post-menopausal patients. Three clinical trials have been completed and published after using AIs in this setting. The uniformity of the results from these trials, especially regarding the disease-free survival (DFS) advantage, in addition to the better toxicity profiles, makes it quite compelling to prescribe AIs in this setting. However, several questions remain unanswered, including which AI to use, sequentially or up front, the order of sequence, duration, optimal follow-up and side-effects. At present, these issues make decision-making challenging for oncologists.

To understand these issues further, we have reviewed the results of the trials which have used AIs in an adjuvant setting (Tables I and II). All of the published trials used a phase III, randomized, double-blind and placebo-controlled approach, except the ITA study.

The Arimidex and Tamoxifen Alone or in Combination (ATAC) trial recruited 9,366 women with breast cancer and randomized them to Tamoxifen, Anastrozole (1 mg once daily by mouth) or a combination of Tamoxifen and Anastrozole, after completing surgery, chemo- and

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Table I. Summary of adjuvant AI trials.

Trial	ATAC	MA-17	IES	ITA
Plan of treatment	Anastrozole alone, Tamoxifen alone, Anastrozole + Tamoxifen for 5yrs	Tamoxifen for 5yrs then Letrozole or placebo for 5yrs	Tamoxifen for 5 yrs vs. Tamoxifen for 2-3 yrs then Exemestane for 2-3 yrs	Tamoxifen for 5 yrs vs. Tamoxifen for 2-3 yrs then Anastrozole for 2-3 yrs
No. of patients	9,366	5,157	4,742	426
Median follow-up (at the time of analysis)	47 months (6% patients completed randomized treatment; 47% patients completed at least 4 yrs)	30 months (<1% patients completed randomized treatment)	30.6 months (>90% patients completed randomized treatment)	36 months (all patients completed randomized treatment)
% ER-positive	84% (8% unknown)	98% (2% unknown)	81% (17% unknown)	86% (Tamoxifen, 14% unknown) vs. 91% (Anastrozole, 8% unknown)
Tumor size <2cm	63.9%	57%	Unknown	44-49%
% Node-positive	35% (5% unknown)	46% (4% unknown)	44% (4% unknown)	100%
Chemotherapy	22%	46%	32%	67%
Improvement in absolute risk of recurrence	2.4% for Anastrozole	Estimated at 4 yrs: 6%	4.7% for Exemestane	10% for Anastrozole
Overall survival reported to date	No difference	No difference	No difference	No difference
Treatment withdrawals	More with Tamoxifen	Equal in both arms	More with Exemestane	Equal in both arms
Comments	DFS benefit consistent and increasing with time	Unblinding and cross-over may not reveal safety, optimal duration and efficacy <i>etc.</i>	Fractures and osteoporosis found more in Exemestane arm as were treatment withdrawals	Relatively small number of patients. All were node-positive therefore earlier and prominent difference

radiation-therapy (9). The combination arm had the same results as the Tamoxifen alone arm and will not be described here. The primary objectives were disease-free survival (DFS) and safety. DFS was defined as the time to earliest local recurrence, distant metastasis, new primary breast cancer or any cause of mortality. At 47 months follow-up, more patients were recurrence-free in the Anastrozole arm (86.9%) compared to the Tamoxifen arm (84.5%), with an absolute difference of 2.4% (10). The hazard ratio was 0.86 (CI: 0.76-0.99, *p*-value: 0.03). Musculoskeletal events and fractures were seen more frequently in the Anastrozole alone arm *versus* Tamoxifen

(Table II). However, hot flashes, vaginal bleeding and discharge, incidence of endometrial cancer, venous thromboembolic and cerebrovascular events were significantly higher in the Tamoxifen arm (*p*-value<0.05). This is the largest trial to compare Tamoxifen in a head-to-head design with Anastrozole and has shown a continued benefit over a reasonably sufficient median follow-up. No overall survival benefit has yet been seen.

The National Cancer Institute of Canada – Clinical Trials Group, jointly with the North American Intergroup and the Breast International Group, conducted the MA-17 trial with over 5,000 post-menopausal women (11). These patients

Table II. Adverse events in AIs adjuvant therapy trials.

Toxicity (%)	ATAC (A vs T)	MA-17 (L vs P)	IES (E vs T)	ITA (A vs T)
Endometrial cancer	0.1 vs 0.7*	NA	NA	NA
Vaginal bleeding	4.8 vs 8.7*	4.3 vs 6*	4 vs 5.5*	NA
Cerebro-vascular events	1.1 vs 2.3*	4.1 vs 3.6	NA	NA
Thrombo-embolism	2.2 vs 3.8*	NA	1.3 vs 2.4*	1.8 vs 1.3
Hot flashes	35 vs 40*	47.2 vs 40.5*	42 vs 39.6	
Musculoskeletal disorders	30.3 vs 23.7*	NA	NA	7.2 vs 5.8
Fractures	7.1 vs 4.4*	3.6 vs 2.9	NA	0.9 vs 0.9
Arthralgia	NA	21.3 vs 16.3*	5.4 vs 3.6*	NA
Myalgia	NA	11.8 vs 9.5*		NA
Diarrhea	NA	NA	4.3 vs 2.3*	NA
Gynecologic symptoms	NA	NA	5.8 vs 9*	6.3 vs 4
Osteoporosis	NA	5.8 vs 4.5 (self reported)	7.4 vs 5.7*	NA
Gastrointestinal symptoms	NA	NA	NA	6.3 vs 1.3*

*Statistically significant

A: Anastrozole

T: Tamoxifen

L: Letrozole

P: Placebo

E: Exemestane

received adjuvant Tamoxifen for four to six and a half years. Within three months of discontinuing Tamoxifen, they were randomized to receive Letrozole 2.5mg orally once daily or placebo. The primary objective was disease-free survival, defined in this trial as loco-regional or metastatic disease or new primary breast cancer in the contra-lateral breast. Secondary cancer, death without a recurrence or a diagnosis of contralateral breast cancer were not considered in the analysis of the results. The data and safety monitoring committee, at a median follow-up of 2.4 years, unblinded the two arms at 207 events when the pre-defined O'Brien-Fleming boundary reached the value of 0.0008. The estimated 4-year DFS was 93% in the Letrozole group versus 87% in the placebo; an absolute benefit of 6%. The hazard ratio was 0.57 (95% CI: 0.43 to 0.75; *p*-value: 0.00008). The overall survival (OS) was same in both arms. An update in 2004 revealed the improvement in the OS and DFS to be more prominent in node-positive women (12). The Letrozole arm had more patients with hot flashes, arthralgia and myalgia. The difference in clinical fracture rates and osteoporosis (self-reported) was not statistically significant. Based on this trial, Letrozole may provide extended adjuvant benefits to post-menopausal women after 5 years of Tamoxifen therapy. Interestingly, two-thirds of the women from the placebo group, after unblinding, elected to go on Letrozole therapy. With this cross-over, any meaningful evaluation of the DFS, OS or side-effects will not be possible. However, this cross-over also shows the preference of these patients to continue with the apparent benefits of Letrozole, despite the short follow-up and lack of information regarding the long-term side-effects.

The Intergroup Exemestane Study (IES) recruited 4,742 patients (13). These patients had received 2 to 3 years of adjuvant Tamoxifen. They were then randomized to either continue on Tamoxifen or to switch to Exemestane (25 mg once daily) to complete 5 years of therapy. The primary objective was DFS, defined as local or metastatic disease, contralateral breast cancer or death. After 30.6 months of follow-up, the hazard ratio in the Exemestane arm compared with Tamoxifen was 0.68 (95% CI: 0.56 to 0.82 and *p*-value <0.001). The absolute benefit was 4.7%. Overall survival was not significantly different in the two arms. Survival free of distant disease was better in the Exemestane-treated patients with a hazard ratio 0.66 (95% confidence interval: 0.52 to 0.83; *p*-value=0.0004). A higher incidence of arthralgia and diarrhea was seen in the Exemestane group, but gynecological symptoms, vaginal bleeding, muscular cramps and thromboembolic events were more common in the Tamoxifen group. Fractures were reported more frequently in the Exemestane group (3.1% versus 2.3%), but without reaching statistical significance. This study has shown the advantage of utilizing AIs (Exemestane) after Tamoxifen in a sequential manner. In addition to improved DFS, more importantly distant disease-free survival was significantly better in patients treated with Exemestane.

The last study was presented at the San Antonio Breast meeting in 2003 and published in abstract form. The Italian Tamoxifen Arimidex trial (ITA) used Anastrozole after 2 to 3 years of initial Tamoxifen to complete a total of 5 years of therapy (14). The competitor arm had women treated with Tamoxifen for 5 years. A total of 426 women, all axillary

lymph node-positive, were randomized on this trial. The initial results, after a median follow-up of 2 years, showed a significant benefit in the Anastrozole group, with a hazard ratio of 0.36 for risk of relapse (95% confidence interval: 0.17 to 0.75; p -value=0.006). The hazard ratio of death was 0.18 (CI: 0.02-1.57; p -value=0.07). Although serious adverse events were reported more frequently in patients on the Tamoxifen arm, detailed results from this study are awaited.

The question of how these results can be applied to our adjuvant therapy decision-making in post-menopausal women with breast cancer requires an understanding of which AI to use and in which situation. Two approaches are considered and discussed below.

Timeline approach. These trials have used three landmarks in the treatment timeline for breast cancer patients (Figure 1). Considering the evidence-based medicine approach, each trial has proved the superiority of a particular AI at one particular time-point in the adjuvant phase of treatment. Thus, logically, an individual patient would be best treated with a particular AI proven efficacious at that treatment time. Taking this approach, Anastrozole appears best for patients starting adjuvant hormonal therapy. Patients who have completed 5 years of adjuvant Tamoxifen will be best suited to start Letrozole, while patients who have been on Tamoxifen for 2 or 3 years will benefit from switching over to Exemestane.

Extrapolated approach. Is it reasonable to consider that the AIs exert their effect as a class of drugs? Based on this assumption, could we replace Tamoxifen or Anastrozole with Letrozole or Exemestane and use them at time-points different from the way they were used in their respective trials? Following the evidence from the published trials, this does not appear to be an acceptable approach. The results from different adjuvant hormonal therapy trials using Exemestane and Letrozole are awaited and will provide the answer to this question. It certainly seems possible that AIs, with their demonstrated superiority in the metastatic setting, will continue to enjoy similar importance in the adjuvant stage of treatment.

Is sequential therapy better? Considering that most recurrences in this population of patients are seen in the first 2-3 years, a sequential approach makes sense (15), to utilize the maximum therapeutic benefit of Tamoxifen and then a continued (and perhaps better) coverage by an AI. There is certainly a hint from both the ITA (Anastrozole) and IES (Exemestane) studies that AIs after an initial use of Tamoxifen, provide an additional benefit of disease-free survival compared to Tamoxifen alone. In addition, the distant disease-free survival seen in the IES trial is an important finding and, perhaps, a better marker for overall

efficacy (16). It is even possible that the results of adjuvant trials with Letrozole and or Exemestane may provide superior results compared to sequential therapy (IES/ITA trials) and may become the standard therapy. At present, it certainly seems better to switch patients who have completed 2 to 3 years of Tamoxifen to Exemestane (based on the IES trial results). The result from the BIG FEMTA trial specifically (comparing Letrozole with Tamoxifen both in a head-to-head and in a cross-over design) may shed more light on this issue and, possibly, in a more conclusive manner.

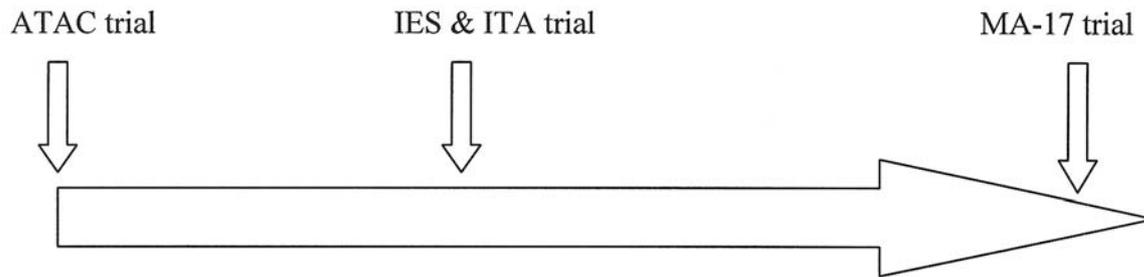
Selection of patients. Many post-menopausal breast cancer patients will have a relatively small risk of recurrence to begin with and, with adjuvant treatment, this risk may significantly decrease. Therefore, it may appear attractive to just treat patients with AIs only if they have a high-risk disease. However, the trials using AIs did not include only high-risk patients. In fact, the majority of participating patients were lymph node-negative or with tumors less than or equal to 2 cms (Table I). Therefore, we recommend discussing the risks and benefits of the treatment of AIs with all women considered eligible for the ATAC, EIS and MA.17 trials, or who are considered eligible for adjuvant Tamoxifen therapy.

Any role of Tamoxifen? Is there now a role for adjuvant Tamoxifen? The efficacy and side-effects of Tamoxifen are particularly well known and discussing the use of Tamoxifen with the patients in an adjuvant setting is quite easy.

Although the results of adjuvant trials with AIs show improved DFS, no survival advantage is evident. In addition, due to a lack of long-term follow-up or cross-over of treatments, the toxicities related to AIs are not well defined. Therefore, it is difficult to discuss the exact risk-benefit ratio and present a balanced picture for patients to decide about using AIs and not Tamoxifen.

From a global angle, however, it appears that AIs are at least as effective as Tamoxifen (considering the overall survival) or better (considering DFS). These agents lack the more serious side-effects of Tamoxifen and have an overall better toxicity profile. Certainly more time is needed to draw absolute conclusions but, at present, AIs appear a better choice in adjuvant therapy plans for post-menopausal women with breast cancer.

Some patients may still opt for Tamoxifen, especially those who have a relatively low risk of recurrence and/or less likelihood of developing serious side-effects (for example a patient with hysterectomy). Patients with severe osteoporosis or arthritis, especially with a low risk of recurrence, may be better off with Tamoxifen. In addition, personal preference and cost may be other factors regarding the choice of Tamoxifen. The field of adjuvant hormonal



Adjuvant therapy with Tamoxifen for 5 years

Figure 1. The use of adjuvant Tamoxifen is currently recommended for 5 years. In post-menopausal women, three different trials have used the AIs at different time-points during these 5 years. The ATAC trial used Anastrozole versus Tamoxifen from the beginning, while the MA-17 trial used Letrozole at the completion of Tamoxifen therapy. A sequential approach was explored in both the IES and ITA trials in which, after 2-3 years of initial Tamoxifen treatment, patients were switched to Exemestane or Anastrozole, respectively, to complete a total of 5 years of therapy.

therapy is in rapid flux and, therefore, it may seem reasonable, in a few cases, to just start with Tamoxifen and reconsider the options when further trial results are available.

Follow-up of patients on AIs. The decision to use an AI should only be made after a full discussion of the benefits and risks of treatment and an appropriate plan of follow-up. We usually recommend that all women starting adjuvant AIs should have a baseline bone density test with follow-up testing every one or two years. Patients with no prior history of osteopenia or fragility fracture should be started on calcium 1,500 mg and Vitamin D 800 U daily. Furthermore, at least 30 minutes of physical activity three times a week is recommended. Those with documented osteopenia or osteoporosis or with prior fragility fracture should be started on an oral bisphosphonate.

Economic considerations. AIs are more expensive than Tamoxifen. On the other hand, several papers have described AIs as cost-effective compared to other medical interventions. Therefore, the cost consideration should not pose any significant problem in using AIs (17, 18).

Quality of life. The results of two different trials show that the quality of life appears unaffected with the use of AIs compared to Tamoxifen or placebo, in the women who participated in the adjuvant AI trials (10, 19). The relatively low toxicity profile of AIs, observed in these trials, compared to placebo or Tamoxifen apparently does not affect the quality of life. However, the quality of life may be dependent on several factors related and unrelated to the therapy used and, therefore, may not reflect the sole impact from AIs.

HER-2/Neu and AIs. Several studies have pointed out a lower response to hormonal therapy, particularly Tamoxifen, in breast cancer patients in whom HER-2/neu is over-expressed (20, 21). Although this effect was not seen in other studies (22, 23), AIs tend to be favored by the oncologists in such patients. At present, with all the published studies, a decision to use specific hormonal therapy based on the HER-2/neu status is not justified (24).

Conclusion

Although Tamoxifen remains the standard therapy for breast cancer patients, the results from AI trials provide compelling evidence that AIs have emerged as superior hormonal agents and offer significant advantages over Tamoxifen. It is expected that, with the support of completed AIs trial data, these agents will be used more frequently in the adjuvant setting. As patients are now better educated through the media and the Internet, the demand for AIs has significantly increased. The long-term follow-up of completed trials and the results from the ongoing AI trials are eagerly awaited and will help present a better risk-benefit picture to our breast cancer patients.

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