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Aromatase inhibitors in the early adjuvant setting – the latest evidence

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ABSTRACT

In early breast cancer, adjuvant therapy significantly reduces the risk of recurrence after complete surgical resection of the tumor mass. For over a decade, 5 years of adjuvant endocrine therapy with the selective estrogen receptor modulator tamoxifen has been the gold standard in hormone-receptor-positive (HR+) disease. Despite therapy with tamoxifen, relapses still occur, and the rate of relapse is particularly high in the first 2–3 years after surgery. More effective therapies are urgently required to prevent these relapses, particularly in patients with higher-risk disease. The third-generation aromatase inhibitors (AIs), letrozole, anastrozole and exemestane, have shown greater efficacy than tamoxifen, with comparable tolerability, in large, randomized, phase III trials in the early adjuvant setting. On the basis of these findings, AIs are now displacing tamoxifen as the preferred adjuvant endocrine therapy for HR+ early breast cancer in postmenopausal women.

Two treatment strategies have been used to investigate AI efficacy in the early adjuvant setting, both with 5 years' tamoxifen as the comparator: upfront AI for 5 years, or switching to an AI after completing between 2 and 3 years of tamoxifen. When given upfront, anastrozole (ATAC trial) and letrozole (BIG 1-98 trial) have been shown to significantly improve disease-free survival compared with tamoxifen. Letrozole also significantly reduced the risk of distant recurrence, a well-recognized predictor of breast cancer death. Indirect comparisons suggest that these two AIs may not be clinically equivalent, but a direct comparison of letrozole and anastrozole in a prospective, randomized trial is required to prove whether these two AIs do differ clinically.

Switching to exemestane or anastrozole therapy after 2–3 years of tamoxifen has also been shown to significantly reduce the risk of relapse compared with 5 years of tamoxifen therapy. However, in these trials, randomization and/or analyses were initiated at the time of switching therapy, including only patients who remained disease-free at this time, thus excluding patients with higher-risk disease who had experienced early relapse, and selecting a more favorable patient population. Trials comparing upfront AIs with the sequential approaches are ongoing: BIG 1-98 and amended TEAM. Of note BIG 1-98 is the only trial to include both switching strategies: tamoxifen followed by letrozole and letrozole followed by tamoxifen.

Trials in the early adjuvant setting have revealed that AIs are generally well tolerated: side effects are predictable and manageable. Although further studies are required to determine the optimum treatment strategy and duration of AI therapy, the third-generation AIs are proving highly effective agents in the treatment of HR+ early breast cancer, and bring into question the validity of tamoxifen as the gold standard for adjuvant therapy. Recently updated international guidelines now recommend that early adjuvant therapy should include an AI.

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1. Introduction

Effective management of early breast cancer continues to be a major challenge to the medical profession. Thanks to improved understanding of the disease and increasing treatment options, many women can now expect to survive for over a decade after initial diagnosis. Adjuvant endocrine therapy has been shown to be an essential part of treatment for hormone-receptor-positive (HR+) breast cancer, and has contributed to significantly improved outcomes for millions of women.

Tamoxifen has been accepted as the gold standard adjuvant therapy following the confirmation of its efficacy in reducing the risk of recurrence and death after tumor resection in the meta-analyses by the Early Breast Cancer Trialists' Collaborative Group.[1] Although tamoxifen reduces the risk of recurrence and death, large collaborative studies have indicated that treatment for longer than 5 years is not beneficial to the patient. Extending tamoxifen therapy beyond 5 years is associated with an unfavorable risk:benefit profile, as acquired resistance gradually reduces the protection afforded, whereas the incidence of some serious adverse events, including thromboembolic disease and endometrial cancer, increases with prolonged treatment.[2] Standard adjuvant endocrine therapy has, therefore, been limited to tamoxifen for 5 years, despite the fact that the majority of breast cancer recurrences and deaths occur more than 5 years after surgery.[1]

Even with adjuvant tamoxifen treatment, the risk of early relapse remains, and is highest in the first 2–3 years after surgery,[3] demonstrating the need for more effective adjuvant therapies. The limitations associated with tamoxifen use have prompted the development of other endocrine agents for the treatment of HR+ early breast cancer. Aromatase inhibitors (AIs) have emerged as effective agents in the adjuvant setting and, on the basis of impressive results from randomized, controlled trials, are displacing tamoxifen as standard adjuvant therapy in postmenopausal women.

Widespread use of the earlier-generation AIs was limited by poor tolerability. The third-generation AIs have greater potency and better tolerability than their predecessors, and are proving effective throughout the treatment continuum in HR+ breast cancer. The three third-generation AIs, letrozole, anastrozole and exemestane, have been shown to have greater or equivalent clinical efficacy compared with the standard of care in advanced breast cancer, and have become established as the agents of choice for first- and second-line therapy in this setting.[4–11] AIs have also shown efficacy in the neoadjuvant setting for newly diagnosed HR+ breast cancer. In this setting, letrozole has shown superior efficacy to tamoxifen, improving objective response rates and increasing the proportion of women who are eligible for breast-conserving surgery (BCS) compared with tamoxifen.[12] Similarly, anastrozole has been shown to increase the proportion of women eligible for BCS, but, unlike letrozole, does not significantly increase the overall response rate to therapy, compared with tamoxifen.[13]

The success of the third-generation AIs in the neoadjuvant and advanced breast cancer settings prompted the study of anastrozole, letrozole and exemestane as adjuvant therapies for HR+ early breast cancer. Large, randomized, phase III trials were initiated to assess the efficacy and tolerability of AIs relative to standard adjuvant tamoxifen therapy. These trials have also examined the optimum therapeutic strategy for AI use. Two strategies have been investigated: upfront AI after surgery, and sequential therapy with tamoxifen and an AI. In these studies, treatment was limited to 5 years because of the use of tamoxifen as the comparator. The therapeutic potential of AIs in women who have successfully completed 5 years of tamoxifen therapy without relapse has also been studied, in what is now called the 'extended adjuvant' setting. The MA.17 study showed that letrozole can significantly reduce the risk of relapse compared with placebo in this setting,[14] and is reviewed by Professor Goss in this supplement. Preliminary results from the small open-label ABCSG-6a trial suggest that anastrozole can also prevent relapses in women who have completed standard adjuvant tamoxifen.[15] This article will provide a comprehensive review of the available data regarding AI use in the early adjuvant setting.

2. AIs in upfront trials

Upfront anastrozole or letrozole has been compared with tamoxifen in the ATAC (Anastrozole, Tamoxifen Alone or in Combination) and BIG (Breast International Group) 1-98 trials, respectively. The ATAC trial was a randomized, double-blind study involving over 9000 women with newly diagnosed, early breast cancer (HR+, HR−, or HR-unknown), designed to compare upfront tamoxifen, anastrozole, and combined therapy for 5 years. The combination arm was closed following the first analysis due to inferior efficacy compared with anastrozole, and no benefit compared with tamoxifen.[16] The primary endpoint was disease-free survival (DFS), defined as the time to local or distant recurrence, new primary breast cancer or death from any cause. Secondary endpoints were time to recurrence (TTR), time to distant recurrence and overall survival (OS).[16]

Upfront treatment with anastrozole was shown to significantly reduce the risk of recurrence compared with tamoxifen treatment (Table 1). At the final analysis, with a median follow-up of 68 months, DFS was significantly longer in women taking anastrozole than in those taking tamoxifen (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.78–0.97, $p = 0.01$).[17] Anastrozole also significantly increased TTR (HR 0.79, 95% CI 0.70–0.90, $p = 0.0005$). Subgroup analysis revealed that the benefits in DFS and TTR were more pronounced in women with HR+ disease than in the whole study population (DFS: HR 0.83, 95% CI 0.73–0.94, $p = 0.005$ [Table 1]; TTR: HR 0.74, 95% CI 0.64–0.87, $p = 0.0002$). The benefits were seen within 1 year of starting treatment, and anastrozole substantially reduced the early relapse rate seen in years 1–3 of adjuvant tamoxifen therapy. The incidence of contralateral breast cancer was reduced by anastrozole therapy in the intent-to-treat (42% reduction, 95% CI 12–62, $p = 0.01$) and HR+ populations (53% reduction, 95% CI 25–71, $p = 0.001$). Anastrozole therapy also significantly prolonged the time to distant recurrence in the intent-to-treat population (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$), but only a trend in favor of anastrozole was seen in the subgroup of patients with HR+ disease (HR 0.84, 95%

Table 1 – Improvement in DFS achieved with AIs in early adjuvant studies

Treatment strategy	Trial	Treatment protocol	Follow-up (months)	Hazard ratio (95% CI)	*p* value	Absolute risk reduction (years from randomization)
Substitution	ATAC[a]	Ana vs Tam	68	0.83 (0.73–0.94)	0.005	2.8% (5)[b]
	BIG 1-98	Let vs Tam	25.8	0.81 (0.70–0.93)	0.003	2.6% (5)
Sequential	IES	Tam → Exe vs Tam	31	0.68 (0.56–0.82)	0.00005	4.7% (3)
	ABCSG-8/ARNO	Tam → Ana vs Tam	28	0.60 (0.44–0.81)	0.0009	3.1% (3)
	ITA	Tam → Ana vs Tam	36	0.35 (0.18–0.68)	0.001	5.8% (3)

a HR+ population.
b Time to recurrence; CI, confidence interval; Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane; NR, not reported.

Table 2 – Improvement in distant DFS achieved with AIs vs tamoxifen therapy in early adjuvant studies

Trial	AI treatment strategy	Follow-up (months)	Hazard ratio	(95% CI)	*p* value
ATAC[a]	Ana 5 years	68	0.84	0.70–1.00	0.06
BIG 1-98	Let 5 years	25.8	0.73	0.60–0.88	0.001
IES	Tam 2–3 years → Exe 2–3 years	31	0.66	0.52–0.83	0.0004
ABCSG/ARNO	Tam 2 years → Ana 2 years	28	0.54	0.37–0.80	0.0016
ITA	Tam 2–3 years → Ana 2–3 years	36	0.49	0.22–1.05	0.06

Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane.
a HR+ population.

CI 0.70–1.00, $p = 0.06$; Table 2). OS did not differ between tamoxifen- and anastrozole-treated patients: a difference of 3% in favor of anastrozole ($p = 0.7$) was seen at the treatment completion analysis. The reduction in breast cancer deaths associated with anastrozole therapy did not reach statistical significance ($p = 0.2$).[17]

Further subgroup analyses revealed that anastrozole provided no benefit over tamoxifen in TTR in patients with higher-risk disease, that is, patients with nodal involvement or who had received chemotherapy prior to adjuvant endocrine therapy.[18]

Retrospective analysis of data from the ATAC trial suggested that the response to anastrozole was influenced by hormone receptor status (estrogen receptor [ER] and/or progesterone receptor [PgR] positivity and negativity). The benefit conferred by anastrozole over tamoxifen was greater in patients with ER+/PgR− tumors (HR 0.43, 95% CI 0.31–0.61, $p < 0.0001$) than in patients with ER+/PgR+ (HR 0.84, 95% CI 0.69–1.02, $p = 0.07$) or ER+/PgR-unknown tumors (HR 1.29, 95% CI 0.71–2.37, $p = 0.4$).[19] The interaction between PgR status and treatment was highly significant ($p = 0.0004$) for ER+ tumors. These data should be interpreted with caution, as this was a retrospective, subgroup analysis.

The BIG 1-98 trial is the only study to date that is directly comparing sequential therapy with an AI before and after tamoxifen, and upfront AI or tamoxifen, in the same patient population. BIG 1-98 is a randomized, double-blind, multicenter trial involving 8010 women with confirmed HR+ early breast cancer. The trial consists of four arms: upfront tamoxifen for 5 years, upfront letrozole for 5 years, tamoxifen for 2 years followed by letrozole for 3 years, and letrozole for 2 years followed by tamoxifen for 3 years (Fig. 1).[20,21] Notably, randomization to all four arms was performed immediately after surgery, that is, before starting adjuvant therapy. The primary endpoint of BIG 1-98 is DFS, including invasive recurrence in the ipsilateral breast, chest wall, regional or distant sites, contralateral invasive breast cancer, second non-breast malignancy and death from any cause. The definition of DFS in BIG 1-98 differs from that in the ATAC trial, being more inclusive of events: second non-breast primaries were included as DFS events in BIG 1-98, but not in ATAC. Secondary endpoints were OS, systemic DFS (excluding locoregional and contralateral events), time to distant metastases, and safety.[21]

The primary core analysis was performed after 779 events, at a median follow-up of 25.8 months. All events in the two upfront arms were included, but in the sequential treatment arms, only events that occurred up to 30 days after treatment switching were recorded (Fig. 1). At this analysis, more than 1200 patients had been followed for at least 5 years. The findings from BIG 1-98 have recently been reported in a peer-reviewed publication,[21] but at the time of the satellite symposium, only abstract data from the study were available.[20] Letrozole significantly increased DFS, reducing the relative risk of relapse by 19% (HR 0.81, 95% CI 0.70–0.93, $p = 0.001$), equating to an absolute risk reduction at 5 years of 2.6% (Table 1 and Fig. 2). A highly significant reduction in

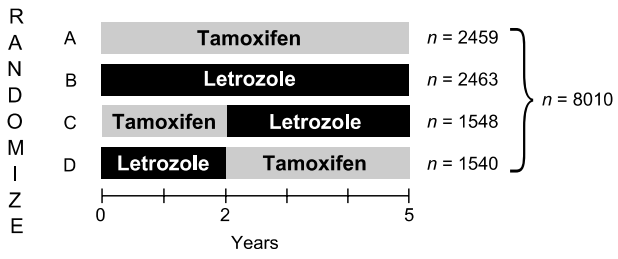
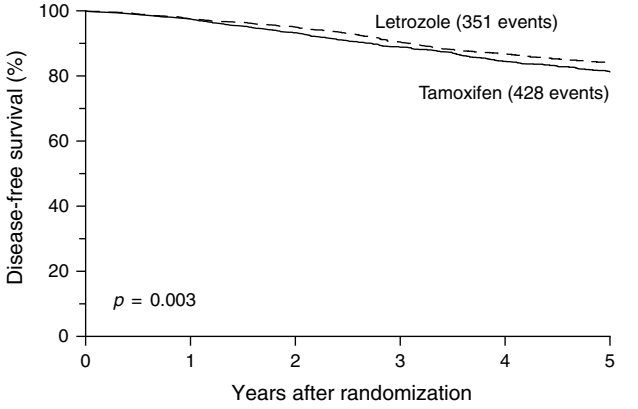


Fig. 1 – BIG 1-98 trial design.



Letrozole						
No. at risk	4003	3892	2964	1261	892	567
Disease-free survival (%)		97.7	95.1	90.5	86.8	84.0
Tamoxifen						
No. at risk	4007	3896	2926	1238	866	544
Disease-free survival (%)		97.6	93.4	89.0	84.6	81.4

Fig. 2 – DFS in BIG 1-98 (reproduced with permission from the International Breast Cancer Study Group).

the cumulative incidence of breast cancer events was also reported for patients receiving letrozole compared with those taking tamoxifen (3.4% reduction at 5 years; $p = 0.0002$).[21]

Distant metastases are strongly associated with death from breast cancer. Letrozole reduced the risk of developing distant metastases by 27% ($p = 0.001$; Table 2) compared with tamoxifen, indicating a substantial clinical advantage for this treatment. Although letrozole did not significantly decrease mortality compared with tamoxifen, there was a trend in favor of letrozole ($p = 0.16$). Letrozole reduced the risk of death by 14% after a median follow-up of only 25.8 months.[21] Longer follow-up will reveal whether this difference will become statistically significant over time.

Preplanned subgroup analyses revealed that letrozole provided a benefit in patients with node-positive disease, and those who had received chemotherapy, that is, patients at higher risk of relapse. DFS was longer in patients receiving letrozole than in those taking tamoxifen, irrespective of whether they had received chemotherapy (patients who had received chemotherapy, HR 0.70; patients who had not received chemotherapy, HR 0.85). In patients without nodal involvement, letrozole did not show any benefit over tamoxifen (HR 0.96) at this early stage of follow-up.[21] Patients with node-negative disease have a good prognosis, and the rate of early relapse is low in these patients. The failure of letrozole to demonstrate a benefit over tamoxifen in this patient population with current follow-up could, therefore, reflect the low number of events that had occurred at the time of the primary core analysis. Longer follow-up will be necessary to reveal the relative efficacies of tamoxifen and letrozole in patients at a lower risk of relapse. In contrast, a significant DFS benefit was associated with letrozole in patients with node-positive disease (HR 0.71), as seen in the whole study population.[21]

Hormone-receptor positivity was an entry requirement for the BIG 1-98 trial, and analysis of subgroups based on ER/PgR status, determined by local assessment, showed that the benefit achieved with letrozole over tamoxifen was similar in all patients with ER+ tumors, irrespective of PgR status (ER+/PgR+, HR 0.84; ER+/PgR−, HR 0.83).[21] A central review of hormone receptor status in patients enrolled in BIG 1-98 is ongoing.

In trials comparing upfront tamoxifen with an AI, the AIs have consistently shown improved efficacy over tamoxifen. However, whether the different AIs have equivalent efficacy is yet to be determined. Differences in inclusion criteria, DFS definitions and current follow-up between the ATAC and BIG 1-98 trials limit the usefulness of comparing these two trials and, in general, cross-trial comparisons must be viewed with caution. Although, some differences can be suggested, a direct comparison in a randomized trial is required for valid conclusions to be made. Despite the limitations of cross-trial comparisons, current data suggest that the benefit over tamoxifen, in terms of distant DFS and OS, may be greater with letrozole than with anastrozole in patients with HR+ disease.[17,21] Differences may also exist between the efficacies of letrozole and anastrozole in patients at increased risk of recurrence: letrozole significantly reduced the risk of recurrence in patients with node-positive disease, or those who received chemotherapy, whereas no significant benefit over tamoxifen was seen with anastrozole.

In addition, the BIG 1-98 and ATAC trials reported conflicting results concerning the influence of ER/PgR status on responsiveness to therapy. The ATAC trial showed that the benefit achieved with anastrozole over tamoxifen was greater in patients with ER+/PgR− tumors (HR 0.43) than in those with ER+/PgR+ tumors (HR 0.84); this latter group accounted for over half of the study population.[19] In contrast, the superiority of letrozole over tamoxifen observed in BIG 1-98 was similar in the ER+/PgR+ and ER+/PgR− subgroups (HR 0.0.84 and 0.83, respectively).[21]

3. AIs in sequential trials

The potential benefit of switching patients already taking tamoxifen onto an AI after 2–3 years has also been studied. Four trials investigating sequential therapy have been reported: the Intergroup Exemestane Study (IES), the Austrian Breast & Colorectal Cancer Study Group (ABCSG)-8 and the Arimidex–Novaldex (ARNO) studies, which have been analyzed together as the ABCSG/ARNO trial, and the smaller Italian Tamoxifen Anastrozole (ITA) trial. Tamoxifen was given for the initial 2–3 years of therapy in all these studies.

In IES, 4742 patients with HR+ or -unknown tumors who had taken tamoxifen for 2–3 years without relapse were randomized to switch to exemestane or continue tamoxifen therapy for the remainder of the 5-year adjuvant period.[22] Similarly, in the ITA trial, randomization to tamoxifen or anastrozole was performed after 2–3 years of tamoxifen therapy.[23] In the ABCSG-8 and ARNO trials, patients either switched to anastrozole after 2 years of tamoxifen therapy or continued on tamoxifen.[24] Randomization was performed immediately after surgery in ABCSG-8, and after 2 years of adjuvant therapy in ARNO: to enable combined analysis of data from the two trials ($n = 3224$), a starting point of 2 years after surgery was used for the analysis. Randomization of

patients who have successfully completed 2 or 2–3 years of adjuvant tamoxifen therapy without relapse excludes those patients with higher-risk disease who had disease relapse during the first 2–3 years of therapy, and selects a relatively favorable patient population for randomization/analysis.

Switching to exemestane after 2–3 years of tamoxifen therapy significantly improved DFS (local or metastatic recurrence, contralateral breast cancer or death from any cause) compared with standard adjuvant tamoxifen therapy (Table 1). After a median follow-up of 30.6 months, 183 first events had occurred in the exemestane group and 266 in the tamoxifen group, giving a hazard ratio of 0.68 (95% CI 0.56–0.82, $p = 0.00005$), corresponding to an absolute DFS benefit of 4.7% at 3 years (exemestane vs tamoxifen: 86.8% vs 91.5%, respectively).[22] Subgroup analyses suggested that switching to exemestane was beneficial to patients with ER+ tumors, irrespective of PgR status (ER+/PgR−, HR 0.58, 95% CI 0.38–0.90; ER+/PgR+, HR 0.66, 95% CI 0.51–0.87). Distant DFS (HR 0.66, 95% CI 0.52–0.83, $p = 0.0004$; Table 2) and risk of contralateral breast cancer (HR 0.44, 95% CI 0.20–0.98, $p = 0.04$) were also significantly better in patients who had switched to exemestane than in those who continued on tamoxifen therapy. Switching to exemestane did not improve OS ($p = 0.37$).[22]

The risk of recurrence was also shown to be significantly reduced by starting anastrozole treatment after 2 years of tamoxifen therapy, compared with continuing tamoxifen for up to 5 years. The ABCSG/ARNO trial reported a 40% reduction in the risk of recurrence (HR 0.60, 95% CI 0.44–0.81, $p = 0.0009$; median follow-up 28 months; Table 1), associated with switching to anastrozole compared with continued tamoxifen therapy. Event-free survival (EFS; recurrence at any site or contralateral breast cancer) 3 years after switching to anastrozole was 92.7% and 95.8% for the tamoxifen and anastrozole groups, respectively, corresponding to an absolute benefit of 3.1% at 3 years.[23] The benefit associated with switching to anastrozole was achieved, irrespective of age at surgery or receptor positivity. The data suggested that the benefit of anastrozole may be more pronounced in patients with ER+/PgR− tumors (HR 0.42, 95% CI 0.19–0.92) than in those with ER+/PgR+ tumors (HR 0.66, 95% CI 0.46–0.93), but the difference between these two patient subgroups did not reach statistical significance.[24] Switching to anastrozole was also more effective in patients with node-negative than with node-positive disease. The risk of relapse was significantly reduced in patients with node-negative disease (HR 0.54, 95% CI 0.35–0.84, $p = 0.0065$), but not in patients with node-positive disease (HR 0.67, 95% CI 0.44–1.02, $p = 0.061$), suggesting that this treatment regimen may be more effective in patients with lower-risk disease.[24]

The risk of developing distant metastases was also significantly reduced by 46% (Table 2) in patients who switched to anastrozole (HR 0.54, 95% CI 0.37–0.80, $p = 0.0016$). OS at 3 years after switching therapy was slightly higher in patients on anastrozole than on tamoxifen (97% and 96%, respectively), but did not reach significance ($p = 0.16$).[24]

A similar benefit was shown to be achieved by switching to anastrozole at 2 years in the small, randomized, open-label ITA trial of 448 postmenopausal women with node-positive early breast cancer. At a median follow-up of 36 months, EFS and local recurrence-free survival, but not distant metastasis-free survival, were significantly improved by switching to anastrozole.[24]

Studies of sequential therapy with tamoxifen followed by an AI demonstrate that switching to an AI significantly reduces the risk of relapse compared with continued tamoxifen therapy. However, the best way to incorporate AIs into adjuvant therapy has yet to be determined. The sequential arms of BIG 1-98, which are yet to be reported, will investigate a switch from tamoxifen to letrozole and vice versa after 2 years of therapy. BIG 1-98 is the only trial that is also studying upfront AI therapy during the period in which relapse is highest (years 1–2) followed by tamoxifen treatment in years 3–5. Results from the TEAM trial,[25] which has been amended to compare upfront 5 years' exemestane with tamoxifen for 3 years followed by exemestane for 2 years, and from the sequential arms of BIG 1-98, are eagerly awaited and will provide valuable insights into the most effective treatment strategy for AIs in the adjuvant setting.

4. Tolerability of AIs in the early adjuvant setting

Monitoring of toxicity associated with early adjuvant AI therapy has indicated that this class of drugs is generally well tolerated, with adverse events being predictable and manageable. Many side effects associated with AIs overlap with those reported for tamoxifen, and are predictable symptoms of estrogen deficiency (e.g. hot flushes). Toxicities that are associated with either AIs or tamoxifen have also been reported. The adverse-event profiles of AIs and their clinical implications are discussed by Dr. Perez in this supplement.

Studies to date have suggested that elevated rates of bone loss/osteoporosis, arthralgia, myalgia, hypercholesterolemia and cardiovascular disease may be associated with AIs. However, when assessing these factors, it is important to consider that tamoxifen was used as the comparator in the early adjuvant trials, and that tamoxifen acts as an estrogen agonist in some tissues. Notably, tamoxifen has been shown to protect against cardiac disease[26] and bone loss,[27] and to have lipid-lowering properties.[28] It is important to consider that some of the adverse events reportedly associated with AIs may, in fact, reflect loss of a protective effect of tamoxifen rather than a detrimental effect of the AI. For this reason, the MA.17 trial in the post-tamoxifen, extended adjuvant setting, which compared letrozole with placebo, may be the most informative trial with respect to the true toxicity profile of AIs. Results from MA.17 suggest that bone loss, arthralgia and myalgia are associated with AI use, but do not support a detrimental effect on the cardiovascular system or lipid profiles,[14] as also emphasized by Dr. Perez in this supplement. The observation that AIs are associated with bone loss reflects the near-complete inhibition of peripheral estrogen production by this highly effective class of drugs. Clearly, AI-induced bone loss is a cause for concern, particularly given that patients with breast cancer, and postmenopausal women in general, are at increased risk of osteoporosis. Early data from ongoing studies have shown that letrozole-associated bone loss can be prevented by concurrent therapy with the bisphosphonate, zoledronic acid (4 mg IV every 6 months), with an acceptable

toxicity profile,[29] suggesting that the detrimental effect of AIs on bone health can be managed.

Some of the more important toxicities associated with tamoxifen are seen less frequently in patients on AIs. Thromboembolic disease was significantly lower in patients taking an AI upfront[17,21] or switching to an AI after 2–3 years[22,23] than in patients on continuous tamoxifen therapy. Gynecological symptoms were also less common in patients taking AIs, including fewer requirements for endometrial biopsies and fewer cases of invasive endometrial cancer in both upfront substitution and sequential studies.[17,21–24]

Available data, therefore, suggest that adverse events associated with AIs are predictable for a class of drugs that virtually eliminates circulating estrogen. Furthermore, toxicities that are associated with AI use but not tamoxifen use, such as bone loss, may be more manageable than those associated with tamoxifen therapy, such as thromboembolic disease. Effects on hypercholesterolemia and cardiac function require further investigation, and longer follow-up from current studies will help to determine what effect, if any, AIs have on non-breast, estrogen-responsive tissues and metabolic processes.

5. Conclusions

Upfront and sequential treatment strategies have demonstrated the superiority of AIs over standard adjuvant tamoxifen in reducing the risk of relapse in postmenopausal women with HR+ early breast cancer, and indicate that tamoxifen is no longer the appropriate standard for early adjuvant therapy. On the basis of these data, updated guidelines from the American Society of Clinical Oncology,[30] the St. Gallen International Expert Consensus on Primary Therapy of Early Breast Cancer[31] and the National Comprehensive Cancer Network[32] now recommend that, in the absence of specific contraindications, an AI should be prescribed in adjuvant therapy.

Despite impressive efficacy data from early adjuvant trials, several questions remain regarding AI use in early breast cancer (Box 1). How to introduce AIs into adjuvant therapy to achieve maximum clinical benefit is still under investigation. Results from the BIG 1-98 and TEAM trials will help to clarify this situation. Furthermore, the suggestion that upfront tamoxifen therapy for approximately 2 years may be beneficial in terms of tolerability, by protecting against bone and cardiac disease, has yet to be proven. Additional studies investigating how to address the effects of AIs on bone metabolism have already begun, and zoledronic acid is emerging as an important agent in preventing AI-induced bone loss.

Box 1. Key questions on the use of adjuvant AIs

- Which is the most effective treatment strategy?
- Are all adjuvant AIs the same?
- Can we predict which patients are most likely to benefit from adjuvant AI therapy (HER2, ER/PgR status)?
- What is the optimum duration of AI therapy?
- What are the long-term benefits of AI therapy?
- What are the long-term adverse events associated with AIs, and what are the management strategies for these events?

The observation that the rate of disease relapse is highest in the first 2–3 years after surgery suggests that upfront use of the more effective therapy, that is, an AI, should reduce the incidence of early relapses, favoring upfront over sequential therapies. BIG 1-98 is the only trial to date designed to assess the efficacy of receiving an AI in the first 2 years, when the risk of relapse is high, followed by tamoxifen therapy, and the opposite sequence. BIG 1-98 will, therefore, provide valuable data on the relative benefits of upfront and sequential therapies in early adjuvant treatment.

Although it is not yet known whether the different third-generation AIs have equivalent clinical efficacy, comparing data across trials suggests that this may not be the case. Although caution should be exercised when drawing conclusions from cross-trial comparisons, the efficacies of upfront letrozole (BIG 1-98) and anastrozole (ATAC), relative to tamoxifen, suggest some advantages to letrozole, which is particularly effective in patients at higher risk of relapse (node-positive disease, and/or with prior chemotherapy). A direct comparison of letrozole and anastrozole adjuvant therapy is currently being performed in a randomized, open-label, phase III trial in postmenopausal patients with node-positive HR+ early breast cancer to confirm whether letrozole is more effective in patients with higher-risk disease. The use of tamoxifen as the comparator in early adjuvant trials has not only complicated the assessment of AI tolerability, but has also limited the study of AIs to 5 years, the standard period of tamoxifen therapy. However, there is currently no evidence to suggest that AIs cannot be taken for longer periods: the optimum duration of adjuvant AI therapy remains to be determined. A recent trial of letrozole in the extended adjuvant period, that is, after completion of the standard, 5-year tamoxifen schedule, has shown that letrozole can be used to extend the adjuvant treatment period beyond 5 years, and that this treatment significantly improves outcomes for women remaining disease-free on completion of tamoxifen therapy.[14]

Although further investigation into long-term safety is required, and concerns surrounding bone and cardiac health still need to be addressed, ongoing and future studies will help to determine the optimum schedule and duration for AI use. The recent updating of guidelines to recommend AI use in the early adjuvant setting demonstrates the importance of this group of agents in the treatment of breast cancer and the great potential that AIs have for significantly improving outcomes for patients with early-stage disease.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**(9472):1687–717.
2. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst* 2001;**93**(9):684–90.

3. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 1996;**14**(10):2738–46.
4. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998;**16**(2):453–61.
5. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001;**19**(14):3357–66.
6. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. *J Clin Oncol* 1996;**14**(7):2000–11.
7. Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. *J Clin Oncol* 2000;**18**(7):1399–411.
8. Gershanovich M, Chaudri HA, Campos D, et al. Letrozole, a new oral aromatase inhibitor: randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Letrozole International Trial Group (AR/BC3). *Ann Oncol* 1998;**9**(6):639–45.
9. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003;**21**(11):2101–9.
10. Bonneterre J, Buzdar A, Nabholtz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001;**92**(9):2247–58.
11. Paridaens R, Dirix L, Lohrisch C, et al. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 2003;**14**(9):1391–8.
12. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001;**12**(11):1527–32.
13. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005;**23**(22):5108–16.
14. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;**97**(17):1262–71.
15. Jakesz R, Samonigg H, Greil R, et al. ABCSG. Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). *J Clin Oncol* 2005;**23**(16S):10S. [abstract 527].
16. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;**359**(9324):2131–9.. Erratum in: *Lancet* 2002;**360**(9344):1520.
17. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;**365**(9453):602.
18. Howell A on behalf of the ATAC Trialists' Group. ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen. *Breast Cancer Res Treat* 2004;**88**:S5. [abstract 1].
19. Dowsett M, Cuzick J, Wale C, et al. Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: an hypothesis-generating study. *J Clin Oncol* 2005;**23**(30):7512–7.
20. Thürlimann B, Keshaviah A, Mouridsen H, et al. BIG 1-98 Collaborative Group. BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. *J Clin Oncol* 2005;**23**(16S):6s. [abstract 511].
21. Thürlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005;**353**:2747–57.
22. Coombes RC, Hall E, Gibson LJ, et al. Intergroup Exemestane Study. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;**350**(11):1081–92.. Erratum in: *N Engl J Med* 2004;**351**(23):2461.
23. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;**366**(9484):455–62.
24. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol* 2005;**23**(22):5138–47.
25. Rea D. Phase III randomized study of adjuvant exemestane versus tamoxifen in postmenopausal women with early breast cancer. Protocol CRC-TU-TEAM. Available at http://clinicaltrials.gov/ct/show/NCT00032136;jsessionid=1D44C3F4F6552E508917E7B85DFF2E38?order=46 [accessed 03.04.06].
26. Braithwaite RS, Chlebowski RT, Lau J, et al. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med* 2003;**18**(11):937–47.
27. Ramaswamy B, Shapiro CL. Osteopenia and osteoporosis in women with breast cancer. *Semin Oncol* 2003;**30**(6):763–75.
28. Herrington DM, Klein KP. Effects of SERMs on important indicators of cardiovascular health: lipoproteins, hemostatic factors, and endothelial function. *Womens Health Issues* 2001;**11**(2):95–102.
29. Brufsky A, Harker W, Beck J, et al. Zoledronic acid (ZA) effectively inhibits cancer treatment-induced bone loss (CTIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (Let): 12 months BMD results of the Z-FAST trial. *J Clin Oncol* 2005;**23**(16S):12s. [abstract 533].
30. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005;**23**(3):619–29.
31. Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol* 2005;**16**(10):1569–83.
32. Rieber AG, Theriault RL. Aromatase inhibitors in postmenopausal breast cancer patients. *J Natl Compr Canc Netw* 2005;**3**(3):309–14.