REVIEW ARTICLE

Role of aromatase inhibitors in the upfront adjuvant hormonal therapy of postmenopausal patients with breast cancer

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Abstract
Tamoxifen has been considered for several decades as the standard upfront hormonal therapy for patients with endocrine-sensitive early breast cancer. The efficacy and favorable toxicity profiles of third-generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, in advanced disease led to their development in early breast cancer. Recent trial results consistently showed the superiority of AIs over tamoxifen in using the two following therapeutic approaches: either the upfront strategy (randomization of newly diagnosed patients: tamoxifen for 5 years vu AI for 5 years) or the sequencial strategy (randomization of newly diagnosed patients: tamoxifen (2–3 years) followed by AI or the inverse for a total of 5 years vs upfront AI for 5 years).

Despite some common characteristics, a body of evidence on AIs suggests some specific differences between the three agents in terms of efficacy as well as toxicity profiles. Thus, these hormonal agents may not be considered interchangeable in clinical practice. This review will explore available results from AIs trials and will try to define their present role in the upfront adjuvant management of postmenopausal patients with breast cancer.

Keywords Breast cancer · Adjuvant treatment · Aromatase inhibitors · Anastrozole · Letrozole · Exemestane · Tamoxifen

Introduction

BREAST cancer is the most common female cancer with a worldwide yearly estimation close to 1.2 million new cases of invasive breast cancer and more than 400,000 deaths.[1] Aging population, screening programs and advances in the treatment of early[2] and metastatic disease[3] are thought to be the main factors related to these facts.

The treatment of patients with positive hormonal receptors breast cancer is based upon locoregional therapies such as surgery and/or radiotherapy, potentially followed by adjuvant endocrine therapy with or without sequential chemotherapy. Most patients are treated with endocrine therapy, since the use of adjuvant hormone therapy was shown to significantly reduce the risk of tumor recurrence and increase the probability of overall survival.[2]

Among the various factors involved in breast cancer carcinogenesis and therapeutic targeting, estrogens and estrogen receptors (ERs) are clearly among the most relevant prognostic and predictive factors.[4–6] As a consequence, antagonising oestrogen is a logical approach to the therapy and prevention of breast cancer. Since the observations of Beatson,[7] the main developments of hormonal therapy of breast cancer have been focused on either oestrogen deprivation by surgical, radiotherapeutic

or chemical means or ER targeting by various hormonal agents.

The selective oestrogen receptor modulator (SERM), tamoxifen, has been, for several decades, the mainstream of endocrine therapy for hormone receptor-positive (HR+ve) breast cancer. The early breast cancer trialists' collaborative group (EBCTCG) overview data showed that tamoxifen, compared to no hormonal therapy, improves significantly disease-free survival (DFS) and overall survival in ER+ve population. However, many advanced ER+ve tumors fail to respond to tamoxifen, and those that do respond ultimately acquire tamoxifen resistance with disease progression.[8]

Tamoxifen is overall well tolerated but has been shown in some cases to induce some harmful and potentially life-threatening side-effects due to its partial oestrogen agonist activity; these include an increased incidence of endometrial cancer[2,9] and thromboembolic events.[10] These observations led to the search of new hormonal agents with the specific goal to improve the therapeutic ratio.

First- and second-generation AIs were developed in advanced breast cancer, but they did not reach the adjuvant setting because of an unfavorable therapeutic ratio compared to tamoxifen.[11] More recently, a new group of AIs, referred to as third generation AIs, were shown to be superior to megestrol acetate in second-line treatment of metastatic breast cancer (MBC) and for the first time ever, to tamoxifen in first-line therapy of MBC.[12–17] These results led to an extensive development of these agents in early breast cancer. In this article, we will review the role of third generation AIs in the upfront adjuvant management of postmenopausal patients with endocrine sensitive breast cancer.

Aromatase inhibitors efficacy in adjuvant treatment

The EBCTCG trialists panel confirmed that adjuvant tamoxifen for 5 years compared to no treatment reduced (only for hormonal receptor-positive disease) the annual breast cancer recurrence rate by 40% and death rate by 31%, irrespective of other potentially interfering factors.[2] Five years duration for tamoxifen treatment was for a long time considered optimal, with a persistent beneficial effect beyond 5 years, despite discontinuing the treatment at 5 years (carry-over effect). Moreover, it was observed that the risk of recurrence was higher in the first 5 years after a diagnosis of breast cancer, with the highest peak being within 2–3 years of diagnosiss.[18] These data clearly support the upfront adjuvant use of the most powerful agents (prevention of the risk of early relapse).

Additionally, caution should be exercised when interpreting overall survival data from AI adjuvant trials in patients with endocrine sensitive breast cancers, as these trials were performed while breast cancer screening programs were being implemented. As a consequence, the large majority of the randomized populations consists of patients with stage 1 breast cancer (T1N0), hence a small number of expected breast cancer events over time and an even smaller number of expected deaths by breast cancer. Thus, long median follow-ups will be needed before being able to draw conclusions on survival. Another issue is raised by longer follow-ups: over time, the proportion of non-breast cancer deaths will increase significantly quicker than breast cancer deaths, introducing a confounding factor in the evaluation of the potential differential impact of the two treatments on overall survival. The overall survival endpoint may become elusive with time and breast cancer survival may become a better endpoint. In any case, long follow-ups (10–12 years), will be needed to evaluate the real impact of new endocrine treatments on overall and breast cancer survival.

The two upfront strategies consist of either upfront AIs for 5 years or upfront sequence of T followed by AI or the inverse (Tables 1 and 2).

Upfront AIs (Table 1)

Three trials compared upfront AIs to tamoxifen given for 5 years: anastrozole in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial,[19–22] letrozole in the BIG (Breast InterGroup) 1–98 trial[23,24] and exemestane in the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial.[25]

These trials differ mostly from several standpoints

(a) **Timing:** the ATAC trial has significantly more mature data than the BIG 1–98 study (follow-ups: ATAC: 100 months/BIG 1–98: 76 months) and the TEAM trial (median follow-up of 2.75 years/33 months). As a consequence, the number of events may vary greatly from one trial to another with impact on the potential capability to draw conclusions from the available data. Thus, comparing data from different trials is totally un-appropriate while simply putting the data in parallel is not free of misinterpretations.

(b) **Change in design over time:** In contrast with the ATAC trial and the BIG 1–98 trial (which had no change in design overtime), the TEAM study was amended in 2004 to account for the ethical issues related to the results of switch trials. These results suggested that patients who did not relapse after 2–3 years on tamoxifen significantly benefited from switching from tamoxifen to an AI rather than continuing tamoxifen for a total of 5 years. Consequently, the arm consisting of 5 years of tamoxifen was

Table 1. Aromatase inhibitors: Upfront adjuvant trials

Trials	ATAC (ref. 22)	BIG1-98 (ref. 23)	TEAM (ref. 25)
No. of patients	6,241	4,922	9,775
Follow-up (median)	100 months	76 months	33 months
Disease-free survival	A > T*	L > T	NSD
	HR = 0.85	HR = 0.88	HR = 0.89
	P = 0.003	P = 0.03	P = 0.12
Time to recurrence	A > T*	HR = 0.85	NSD
	HR = 0.76	N/A	P = 0.05
	P = 0.0001		HR = 0.85
Time to distant recurrence	A > T*	NSD	E > T
	HR = 0.84	HR = 0.85	HR=0.81
	P = 0.022	P = 0.05	P < 0.03
Controlateral breast cancer	A > T*	N/A	N/A
	HR = 0.60		
	P = 0.004		
Overall survival	NSD	NSD	N/A
	HR = 0.97	HR = 0.87	
	P = 0.70	P = 0.08	

NSD: Not statistically different; N/A: Not available; A: anastrozole; L: letrozole; E: exeme-stane; * Hormonal receptor positive patients.

considered unethical to continue and thus, this upfront trial comparing 5 years of tamoxifen to 5 years of exeme-stane became a sequence trial comparing 2–3 years of tamoxifen followed by 2–3 years of exemestane versus 5 years of exemestane. As a consequence, no further upfront data will be available with exemestane versus tamoxifen beyond the recent preliminary results presented at 33 months median follow-up.

(c) Definition of endpoints: It is not advised to compare self-standing randomized trials, as trial populations, follow-ups, statistical plans are different. In regard to upfront AI trials, caution should be further exercised, as even the definition of some of the main prospectively defined endpoints, such as DFS or time to distant recurrence, are different from one study to another. The only similarly defined endpoints between the trials appears to be time to recurrence, called also time to relapse (TTR), corresponding exclusively to breast cancer events. Thus, particular attention and emphasis should be given to TTR data.

1.1 The ATAC trial is a large international study (n = 9366),[19–22] which reported, in the first published analysis (median follow-up 33 months), a significantly prolonged DFS in favor of anastrozole (DFS defined as time to ealiest occurence of local or distant recurrence, new primary breast cancer or death from any cause). TTR was also improved and the incidence of contralateral breast cancer was reduced for patients treated with ana-strozole compared those receiving tamoxifen.[19] The supe-riority of anastrozole over tamoxifen was confirmed in 6,241 patients in an updated analysis at a median follow-up of 47 months[20] and in the 'completed treatment analy-sis' performed at a median follow-up of 68 months.[21] The 100-month median follow-up analysis was published in December 2007 (ref. 22) and confirmed that, for patients with HR+ve tumors, 5 years of anastrozole therapy sig-nificantly improved DFS (hazard ratio [HR] = 0.85; 95% confidence interval [CI]: 0.76–0.94, P = 0.003). The most clinically relevant efficacy endpoint, TTR (breast cancer events), showed a 24% reduction in the odds of recur-rence in favor of anastrozole compared to tamoxifen (HR = 0.76; 95% CI: 0.67–0.87, P = 0.0001). The abso-lute difference in terms of TTR was 4.8% at 9 years, con-firming a large carry-over effect in favor of anastrozole compared with tamoxifen (TTR absolute difference at 5 years: 2.8%). Also, anastrozole reduced the risk of con-trolateral breast cancer by 40% and of distant recurrence by 16% (HR = 0.84; 95% CI: 0.72–0.97, P = 0.022), but without significant impact on overall survival (HR = 0.97; 95% CI: 0.86–1.11, P = 0.70) and mortality after recurrence (HR = 0.90; 95% CI: 0.75–1.07, P = 0.20).

1.2 The BIG 1–98 trial, double-blind, double-dummy study (important for clinical toxicity analysis), was a combination of two trials. The first subtrial, started in 1998, was initially designed to compare letrozole (arm A) with tamoxifen (arm B) given for 5 years in postmeno-pausal patients with HR+ve breast cancer.[23] A second sub-trial was launched in parallel (1999) and consisted of four arms: tamoxifen 5 years (arm B), letrozole 5 years

Table 2.   Aromatase inhibitors: Sequential adjuvant trials

Trials	BIG 1–98 (ref. 24)	BIG 1–98 (ref. 24)	TEAM (ref. 25)	ABCSG 8 (ref. 27)
Design	Tamoxifen → Letrozole vs Letrozole	Letrozole → Tamoxifen vs Letrozole	Tamoxifen → Exemestane vs exemestane	Tamoxifen → Anastrozole vs Tamoxifen
No. of patients	3,098	3,086	N/A	2,921
Follow-up (median)	71 months	71 months	N/A	N/A
Disease-free survival	NSD HR = 1.05	NSD HR = 0.96	N/A	N/A
Time to recurrence	N/A	N/A	N/A	Sequence > Tamoxifen HR = 0.79 P = 0.038
Time to distant recurrence	NSD HR = 1.22	NSD HR = 1.05	N/A	N/A
Overall survival	NSD HR = 1.13	NSD HR = 0.90	N/A	Sequence > Tamoxifen* HR = 0.77 P = 0.025

NSD: Not statistically different; N/A: Not available. *Retrospective analysis, including censored patients.

(arm A) and two other arms in which patients would be treated sequentially with 2 years of tamoxifen followed by 3 years of letrozole (arm C), or with two years of letrozole followed by three years of tamoxifen (arm D). Finally, the 2 trials were merged in order to increase the statistical power related to the upfront question. A total of 8,028 postmenopausal women were randomized: 1,835 in the two-arm first subtrial (from March 1998 to March 2000) and 6,193 in the four-arm second subtrial (from April 1999 to May 2003).

The primary core analysis of this trial (letrozole vs tamoxifen), which included a total of 4,922 patients (2,463 on letrozole and 2,459 on tamoxifen), was reported with a 51 months follow-up.[23] DFS, defined as breast cancer recurrence (local, regional and distant) or invasive controlateral breast cancer or non-breast cancer death (without recurrence, was significantly improved with letrozole compared to tamoxifen (HR = 0.82; 95% CI: 0.71–0.95, P = 0.007), as was TTR (breast cancer events) (HR = 0.78; 95% CI: 0.65–0.92, P = 0.004), with an absolute difference of 3.2% at 5 years. No significant difference was reported in terms of overall survival (HR =0.91, 95% CI: 0.75–1.11, P = non-significant). However, time to distant recurrence was significantly better with letrozole (HR = 0.81; 95% CI: 0.67–0.98, P = 0.03).

A recent analysis comparing letrozole to tamoxifen was presented with 76 months median follow-up.[27] However, 619 patients' (25.2%) on tamoxifen were censored because of selective crossover to letrozole requested by patients or physicians, for ethical reasons. The consequence is a decreased statistical power for the comparison letrozole versus tamoxifen. The analysis of DFS, on an intent-to-treat (ITT) basis, showed a significant advantage for letrozole over tamoxifen (HR = 0.88; 95% CI:

0.78–0.99, P = 0.03). Kaplan-Meier curves were not presented. However, the increase of the HR from 0.82 at 51 months to 0.88 at 76 months is not consistent with a carry-over effect with letrozole. No significant difference was reported for overall survival (HR = 0.87, 95% CI: 0.75–1.02, P = 0.08, non-significant) and time to distant recurrence was not anymore significantly improved in favor of letrozole versus tamoxifen (HR = 0.85; 95% CI: 0.72–1.00, P = 0.05). TTR was not presented. No toxicity data were available.[24]

1.3   Preliminary results evaluating exemestane versus tamoxifen as upfront therapy (TEAM trial) were recently presented.[25] More than 9,700 patients were accrued in this trial. Results, triggered by 723 events at 33 months median follow-up, showed, on an ITT basis, a statistically non-significant improvement of DFS in favor of exemestane versus tamoxifen (HR = 0.85, 95% CI: 0.77–1.03, P = 0.12). Secondary endpoints such as relapse-free survival (RFS) were borderline significant for exemestane (HR = 0.85, 95% CI: 0.72–1.00, P = 0.05) while time to distant metastases (TDM) was significantly improved in favor of exemestane (HR = 0.81, 95% CI: 0.67–0.98, P < 0.03) as was on-study drug DFS (HR = 0.83, 95% CI: 0.71–0.97, P = 0.02). Specific AI toxicities were confirmed for exemestane in particular in terms of musculoskeletal side-effects, suggesting no potential protective effect of the steroidal AI on bones.

Sequential strategy (Table 3)

Two studies investigated this strategy comparing a sequential approach over 5 years to 5 years of upfront AIs: a) BIG 1-98 trial with letrozole; and b) the

amended TEAM trial with exemestane. Early results of the BIG 1-98 were presented at the 2008 SABCS, while no sequential data are so far available from the TEAM study.

Additionally, the Austrian Breast Cancer Study Group (ABCSG) presented at the 2008 SABCS data from the ABCSG 8 trial comparing a sequence of tamoxifen for 2–3 years followed by anastrozole for a total duration of treatment of 5 years to 5 years of tamoxifen.[26]

The protocol-specified analysis of the sequential component of the BIG 1–98 trial was presented at 71 months median follow-up.[25] Six thousand one hundred and eighty-two (6,182) patients were enrolled in this four arms study comparing tamoxifen 5 years versus letrozole 5 years versus tamoxifen for 2 years followed by letrozole for a total of 5 years versus the inverse (letrozole for 2 years followed by tamoxifen for a total of 5 years). A total of 612 patients (39.5%) from the tamoxifen arm were selectively crossed over to letrozole following the unblinding of this arm, thus, the analysis included only the three remaining unblinded arms.

The first analysis, on an ITT basis, compared the sequence tamoxifen followed by letrozole (T → L) versus upfront letrozole (L). Data from 3,094 patients were included in this analysis. Results suggested a non-statistically significant benefit in favor of upfront letrozole for DFS (HR = 1.05, 99% CI: 0.84–1.32), overall survival (OS) (HR = 1.13, 99% CI: 0.83–1.53) and time to distant relapse (TDR) (HR = 1.22, 99% CI: 0.88–1.69. The difference in breast cancer events at 5 years favoring upfront letrozole (T→L: 9.1% vs L: 7.3%) and the 22% relative increase in the odds of getting a distant relapse with T → L versus L did not clearly validate the sequence tamoxifen followed by letrozole.

The second analysis evaluated the sequence letrozole followed by tamoxifen versus upfront letrozole. Results on 3,086 patients showed no difference between the 2 arms either in terms of DFS (HR = 0.96, 99% CI: 0.76–1.21), OS (HR = 0.90, 99% CI: 0.65–1.24) or TDR (HR = 1.05, 99% CI: 0.75–1.47).

Table 3. Aromatase inhibitors: summary of adverse events

Adverse events with AI class effect[22,23,25]	
Favorable to tamoxifen	Favorable to AIs
Sexual dysfunction	Hot flushes
Skeletal events	Gynecologic events
Musculoskeletal pain and arthralgia	Thromboembolic events
Adverse events without AI class effect, specific to AI	
Cardiac events[27]	
Lipid metabolism[27]	
Ischemic cerebrovascular events[41]*	

*Significantly reduced with anastrozole, but not with letrozole or exemestane as compared to tamoxifen

2.2 The ABCSG 8 trial compared 5 years of tamoxifen to the sequence tamoxifen for 2 years followed by 3 years of anastrozole. With 2,921 randomized patients, the analysis of the main endpoint (RFS) confirmed a significant improvement in favor of the sequence versus upfront tamoxifen (HR = 0.82, 95% CI: 0.68–0.99, P = 0.038). A retrospective analysis, including patients who violated the protocol by crossing over from tamoxifen to anastrozole showed a significantly better overall survival for the sequence (HR = 0.77, 95% CI: 0.61–0.99, P = 0.025), however this unplanned analysis appears methodologically biased and subject to criticism.

Toxicity profile from AI adjuvant trials

Overall, anastrozole given for 5 years appears to be less toxic than tamoxifen in terms of serious adverse events (SAE). However, preliminary results of the BIG 1–98 trial at 51 months' median follow-up showed the same incidence of SAE between letrozole and tamoxifen, while no long-term data are available with exemestane.

When analyzing all side-effects induced by the long-term use of AIs versus tamoxifen, a trend seems to emerge (Table 3). A first series of side-effects seems to be specific and favorable to AIs (hot flushes, gynecological side-effects and cardiovascular events including thromboembolism), a second series specific to all AIs but favorable to tamoxifen (bone fractures/osteoporosis and arthralgia), and a third series more specific to given AIs (lipid metabolism, cardiac and cerebrovascular events).

AI-specific toxicity favorable to AIs

Hot flushes are frequently observed in adjuvant studies with endocrine agents, independent of the type of hormone therapy used. Overall, when compared with tamoxifen, non-steroidal AIs (anastrozole and letrozole) lead to significantly fewer hot flushes than tamoxifen, while patients treated with exemestane experienced a comparable rate of hot flushes and menopausal symptoms.

Tamoxifen is known to have an estrogenic effect on healthy endometrial tissue, which could lead to endometrial proliferation and thickening, increased risk of polyp formation, vaginal bleeding and increased incidence of endometrial cancer.[2] In contrast, AIs induce uterine atrophy and may decrease tamoxifen-induced changes. As a consequence, when compared with tamoxifen, AI therapy resulted in significantly fewer gynecological adverse events, including endometrial cancer.

Tamoxifen has also been associated with a small but significant increased risk of venous thromboembolism, which is further worsened by the addition of chemotherapy. All AIs, being potent inhibitors of estrogen synthe-

Table 4. Fractures and arthralgia in aromatase inhibitor adjuvant trials

Study	ATAC Anastrozole vs tam (ref. 22)	BIG 1-98 Letrozole vs tam (ref. 23)	TEAM Exemestane vs tam (ref. 25)
Median exposure to AI	5 years	4.2 years	2.75 years
Fractures	11.0% vs 7.7% $P < 0.0001$	8.6% vs 5.8% $P < 0.001$	2.7% vs 2.1% $P = 0.015$
Arthralgia	35.6% vs 29.4%* $P < 0.0001$	20% vs 13.5%** $P < 0.001$	N/A

N/A, Not available; tam, Tamoxifen

Table 5. Proposed management of bone side-effects with aromatase inhibitors

Bone marrow density (BMD) at baseline	Treatment with AIs	Control BMD	Treatment with biphosphonates
Normal T-score > –1.0	Yes	At completion of AI therapy	No
Osteopenia –1.0 < T-score >–2.5	Yes	1 or 2 years after initiation of AI therapy	No
Osteoporosis T-score < –2.5	Yes	1 year after initiation of AI therapy	Yes

sis, have been shown to significantly reduce the risk of thromboembolism compared with tamoxifen.

AI-specific toxicity favorable to tamoxifen

Tamoxifen has a positive effect on bone mineral density (BMD) in postmenopausal breast cancer patients.[27] Patients treated with the three AIs clearly have an increased rate of musculoskeletal disorders, particularly osteoporosis and bone fractures, in trials comparing them to tamoxifen (Table 4)[28]. However, the management of bonbe toxicity is now well established and there is no absolute contraindication for the use of AIs because of bone issues (Table 5).[29,30]

In clinical practice, the main symptomatic issue with AIs remains arthralgias and fibromyalgias, for which no clear physiopathological explanation is known (Table 4).

Sexual dysfunction is a frequent event for patients treated with endocrine therapy, although potentially under-reported in breast cancer studies. Secondary to low estrogen levels, vaginal dryness can induce dyspareunia as well as decrease libido. As expected, vaginal dryness was more frequently seen with AIs and more patients reported dyspareunia with anastrozole than with tamoxifen.[31]

5.3   Toxicity specific to given AIs

Postmenopausal women are known to have lipid profile changes with increased low-density lipoprotein choles-

terolemia (LDL-C) and decreased high-density lipoprotein cholesterolemia (HDL-C) leading to a potential inreased risk of coronary heart disease.[32–34] There is no clear evidence that tamoxifen favorably influences the lipid metabolism.[34] In the BIG 1-98 trial, hypercholesterolemia (prospectively defined) was more frequent with letrozole than with tamoxifen (50.6% vs 24.6% respectively, $P < 0.001$). However, most (99%) of these hypercholesterolemias were graded 1 or 2.[23] In the ATAC study, hypercholesterolemia (not prospectively defined) was also seen with an increased incidence with anastrozole vs tamoxifen (9% versus 3%, $P < 0.0001$).[28]

No cardiac safety issues were identified for any of the AIs in advanced breast cancer studies. However, the duration of exposure to AIs was relatively short.[35] In adjuvant setting,[33,35] patients on letrozole in the BIG 1–98 trial experienced a significantly higher incidence of grade 3–5 cardiac events than those on tamoxifen (74 cases vs 35 cases, respectively, $P < 0.05$). These events consisted mostly of ischemic heart disease (42 cases vs 21 cases respectively, $P < 0.05$) and cardiac failures (24 cases vs 14 cases, respectively). No update of cardiac toxicity was presented with the 76 months median follow-up analysis. In the ATAC trial, the incidence of ischemic cardiac disease was comparable for anastrozole and tamoxifen (4.1% vs 3.4%, $P = 0.10$). No cardiac issue was raised in the preliminary results of the TEAM trial.[25]

Ischemic cerebrovascular events were significantly reduced in the ATAC trial for patients on anastrozole compared with those on tamoxifen (62 cases/2% vs 88 cases/3%, $P = 0.03$).[28] Trials with letrozole and exeme-

stane did not show a decreased incidence of cerebrovascular events compared with tamoxifen or placebo.

The full definition of long-term safety profiles for AIs correlates to the maturity of available safety data. Reports on anastrozole at 68 and 100 months' median follow-up show a favorable risk-benefit ratio compared with tamoxifen.[28] Recent publications on letrozole and exemestane, with 51 and 33 months' median follow-ups, respectively, have added useful information. However, full safety data are required for these agents over the full 5 year therapy before being able to fully determine their respective risk-benefit ratios.

Conclusions

Third-generation AIs are now part of the hormonal therapy for postmenopausal patients with endocrine-sensitive breast cancer. Recent results consistently show the superiority of these agents over tamoxifen. Upfront treatment with an AI for 5 years represents in 2009 the best option to prevent breast cancer recurrence in this patient population, since the sequential strategy is not validated. However, several questions remain unanswered including in particular the duration of AI therapy beyond 5 years.

There is no direct comparison between the three available AIs in an adjuvant setting so the decision to use one specific AI should be based on their respective efficacy and toxicity profiles, maturity of data and availability of clinical trial results within the chosen clinical strategies.

The overall therapeutic index of AIs appears to be superior to that of tamoxifen with proven improved efficacy and a better toxicity profile. Despite recently published comments,[36] tamoxifen is no longer the gold standard of care in the adjuvant therapy of postmenopausal women with breast cancer and AIs should now be used in this patient population.

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