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INVITED ARTICLE

Advances in Endocrine Therapy for Early and Advanced Breast Cancer

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ABSTRACT

Significant advances have been made in the treatment of breast cancer since the link was made between the endocrine system and the disease more than 100 years ago. Tamoxifen was the first successful endocrine therapy although, despite its proven effectiveness, it is associated with side effects such as an increased incidence of endometrial cancer and thromboembolic events, and the development of tamoxifen-resistant tumours is common. Alternative endocrine therapies are now available, including aromatase inhibitors and the oestrogen receptor downregulator fulvestrant. The new third-generation aromatase inhibitors anastrozole and letrozole have both shown superior efficacy to tamoxifen for the first-line treatment of advanced breast cancer. In addition, they have both shown efficacy benefits compared with megestrol acetate for patients failing with tamoxifen, as has the steroidal aromatase inhibitor exemestane. More recently, fulvestrant has been shown to be as effective as anastrozole in the second-line setting and is not significantly different from tamoxifen as first-line treatment for advanced disease. Based on the superior activity compared with tamoxifen in the first-line advanced disease setting, several ongoing trials are investigating the use of third-generation aromatase inhibitors in the adjuvant setting. The Arimidex, Tamoxifen, Alone or in Combination trial found that anastrozole was superior to tamoxifen for several efficacy endpoints, including disease-free survival, time to recurrence, and the incidence of contralateral breast cancer, and showed several important tolerability benefits. An efficacy update confirmed the benefits shown for anastrozole versus tamoxifen, and a safety update showed that anastrozole's tolerability benefits were maintained in the longer-term. The third-generation aromatase inhibitors offer a choice of endocrine treatment for the first- and second-line treatment of advanced disease, while fulvestrant offers an additional choice for the second-line treatment for patients progressing with prior anti-oestrogens. In the adjuvant setting, anastrozole is currently the only aromatase inhibitor to have proven superiority over tamoxifen so, for the first time, there is now a choice of endocrine therapy for postmenopausal women with early breast cancer.

Key words: *Adjuvant, Breast cancer, Endocrine therapy, First-line, Second-line, Tamoxifen*

HISTORY OF THE HORMONAL TREATMENT OF BREAST CANCER

Breast cancer is the most common female cancer, accounting for almost 1 in 3 cancers diagnosed in American women.[1] Although the incidence of breast cancer has been increasing for several decades, the mortality rate has shown a gradual decline.[2] This is probably due to increased awareness of the disease, leading to earlier diagnosis, and improved treatments.

Since Beatson first made the link between the endocrine system and breast cancer 100 years ago,[3] significant advances have been made in the treatment of the disease. Tamoxifen became accepted as the first-line endocrine treatment of choice for advanced breast cancer because it was as effective as other available endocrine therapies, including high-dose oestrogens, androgens, progestins, and aminoglutethimide, but with low toxicity.[4] Tamoxifen remained the mainstay

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of endocrine therapy in postmenopausal women with early and advanced breast cancer for more than a quarter of a century.

Despite tamoxifen's proven effectiveness as treatment for breast cancer, it is associated with an increased incidence of endometrial cancer,[5] uterine sarcoma[6] and thromboembolic disease.[5,7] Furthermore, most tumours eventually become resistant to tamoxifen so that alternative treatments are then required. These shortcomings are associated with the partial oestrogen agonist effect that tamoxifen has on some tissues. Thus, there is a clear need for additional effective and well-tolerated endocrine therapies for the treatment of breast cancer.

DEVELOPMENTS IN ENDOCRINE BREAST CANCER THERAPY

During the period when tamoxifen was the first-choice of endocrine treatment for early and advanced breast cancer in postmenopausal women, exciting developments were occurring with other classes of endocrine agents. Hormonal therapies with different mechanisms of action to tamoxifen such as the aromatase inhibitors (AIs) were developed. A major objective in the development of the AIs was to find a compound that was effective and also lacked the partial oestrogen agonist effects of tamoxifen. Rather than blocking the effect of oestrogens on breast tissue, AIs inhibit oestrogen production via the aromatase pathway. These agents have been developed for use in postmenopausal women, in whom the aromatase pathway is the primary source of oestrogen. More recently, fulvestrant, an oestrogen receptor downregulator that, unlike tamoxifen, has no known agonist activity has been developed for treatment of breast cancer.

ADVANCED DISEASE

Aminoglutethimide was the first AI to become available as a breast cancer therapy, approximately 25 years ago.[8] Although efficacious, aminoglutethimide was unable to rival tamoxifen due to its overall toxicity and lack of selectivity for the aromatase enzyme, creating the need for concurrent corticosteroid supplementation. Formestane, an effective second-generation AI, became available in 1993. Its increased selectivity meant that formestane had fewer side effects than aminoglutethimide.[9] However, formestane must be administered as an injection every 2 weeks and, as such, is associated with a high incidence of injection site reactions, which limits its use. Furthermore, it has been unable to demonstrate any efficacy benefits over megestrol acetate (MA) or tamoxifen in trials of advanced disease.[10,11] The third-generation AIs represent a significant step forward in the area of hormonal breast cancer therapy, providing drugs that are both orally administered and selective for the aromatase enzyme, thus avoiding issues associated with earlier AIs.

Second-line Therapy in the Advanced Disease Setting

Third-generation AIs, anastrozole, letrozole, and exemestane, offer significant efficacy benefits over MA as second-line therapies following tamoxifen (Table 1).[12-16] Anastrozole was compared with MA in 2 large randomised trials.[17,18] After a median follow-up of 6 months, data from the combined analysis of these studies showed that time to progression (TTP) did not differ significantly for anastrozole 1 mg compared once daily (od) with MA 40 mg 4 times daily (qd) [Table 1], and neither did the objective response (OR; 10.3% and 7.9%, respectively).[19] However, at a median follow-up of 31 months, survival was significantly better

Table 1. Key efficacy results from phase III trials comparing megestrol acetate with anastrozole, letrozole, and exemestane for second-line treatment of advanced breast cancer in patients who have failed with tamoxifen.[12-16,19]

	European and USA combined analysis		European trial		US trial		International trial	
	Anastrozole (n = 263)	Megestrol acetate (n = 253)	Letrozole (n = 174)	Megestrol acetate (n = 189)	Letrozole (n = 199)	Megestrol acetate (n = 201)	Exemestane (n = 366)	Megestrol acetate (n = 403)
Dose	1 mg od	40 mg qd	2.5 mg od	40 mg qd	2.5 mg od	40 mg qd	2.5 mg od	40 mg qd
Median follow-up (months)	31		33		37		11	
Median TTP (months)	4.8	4.6	5.6	5.5	3.0	6.0	4.7	3.8
p Value	NS		NS		NS		0.037	
Median survival (months)	26.7	22.5	25.3*	21.5*	29.0	26.0	NR	28.4
p Value	<0.025		NS		NS		0.039	

*Survival data from an extended 51-month follow-up analysis

Abbreviations: od = once daily; qd = 4 times daily; TTP = time to disease progression; NR = not reached; NS = non-significant.

for anastrozole 1 mg than for MA ($p < 0.025$), with a lower death rate (57.4% versus 67.6%, $p < 0.025$) and longer median time to death (26.7 versus 22.5 months) [Table 1].[12] In addition, the proportion of patients surviving for longer than 2 years was greater for anastrozole than for MA (56% versus 46%).[12]

Letrozole has also shown a significant efficacy advantage when compared with MA in 1 study. However, a second study did not confirm this advantage. In the European study,[13] letrozole 2.5 mg od produced a better OR rate than MA (24% and 16%, respectively; $p = 0.04$) and was superior in terms of time to treatment failure (TTF) compared with MA (5.1 and 3.9 months, respectively; $p = 0.04$).[13] There was no significant difference between letrozole 2.5 mg and MA for TTP or in terms of survival (Table 1). In contrast to the European study, the study from the USA showed that letrozole 2.5 mg od produced an OR rate only equivalent to that seen with MA (16% and 15%, respectively) and there was no significant difference between letrozole 2.5 mg and MA for TTF.[14] As in the European trial, there was no significant difference between letrozole 2.5 mg and MA for TTP or survival (Table 1).

In a trial comparing exemestane 25 mg od with MA 40 mg qd, patients receiving exemestane showed a significant improvement in TTP compared with MA (Table 1), while the OR rate was not significantly different between the groups.[15] At a median follow-up of 11 months, exemestane also provided a significant survival advantage compared with MA ($p = 0.039$; Table 1).[15] However, this was after a much shorter median follow-up compared with the anastrozole studies and no mature data are available.

In addition to the AIs, the oestrogen receptor downregulator fulvestrant has recently been assessed for use as second-line therapy of advanced breast cancer for patients failing with tamoxifen. Fulvestrant 250 mg once monthly intramuscular injection was compared with anastrozole 1 mg od in 2 phase III studies in postmenopausal women who had progressed with prior endocrine therapy — 1 study was performed in Europe, Australia, and South Africa[20] and the other in North America.[21] In the combined analysis of these studies,[22] fulvestrant was at least as effective as anastrozole for TTP (median TTP, 5.5 versus 4.1 months; hazard ratio [HR], 95% confidence interval [CI], 0.82-1.10; $p = 0.48$). Both OR (19.2% versus 16.5%; odds ratio [OR] 1.1; 95% CI, 0.84-1.74; $p = 0.31$) and clinical benefit (complete response plus partial response plus stable disease ≥24 weeks; 43.5% versus 40.9%) were similar in the 2 groups. Median duration of response (DOR; from randomisation to progression) was 16.7 and 13.7 months for fulvestrant and anastrozole, respectively. After an extended follow-up (22.1 months) the mean DOR for all randomised patients (from onset of response to progression) was significantly greater for fulvestrant compared with anastrozole ($p < 0.01$).

First-line Therapy in the Advanced Disease Setting

As first-line treatment for advanced disease, anastrozole was the first endocrine treatment to show significant benefit over tamoxifen.[23-25] Combined analysis of the North American[23] and TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability)[25] studies revealed a significant improvement in TTP for anastrozole over tamoxifen in patients with hormone-sensitive tumours (10.7 versus 6.4 months; $p = 0.022$).[24]

Letrozole has also shown superior efficacy compared with tamoxifen as first-line treatment.[26] In a single phase III trial, TTP was increased in the letrozole group for both the overall population (HR 0.70; 95% CI, 0.60-0.82; $p = 0.0001$) and hormone receptor-positive (oestrogen and/or progesterone receptor) population (HR 0.70; 95% CI, 0.58-0.84; $p = 0.0002$).

Although no data from phase III trials comparing exemestane with tamoxifen are currently available, the results of a small open-label phase II trial of exemestane 25 mg od ($n = 31$) versus tamoxifen 20 mg od ($n = 32$) are promising.[27] The most recent update of this trial shows a benefit in terms of OR for exemestane (45% versus 14%), although there are no statistics available to date. A phase III trial is currently ongoing. Fulvestrant 250 mg once monthly intramuscular injection has also been compared with tamoxifen 20 mg od as first-line therapy for postmenopausal women with advanced breast cancer.[28] There was no significant difference between the fulvestrant and tamoxifen groups in the hormone receptor-positive population for TTP (median TTP, 8.2 versus 8.3 months; HR 1.10; 95% CI, 0.89-1.36; $p = 0.388$), CB (57.1% versus 62.7%; $p = 0.218$) or OR (33.2% versus 31.1%; $p = 0.637$).

EARLY DISEASE

Aromatase Inhibitors in the Adjuvant Setting

Based on the superior activity of third-generation AIs compared with tamoxifen in the advanced setting, these

agents are currently being evaluated in the adjuvant setting.

At present, anastrozole is the only agent, other than tamoxifen, proven to be an effective adjuvant hormonal therapy for postmenopausal women with early breast cancer, and has recently been approved for the adjuvant treatment of hormone receptor-positive disease in this population. The ongoing ATAC (Arimidex, Tamoxifen Alone or in Combination) trial is comparing the safety and efficacy of tamoxifen with anastrozole alone and the combination of anastrozole plus tamoxifen as adjuvant therapy for postmenopausal women with early breast cancer. The primary objectives of the trial are to evaluate disease-free survival (DFS) and safety/tolerability. Secondary endpoints are time to recurrence (TTR; defined similarly to DFS but censoring patients who had died from non-breast cancer-related deaths) and incidence of new contralateral primary breast tumours.[29]

The first analysis was carried out at a median follow-up of 33 months for disease-free survival. Results of this analysis were first presented at the San Antonio Breast Cancer Symposium in December 2001, and showed that anastrozole was significantly more effective than tamoxifen with an overall favourable tolerability profile. Disease-free survival was significantly longer in the anastrozole group compared with the tamoxifen group and the combination group (Table 2).[29] The DFS estimates at 3 years were 89.4%, 87.4%, and 87.2% for anastrozole, tamoxifen, and the combination, respectively. Thus, event rates for anastrozole, tamoxifen, and the combination are 10.6%, 12.6%, and 12.8%, respectively. In the hormone receptor-positive group (representing 84% of the total population), DFS was also significantly longer for the anastrozole group compared with tamoxifen and the combination (Table 2). Anastrozole was also superior to tamoxifen for TTR in both the overall and the hormone receptor-positive population (Table 2).[29] In the overall population, there was a significant reduction in contralateral breast cancers as a first event in the anastrozole group (0.5%; 14/3125) versus the tamoxifen group (1.1%; 33/3116) [Table 2],[29] which, based on the odds ratio of 0.42 ($p = 0.007$) represented a 58% reduction in the risk of developing contralateral breast cancer for those women in the anastrozole group compared with the tamoxifen group. Findings for the hormone receptor-positive population were consistent with the overall results (Table 2).

In terms of tolerability, the overall risk:benefit profile strongly favoured anastrozole. At the first analysis (median treatment duration, 30.7 months) anastrozole was superior to tamoxifen for hot flushes ($p < 0.0001$), vaginal discharge ($p < 0.0001$), vaginal bleeding ($p < 0.0001$), cerebrovascular events ($p = 0.0006$), thromboembolic events ($p = 0.0006$), including deep vein thrombosis ($p = 0.02$), and endometrial cancer ($p = 0.02$) [Table 3]. Tamoxifen was superior to anastrozole for musculoskeletal disorders and fractures ($p < 0.0001$ for each) [Table 3].[29] Adverse event rates were similar between the combination and tamoxifen groups at the first analysis. Anastrozole was associated with significantly fewer withdrawals from treatment than tamoxifen (21.9% versus 26.0%; $p = 0.0002$), including fewer withdrawals due to drug-related adverse events (5.1% versus 7.2%).[29] Since the combination

Table 2. Major efficacy endpoints at the first and updated analyses of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.[29,30]

Efficacy endpoint	At first analysis (median follow-up 33 months for disease-free survival)		At updated analysis (median follow-up 47 months for disease-free survival)	
	Hazard ratio (95% confidence interval)*	p Value	Hazard ratio (95% confidence interval)*	p Value
DFS overall population A versus T	0.83 (0.71-0.96)	0.013	0.86 (0.76-0.99)	0.030
DFS overall population A versus C	0.81 (0.70-0.94)	0.0006	NA	NA
DFS HR+ population A versus T	0.78 (0.65-0.93)	0.005	0.82 (0.70-0.96)	0.014
DFS HR+ population A versus C	0.76 (0.63-0.91)	0.002	NA	NA
TTR overall population A versus T	0.79 (0.67-0.94)	0.008	0.83 (0.71-0.96)	0.015
TTR HR+ population A versus T	0.73 (0.59-0.90)	0.003	0.78 (0.65-0.93)	0.007
Contralateral breast cancer incidence A versus T	0.42 (0.22-0.79)	0.007	0.62 (0.38-1.02)	0.062
Contralateral breast cancer incidence HR+ population A versus T	0.29 (0.13-0.64)	0.002	0.56 (0.32-0.98)	0.042

*Except contralateral breast cancer incidence, which is presented as an odds ratio (95% confidence interval).
Abbreviations: DFS = disease-free survival; A = anastrozole; T = tamoxifen; C = combination; HR+ = hormone receptor-positive; NA = not applicable; TTR = time to recurrence.

Table 3. Incidence of predefined adverse events at the first and updated analyses of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial for which there were significant differences between anastrozole and tamoxifen at the first analysis.[29,30]

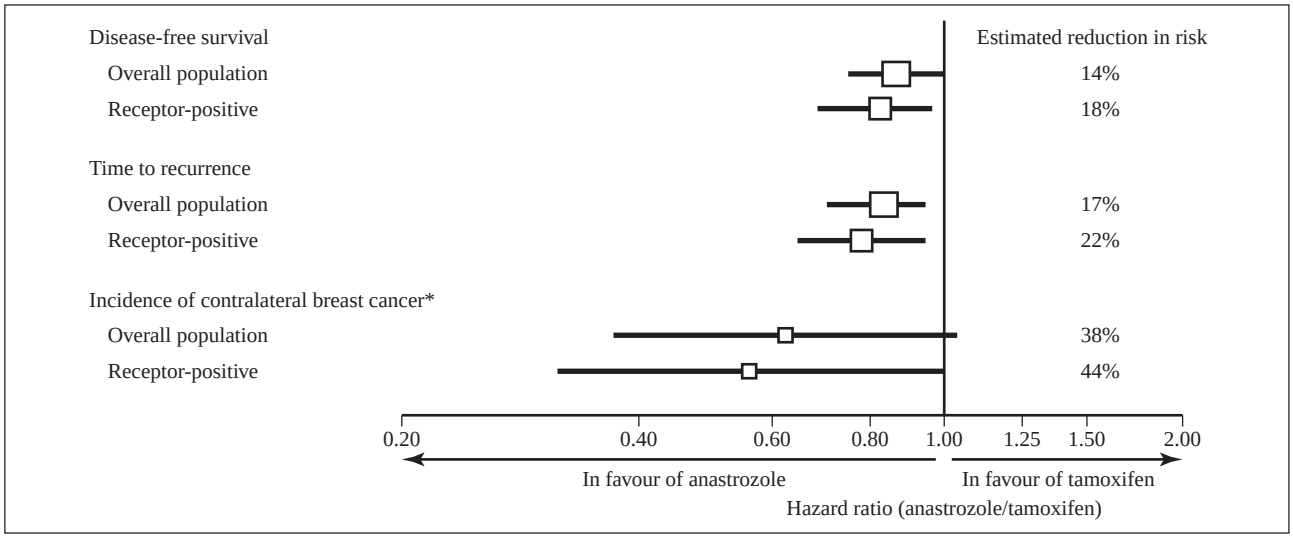
Adverse events	At first analysis (median duration of treatment, 30.7 months)			At updated analysis (median duration of treatment, 37.0 months)		
	Anastrozole (n = 3092)	Tamoxifen (n = 3093)	Relative risk A/T	Anastrozole (n = 3092)	Tamoxifen (n = 3093)	Relative risk A/T
Median therapy duration (months)	30.9	30.8		37.3	36.9	
Endometrial cancer (%)*	0.1	0.5	0.23	0.1	0.7	0.20
Vaginal bleeding (%)	4.5	8.2	0.55	4.8	8.7	0.54
Vaginal discharge (%)	2.8	11.4	0.24	3.0	12.2	0.25
Cerebrovascular events (%)	1.0	2.1	0.48	1.1	2.3	0.49
Thromoboembolic events (%)	2.1	3.5	0.59	2.2	3.8	0.59
Hot flushes (%)	34.3	39.7	0.86	35.0	40.3	0.87
Musculoskeletal disorders (%)	27.8	21.3	1.30	30.3	23.7	1.28
Fractures (%)	5.9	3.7	1.59	7.1	4.4	1.60

* Excluding patients with hysterectomy at baseline from the denominator.
Abbreviations: A = anastrozole; T = tamoxifen.

showed no efficacy or tolerability benefit over tamoxifen alone, the combination group of the trial was discontinued after this analysis.

An efficacy update at a median follow-up of 47 months confirmed that the benefit seen with DFS in the anastrozole-treated group was sustained.[30] This benefit was accentuated in the known receptor-positive population (Table 2 and Figure 1). Again, time to recurrence was significantly longer for the anastrozole group versus the tamoxifen group in the overall population, with a larger benefit seen in the hormone receptor-positive population (Table 2 and Figure 1). A reduction in contralateral breast cancer continued to be seen with anastrozole, which was significant in the hormone receptor-positive group (Table 2 and Figure 1). DFS estimates at 4 years were 86.9% and 84.5% for anastrozole and tamoxifen, respectively.[30] The updated analysis demonstrated that the absolute benefit for anastrozole compared with tamoxifen continues to increase over time.

The analysis of the updated safety data was performed after an additional 7 months of follow-up from the first safety analysis,[31] in line with normal USA Food and Drug Administration (FDA) requirements (median treatment duration was 37 months). The results were similar to those at the first analysis (Table 3) showing that tolerability benefits seen with anastrozole over tamoxifen are maintained in the longer term — no increase in the risks of fractures or musculoskeletal disorders were observed with anastrozole. In line with



* Odds ratio

Figure 1. Hazard ratios, 95% confidence intervals, and estimated risk reduction for disease-free survival, time to recurrence, and incidence of contralateral breast cancer for anastrozole versus tamoxifen at the updated efficacy analysis.

the generally better tolerability pattern, anastrozole was associated with fewer withdrawals from treatment than tamoxifen (24.1% versus 28.3%), including fewer withdrawals due to drug-related adverse events (5.6% versus 8.1%).[31]

Several ongoing trials involving anastrozole in the adjuvant setting are also underway. The ARNO (Arimidex or Nolvadex) study and the ABCSG 8 (Austrian Breast Cancer Study Group 8) trial are investigating treatment with tamoxifen for 5 years compared with tamoxifen for 2 years followed by 3 years of anastrozole and, in the ABCSG 6a trial, patients will receive 5 years of tamoxifen or tamoxifen plus aminoglutethimide followed by 3 years of anastrozole or placebo. In addition, sequential adjuvant treatments involving letrozole and exemestane are being investigated. The superior efficacy of anastrozole compared with tamoxifen, coupled with its excellent tolerability profile, means that it is the ideal agent to evaluate in the prevention of breast cancer. The IBIS-II (the second International Breast Cancer Intervention Study) trial, which initiated recruitment in February 2003, will investigate the chemopreventive effects of anastrozole compared with placebo.[32]

Other AIs, letrozole and exemestane, are currently undergoing adjuvant trials with results expected in the next few years. Letrozole is being compared with tamoxifen in 2 trials. The Breast International Group (BIG) are conducting a 4-group study, BIG 01–98, where patients will receive letrozole or tamoxifen for 3 years following 2 years of tamoxifen or letrozole,[33,34] and the National Cancer Institute of Canada are conducting the MA.17 trial,[33] in which 5 years of letrozole treatment or 5 years of placebo will follow 5 years of tamoxifen treatment. Trials involving exemestane are comparing 2 years of exemestane with no further treatment after 5 years of tamoxifen (National Surgical Adjuvant Breast and Bowel Project [NSABP] B33 trial)[33] and 5 years of tamoxifen versus 2 years of tamoxifen followed by 3 years of exemestane (BIG 02–97).[35]

IMPACT ON TREATMENT STRATEGIES

During the past 5 years, the sequence in which hormonal therapies are used to treat advanced breast cancer has changed based on the outcome of major clinical trials — AIs are now established as first-line therapy, tamoxifen as second-line therapy after failure of AIs, and MA consigned to third- or fourth-line use.

The only endocrine therapies to be approved for adjuvant therapy in postmenopausal women with early breast cancer are anastrozole and tamoxifen. Now that results from the first and updated analyses of the ATAC trial indicate that anastrozole is more effective than tamoxifen as adjuvant therapy, with a number of important tolerability benefits,[29-31] the treatment algorithms for early breast cancer may also change, with anastrozole becoming the preferred adjuvant endocrine therapy. Patients in whom adjuvant anastrozole treatment is successful but who have a recurrence are unlikely to respond to other non-steroidal AIs such as letrozole. Therefore, alternative treatment strategies for advanced breast cancer will need to be determined. Tamoxifen has been shown to be an effective second-line to anastrozole in a trial investigating the efficacy of different treatment sequences of anastrozole and tamoxifen in the advanced setting.[10] This study demonstrated prolonged time to second progression in patients treated with anastrozole then tamoxifen (median TTP, 28.2 months) compared with those treated with tamoxifen then anastrozole (median TTP, 19.5 months). In addition, as exemestane is a steroidal AI, it may also be effective following progression with anastrozole. Although there are no available data from phase III trials of exemestane in the first-line setting, data from a phase II trial suggest that there is a lack of complete cross-resistance between exemestane and non-steroidal AIs.[36] Another option may be the oestrogen receptor downregulator fulvestrant, which has recently been shown to be as effective as anastrozole in the second-line setting, and was not significantly different to tamoxifen as first-line treatment for advanced disease.[22,28] Therefore, tamoxifen or fulvestrant may be the preferred option for treatment of postmenopausal women who have progressed with anastrozole.

CONCLUSION

The emerging benefits of AIs in the treatment of both early and advanced breast cancer in postmenopausal women represent a significant step forward in the development of hormonal breast cancer therapies that are both efficacious and better tolerated than previous therapies. Approval of anastrozole, letrozole, and exemestane for treatment of postmenopausal patients with advanced breast cancer has had an impact on the sequence in which hormonal breast cancer therapies can be administered, offering a choice of treatment, both first- and second-line. Based on their superior activity compared with tamoxifen, anastrozole and letrozole can now be considered the first-line therapies of choice

in the advanced setting. Fulvestrant, an additional endocrine option, has also been shown to be as effective as anastrozole in the second-line setting, and was of similar efficacy to tamoxifen as first-line treatment for hormone receptor-positive advanced disease. Therefore, physicians now have a greater choice for patients who fail to respond to adjuvant and first-line hormonal therapy.

The proven benefits of anastrozole in the treatment of early breast cancer and its recent approval for use in this setting mean that, for the first time, there is also a valid choice of adjuvant endocrine therapy for postmenopausal women with hormone-sensitive tumours. Longer follow-up will determine whether anastrozole will ultimately replace tamoxifen as the treatment of choice across the entire breast cancer continuum. If this is the case, the most effective therapy for postmenopausal women who have progressed with anastrozole will need to be reassessed, and fulvestrant or tamoxifen may become the preferred treatment options.

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