Aromatase Inhibitors – The New Standard for Postmenopausal Women with Hormone-responsive Breast Cancer

a report by
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Endocrine Therapy

Worldwide, breast cancer is the most common cause of cancer-related mortality among women, accounting for 14% of all female cancer deaths in 2002.[1] Since approximately one-third of breast tumours are dependent on oestrogen for continued growth and proliferation, measures that either inhibit the synthesis or block the mechanism of action of oestrogens are attractive strategies for therapeutic intervention. For more than 20 years, tamoxifen, which significantly decreases oestrogen levels through its antagonist action at the oestrogen receptor, has been the standard endocrine adjuvant therapy for postmenopausal women with early breast cancer.[2] However, as tamoxifen also has partial oestrogen-agonist properties, it is associated with an increased risk of endometrial cancer and thromboembolic complications.[3,4] Moreover, during long-term treatment, resistance to tamoxifen can also develop, resulting in treatment failure.[5] Consequently, alternative endocrine therapies for the treatment of hormone-responsive breast cancer, with increased efficacy and fewer long-term complications, are desirable.

Aromatase Inhibitors

In postmenopausal women – in whom hormone responsiveness is common – oestrogen is primarily synthesised peripherally in adipose tissue, muscle and breast tissue, rather than in the ovaries as in premenopausal women (see *Figure 1*). In this population, the most specific therapeutic effects are achieved by blocking the last step in biosynthesis – the conversion of androgens to oestrogens by the aromatase enzyme (see *Figure 1*). The major breakthrough in the improvement of hormonal treatment for postmenopausal women with breast cancer has therefore come from the development of the aromatase inhibitors (AIs).

The highly selective third-generation AIs – anastrozole, letrozole and exemestane – are more effective and generally better tolerated than tamoxifen, offering a reduced risk of serious side effects and gynaecological adverse events.[6] Anastrozole (Arimidex®) and letrozole (Femara®) are both non-steroidal, competitive AIs, while exemestane (Aromasin®) is a steroidal, non-competitive AI. The first studies of these treatments showed that anastrozole (1mg) daily) and letrozole (2.5mg daily) were more effective than tamoxifen in postmenopausal women with advanced hormone-receptor-positive breast cancer.[7,8] Similar results were subsequently reported for exemestane (25mg daily)[9] and all three AIs are now licensed for use in advanced therapy.

Primary Adjuvant Treatment with an AI

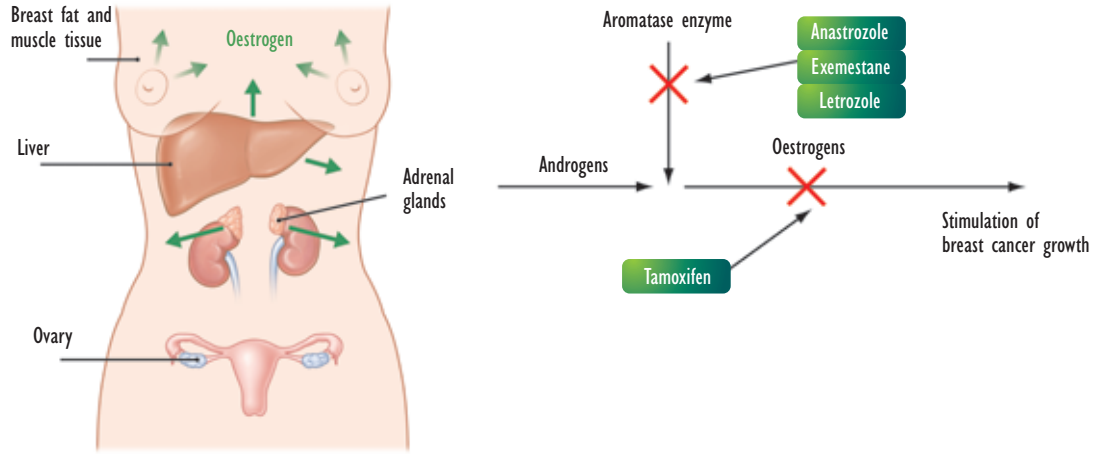
More recently, clinical trials have shown that anastrozole and letrozole are also more effective than tamoxifen in the primary adjuvant treatment of postmenopausal women with early breast cancer (see *Table 1*).[10-16] Currently, anastrozole has the most mature efficacy and tolerability data of all of the AIs, with follow-up extending beyond the standard five-year treatment period.[10] The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared anastrozole with tamoxifen, or the combination of both treatments, as adjuvant therapy in 9,366 postmenopausal women with early breast cancer (see *Table 1*). The combination arm was dropped after the first analysis at 33 months as it offered no efficacy or safety benefits over tamoxifen alone. After a median follow-up of 68 months, anastrozole treatment significantly prolonged disease-free survival, time to recurrence and time to distant recurrence, and significantly reduced the occurrence of contralateral breast cancers compared with tamoxifen. The absolute benefit for anastrozole over tamoxifen continues to increase with time and extends beyond the completion of therapy.[10]

Early results from the Breast International Group (BIG) 1–98 trial at 26 months of median follow-up show that primary adjuvant therapy with letrozole also has efficacy benefits over tamoxifen.[17]

Switching Strategies

Since many patients already receiving tamoxifen

Figure 1: Sources of Oestrogen and Endocrine Therapy Options in Postmenopausal Women



During and after menopause, ovarian oestrogen production declines. In postmenopausal wemen, fat, muscle, liver and the adrenal glands produce most of the circulating oestrogen. The aromatase inhibitors act to prevent the conversion of androgens to oestroges by the aromatase enzyme, whereas tamoxifen prevents oestrogen binding to its receptor.

treatment will also be suitable for AI therapy, a number of trials have compared 'switching' strategies, in which tamoxifen has been used as the initial adjuvant therapy for two to three years, before a switch is made to an AI for the remainder of the five-year adjuvant treatment period. Data from switching trials illustrate that recurrence rates are reduced when patients change to an AI prior to disease progression on tamoxifen.

Switching to anastrozole compared with continued tamoxifen treatment was associated with significantly longer disease-free survival in the Italian Tamoxifen Arimidex trial, median follow-up 64 months[12]; and event-free survival in the combined Austrian Breast & Colorectal Cancer Study Group (ABCSG) 8/Arimidex-Nolvadex 95 trials, median follow-up 28 months (see *Table 1*).[13] A meta analysis of all three switching trials showed that patients who switched to anastrozole had a 41% improvement in disease-free survival ($p < 0.0001$), a 45% improvement in event-free survival ($p < 0.0001$), a 39% improvement in distant recurrence-free survival ($p = 0.0015$) and a 29% improvement in overall survival ($p = 0.0377$), compared with those remaining on tamoxifen.[18] Similarly, the benefits of switching to exemestane treatment after two to three years of tamoxifen, compared with continuing with tamoxifen, were examined by the Intergroup Exemestane Study (IES).[19,20] After a median follow-up of 56 months, this study showed that switching to exemestane significantly improved disease-free survival (see *Table 1*).[21]

Trials extending adjuvant hormonal therapy – by administering an AI after completing five-years of tamoxifen therapy – have also resulted in recurrence benefits (see *Table 1*). In the ABCSG 6a and National Institute of Cancer MA17 extended adjuvant trials, women receiving anastrozole and letrozole, respectively, experienced a reduced risk of disease recurrence compared with those who were either administered a placebo or undertook no further treatment.[16,22]

Findings from these switching trials are not directly comparable with primary adjuvant data because recurrences occurring during the initial period of tamoxifen treatment are not accounted for in the switching results. Since all patients in these studies were treated with tamoxifen before switching to an AI, the recurrence/survival data relate to patients with a good response to endocrine therapy who have not withdrawn from therapy due to adverse events, rather than the more general patient population, which would be treated with primary adjuvant therapy.

Optimal Hormonal Therapy

Data directly comparing AI monotherapy with a switching strategy are not yet available. However, it should be noted that the risk of recurrence is, at its greatest, approximately one to three years after surgery.[23,24] Therefore, although switching to an AI after tamoxifen treatment has been initiated is superior to continuing with tamoxifen, delaying the start of AI therapy may have significant implications for relapse. Data from the ATAC trial show that the greatest divergence between anastrozole and tamoxifen in disease-free survival and time to recurrence occurs during the first 2.5 years of adjuvant treatment.[25] Initiating treatment with tamoxifen with the intention of switching to

Table 1: Details of Adjuvant AI Trials

	Primary AI therapy		Switch to AI after two to three years/tamoxifen			Switch to AI after five years/tamoxifen[a]	
	ATAC[10]	BIG 1–98[11]	ITA[12]	ABCSG8/ ARNO[13]	IES[21]	MA17[22]	ABCSG6a[16]
AI studied	Anastrozole	Letrozole	Anastrozole	Anastrozole	Exemestane	Letrozole	Anastrozole
AI (*n*)	3,215	4,003	208	1,618	2,362	2,575	387
Tamoxifen (*n*)	3,116	4,007	218	1,606	2,372	2,582	409
Median age (years)	64	61	63	63	64	62	63
Hormone-receptor-positive[b] (%)	84	100	100	100	82	98	94
Node-positive (%)	39	42	100	26	49	50	32
Median follow-up (months)	68	26	64	28	56	29	60
HR, disease-free survival	0.83[c]	0.81	0.42	-	0.75[d]	-	-
HR, recurrence/ relapse-free survival	0.74[c]	0.72	0.56	0.60	0.75[d]	0.58	0.64

a=AI versus placebo after five years tamoxifen
b=oestrogen receptor/progesterone receptor
c=for receptor-positive patients only
d=receptor-positive and receptor-unknown patients;
ABCSG = Austrian Breast & Colorectal Study Group 8/Arimidex-Nolvadex 95 trials; AI = aromatase inhibitor; ARNO 95 = Arimidex, Nolvadex 95 trial; ATAC = Arimidex, Tamoxifen, Alone or in Combination trial; BIG 1–98 = Breast International Group 1-98 trial; HR = hazard ratio; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Anastrozole trial; MA17 = National Institute of Cancer trial MA17.

anastrozole could therefore mean that many patients are lost to recurrence or death before the switch occurs.

Tolerability

Currently, anastrozole is the only AI in the initial adjuvant setting with a detailed safety, and thus mature, risk/benefit profile from follow-up of greater than five years.[26] Treatment with anastrozole results in a lower incidence of serious adverse events and significantly fewer withdrawals from treatment compared with tamoxifen treatment. The major gains with anastrozole were fewer endometrial cancers, thromboembolic and cerebrovascular events, and fewer vasomotor and gynaecological symptoms and procedures, although an increase in fractures and joint symptoms was also reported.

Data from the BIG 1–98 study at 26 months of median follow-up showed that the overall incidence of adverse events was higher in the letrozole group than in the tamoxifen group, although the frequency of serious adverse events and withdrawals due to adverse events were not significantly different between the two groups.[17,27] Treatment with letrozole reduced the risk of developing thromboembolism, hot flushes and vaginal bleeding compared with tamoxifen treatment, but increased the risk of fractures, arthralgia and hypercholesterolaemia.

Data comparing initial adjuvant exemestane treatment with tamoxifen are not yet available, although the IES provides evidence supporting the efficacy and tolerability of AI therapy in women already receiving tamoxifen.[19] Exemestane has been shown to be associated with a higher incidence of fractures, arthralgia and diarrhoea than tamoxifen in the IES, but gynaecological symptoms (such as endometrial cancer and vaginal bleeding) were reduced. However, more patients who were switched to exemestane treatment after two to three years of tamoxifen withdrew due to adverse events, compared with patients who continued taking tamoxifen.[21]

Due to their mode of action, the AIs as a class have the potential to have a deleterious effect on the skeletal health of postmenopausal women receiving these drugs as adjuvant treatment for early breast cancer. As mentioned, all three of the third-generation AIs have been associated with an increased risk of fractures compared with tamoxifen treatment in clinical trials.[10,11,19,22] However, tamoxifen treatment is

associated with a protective effect on bone in postmenopausal women,[28] and it should be remembered that, due to decreasing levels of oestrogen following the menopause, all postmenopausal women are at increased risk of developing osteoporosis and fragility fractures. With anastrozole in the ATAC trial, it is seen that the fracture rate stabilises after one to two years and decreases upon treatment cessation.[26] The data show that no patients with normal bone mineral density at baseline became osteoporotic after five years of treatment with anastrozole.[29] Furthermore, clinical trials suggest that these skeletal-adverse effects may by adequately managed with the use of bisphosphonates in at-risk patients.[30] The effects of AIs on bone should therefore be weighed against the overall superior efficacy and tolerability profile of AIs versus tamoxifen when making treatment choices.

Current Guidelines

AIs consistently offer efficacy benefits over tamoxifen in the adjuvant setting, regardless of the strategy used. Adjuvant AI therapy, either from the start of treatment or after several years of tamoxifen treatment, reduces the risk of disease recurrence compared with tamoxifen treatment. The American Society of Clinical Oncology (ASCO) currently recommends that postmenopausal women be treated with an AI to reduce their risk of a breast cancer recurrence, either in a primary adjuvant setting or after treatment with tamoxifen.[31] Together, the conclusions of clinical trials and recommendations of guidelines suggest that treatment with an AI should now be the first-choice therapy for postmenopausal women with hormone-receptor-positive breast cancer. ■

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