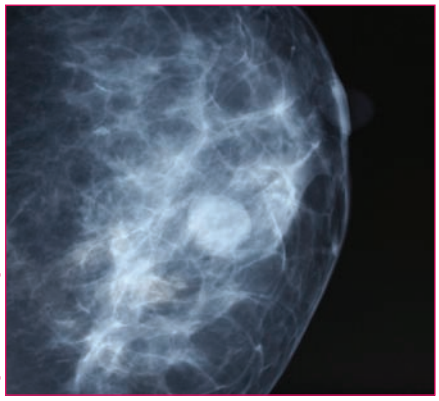
Early oestrogen receptor-positive breast cancer in postmenopausal women may be treated with aromatase inhibitors



above: Close up of a mammogram

Introduction

Approximately two thirds of women diagnosed with breast cancer have hormone receptor-positive tumours.[1] The growth of tumour cells in these patients is regulated by the activity of oestrogen.[2] Blocking its action or depriving the cells of oestrogen will inhibit tumour growth and development.[3]

The aim of adjuvant treatment is to prevent recurrence of disease after initial curative surgery, because approximately 25% of patients with node-negative breast cancer will have recurrence — with 25% of recurrences occurring after 10 years.[4] The mainstay of treatment has been tamoxifen — meta-analysis has shown that treatment for five years in all women with oestrogen-positive tumours results in a reduction in recurrence of 47% and a reduction in death of 26%.[5] Tamoxifen remains the treatment of choice for early oestrogen receptor-positive breast cancer in pre-menopausal women.[6]

The advent of aromatase inhibitors has increased the choice of adjuvant treatment options for postmenopausal early oestrogen receptor-positive breast cancer. Also several different approaches are now available to treat oestrogen receptor-positive breast cancer. In addition to the traditional approach of five years of treatment with tamoxifen, patients can be offered what seems to be a bewildering array of treatment options with the aromatase inhibitors — categorised as upfront, switch or extended treatment. Upfront means using an aromatase inhibitor as primary therapy for a period of five years. Switch refers to an initial 2–3 year treatment with tamoxifen followed by a switch to an aromatase inhibitor for a further period to bring the total hormonal treatment time to five years. In extended treatment five years of treatment with tamoxifen (as in upfront) is followed by 2–3 years of treatment with an aromatase inhibitor. The NICE technology appraisal guidance of 2006 *Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer*,[7] recommending the use of the aromatase inhibitors within their (then) licensed indications provides an opportunity to consider the use of the individual agents. Currently available aromatase inhibitors are described below.

Anastrozole (Arimidex®)

Anastrozole is a reversible, non-steroidal aromatase inhibitor. In keeping with all aromatase inhibitors it acts by blocking the conversion of endogenous androgens to oestrogens both within peripheral tissues and within tumour cells, thereby lowering oestrogen to negligible levels and removing the direct effect of oestrogen on the breast cancer cells.

Within this context, anastrozole is licensed for adjuvant treatment of postmenopausal women with hormone receptor-positive (a) early invasive breast cancer and (b) early breast cancer and who have received adjuvant tamoxifen for 2–3 years (Table 1). The standard dose is 1mg daily.

The main evidence base for anastrozole is derived from the arimidex and tamoxifen alone and in combination (ATAC) study.[8] This study involved the randomisation of more than 9000 women to one of three different treatment strategies: five years treatment with either anastrozole or tamoxifen alone, or five years treatment with the two drugs in combination. Interim analyses at 33 and 47 months showed that anastrozole alone produced significant prolongation of disease-free survival (89.4% vs 87.4% at three years, the absolute risk reduction, ARR, is 2% and number needed to treat, NNT, is 50) and time to recurrence (RRR 0.27), and reduced the incidence of contralateral breast cancer by 58% compared to tamoxifen alone (ARR 0.6%, NNT 163).[9] Because of low efficacy the combination arm was closed. Combining anastrozole with tamoxifen produced results significantly worse than anastrozole alone and no better than tamoxifen alone. Although the authors speculated that there could be a pharmacokinetic interaction resulting in 27% lower anastrozole concentrations, suppression of oestradiols in the two groups was the same.[9] After a median of

Table 1. Summary of current product licenses for adjuvant treatments of early oestrogen receptor-positive breast cancer in postmenopausal women

Drug	Primary adjuvant	Planned/unplanned switch	Extended adjuvant
Anastrozole	X	X	
Exemestane		X	
Letrozole	X		X

Key: X=licensed for indicated use

68 months follow-up, anastrozole significantly prolonged disease free survival with a hazard ratio (HR) of 0.87 (p=0.01). This means that for every 100 women relapsing in the tamoxifen alone group only 87 in the anastrozole group relapsed. Anastrozole also significantly prolonged time to recurrence (HR 0.79, p=0.0005), reduced distant metastases (HR 0.86, p=0.04) and reduced contralateral breast cancers by 42% (p=0.01) compared with tamoxifen.[9]

Because of the short follow-up period it is not possible to make any judgments about the actual prolongation time for either treatment strategy.

The Austrian breast and colorectal study group phase III trial — ABCSG8 — recruited more than 2500 postmenopausal women with oestrogen receptor-positive early breast cancer.[10] Outcomes were compared in patients who were switched to anastrozole after two years of adjuvant treatment with those who continued to take tamoxifen for a further three years. The results from this trial were combined with the Arimidex/Nolvadex (ARNO 95) study, which had the same design[11] giving 1600 patients in each of the two combined arms. After a median follow-up of 28 months there was a statistical advantage in favour of anastrozole for disease free survival and time to recurrence. Event free survival three years after switching was 92.7% (SD 0.81) for the tamoxifen group compared to 95.8% (0.65) for the group switched to anastrozole, corresponding to an absolute benefit of 3.1%. Difference in the incidence of contralateral disease did not reach significance — occurring in 16 patients in the tamoxifen group compared to 12 in the anastrozole group. There was no difference in overall survival.[11]

Exemestane (Aromasin®)

Exemestane is an irreversible, steroidal aromatase inhibitor. In early breast cancer, exemestane is indicated for the adjuvant treatment of postmenopausal women who are oestrogen receptor-positive, following 2–3 years of initial adjuvant tamoxifen therapy (Table 1). The recommended dose is 25mg once daily, preferably taken after a meal. The UK license was supported by data from the intergroup exemestane study (IES).[12] In IES more than 4500 postmenopausal women with oestrogen receptor-positive early breast cancer who had taken tamoxifen for 2–3 years were randomised to either continue taking tamoxifen or to switch to exemestane to complete five years adjuvant hormonal treatment.[12]

After a median of 30.6 months follow-up exemestane significantly prolonged disease-free survival (HR 0.68 p<0.001, ARR 4.7%, NNT 21).[12] Patients in the switching arm were two thirds as likely to relapse compared to the patients who continued to take tamoxifen. Contralateral breast cancer was significantly reduced with nine occurrences in patients in the exemestane group compared to 20 in the tamoxifen group (p=0.04). As found with the anastrozole studies overall survival was not significantly different in the two groups.[12]

Letrozole (Femara®)

Letrozole is a reversible, non-steroidal aromatase inhibitor. It is indicated in early breast cancer for adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer and treatment of early invasive breast cancer in postmenopausal women who have received standard adjuvant tamoxifen therapy — extended adjuvant therapy (Table 1). The recommended dose is 2.5mg daily. These licensed uses are supported by the breast international group (BIG 1-98)[13] and National Cancer Institute of Canada clinical trials group (MA-17)[14] studies.

In the BIG 1-98 study more than 8,000 women were randomised to one of four study arms. These were (a) adjuvant letrozole for 5 years, (b) adjuvant tamoxifen for 5 years, (c) 2 years letrozole followed by 3 years tamoxifen and (d) 2 years tamoxifen followed by 3 years letrozole.[13] This analysis compared the two groups assigned to receive letrozole initially with those assigned to receive tamoxifen initially. Events and follow-up in the sequential treatment groups were included up to the time that treatments were switched.

After a median follow-up of 25.8 months, letrozole significantly reduced the risk of an event ending a period of disease-free survival (HR 0.81 p=0.003, ARR 2.2%, NNT 45) and the time of distant recurrence (HR 0.73 p=0.001, ARR 1.6%, NNT 62). Modelling long-term outcomes on these short-term data gives estimated 5-year disease-free survival of 84.0% for letrozole and 81.4% for tamoxifen. These estimates are consistent with other trials in this setting previously described.

The MA-17 study randomised more than 5100 postmenopausal women with primary breast cancer who had remained disease free after completion of adjuvant treatment with tamoxifen (4.5–6 years) to either letrozole or placebo.[14] At a median follow-up of around 28 months letrozole significantly reduced the risk of recurrence by 42% compared with placebo (HR 0.58 p=0.00003, ARR 2.4%, NNT 42), an absolute reduction of 2.4%.[14] There was no significant difference between treatments in overall survival (HR 0.82, p=0.29).[14]

Toxicities

Adverse events observed in the above studies (Table 2) were consistent with the known side-effect profile for each drug. Patients in the tamoxifen arms were more likely to be at risk for thromboembolic events, vaginal bleeding and endometrial cancer. Generally in the arms involving aromatase inhibitors patients were more at risk for decreased bone density, fractures and musculoskeletal problems. The effects of lowered oestrogen levels, such as hot flushes were experienced by all patient groups.

Summary

The published studies of the aromatase inhibitors in the adjuvant setting, involving approximately 30,000 women worldwide, consistently show an advantage in disease free survival for the aromatase inhibitors over tamoxifen regardless of the treatment strategy employed. Based on these trial results and an economic analysis NICE have issued guidance supporting the use of the aromatase inhibitors in early breast cancer within their licensed (in 2006) indications as discussed above.[7]

Table 2. Adverse effects of aromatase inhibitors[15–17]

Very common (>10%)	Anastrozole	Exemestane	Letrozole
Hot flushes	X	X	X
Insomnia		X	
Arthralgia		X	X
Headache		X	
Nausea		X	
Fatigue		X	
Common (>1% and <10%)			
Fatigue	X		X
Vaginal dryness	X		
Hair thinning	X	X	X
Nausea	X	X	X
Diarrhoea	X	X	X
Headache	X		X
Anorexia		X	X
Depression		X	X
Dizziness		X	X
Rash		X	X
Peripheral oedema		X	X
Arthralgia	X		
Uncommon (>0.1% and <1%)			
Vaginal bleeding	X		X
Vomiting	X		
Hypercholesterolaemia	X		
Anorexia	X		X
Somnolence	X	X	
Rare (<0.1%)/Very rare (<0.01%)			
Allergic reactions	X		
Pulmonary embolism			X

Key: X=effect experienced at the frequency indicated

The difference in study design and treatment strategies makes it impossible to directly compare the studies. Consequently, no one aromatase inhibitor or treatment sequence strategy has been seen as being superior to any other and treatment decisions have to be made on an individual patient basis.

The side-effect profile of each agent differs, but because they all lower oestrogen to negligible levels, a reduction in bone mineral density can be expected. During adjuvant treatment, women with osteoporosis or those who are at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry — DEXA scanning — at the start of treatment. Prophylactic use of calcium and vitamin D or treatment for osteoporosis should be started as appropriate and patients treated with aromatase inhibitors should be carefully monitored. This advice is included in the summary of product characteristics for each of the aromatase inhibitors.[15–17] There is currently no evidence to support the routine use of bisphosphonates in this setting.

The individual treatment strategy should be decided between patients and their practitioners based on the perceived level of risk of recurrence and acceptability of the different side-effect profile of each drug.

Pharmacists can help by advising patients how to handle some of the troublesome side-effects of the aromatase inhibitors — such as increased incidence of arthralgia — which may be linked to the decreased levels of oestrogens. This can be managed with simple analgesics such as paracetamol or non-steroidal anti-inflammatory agents combined with increased low-impact exercise. It is important to ensure that patients understand that this is a recognised effect of hormonal therapy because many fear that increased aches and pains are associated with disease recurrence.

Patients' willingness to comply with the treatment plan is an important issue for consideration. Although it might be thought that patients with cancer are more likely than most to take their medication exactly as instructed there is evidence showing that some patients taking long-term hormonal control therapy for breast cancer can act like many other patients being treated for chronic conditions and take breaks from treatment. One estimate suggests that as much as one year's treatment could be lost from an average five-year course.[18]

Declaration of interests

The author wishes to declare that he undertakes occasional consultancy work involving products manufactured by Astra Zeneca, Pfizer and Novartis.

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