The aromatase inhibitors in early breast cancer: who, when, and why?

Ilona C Nordman, Andrew J Spillane and Anne L Hamilton

ABSTRACT

- The aromatase inhibitors deplete oestrogen by inhibiting aromatase, the enzyme that synthesises oestrogen from androgens. They are effective as therapies for breast cancer only in postmenopausal women whose tumours express oestrogen or progesterone receptors.
- As adjuvant therapy, tamoxifen and the aromatase inhibitors have similar efficacy in the first 5 years of treatment. Aromatase inhibitors can be used as an alternative to tamoxifen in women with symptomatic intolerance or a contraindication to tamoxifen.
- Early data suggest that switching to an aromatase inhibitor after 2–5 years of tamoxifen therapy is beneficial in women with high-risk disease.
- Aromatase inhibitors are associated with more hot flushes than placebo, but with fewer hot flushes, less endometrial toxicity and venous thromboembolism, and more arthralgia, myalgia and bone fracture than tamoxifen.

MJA 2005; 183: 24–27

About 10 000 women are diagnosed with breast cancer in Australia each year.[1] Of these, 40% will be postmenopausal and have tumours that express oestrogen receptors (ER-positive) or progesterone receptors (PR-positive). For these women, the aromatase inhibitors anastrozole, letrozole and exemestane are now challenging the anti-oestrogen drug, tamoxifen, as the hormonal "standard" in breast cancer.

Aromatase is the enzyme that converts androgens to oestrogens. In premenopausal women, this occurs mainly in the ovary and produces high levels of circulating oestrogen, but in postmenopausal women, most oestrogen is synthesised in peripheral tissues, and acts locally.[2] The aromatase inhibitors are all orally active. Anastrozole and letrozole are non-steroidal competitive inhibitors, while exemestane is steroidal, and binds irreversibly. All three agents cause near-complete inhibition of aromatase activity and profoundly deplete oestrogen levels in postmenopausal women within 2–4 days of commencing therapy.[3,4] They are now the leading agents for treating postmenopausal women with ER-positive metastatic breast cancer, since randomised trials have shown advantages over aminoglutethimide, megestrol acetate, and tamoxifen in this setting.[5-8] They are not recommended in premenopausal women, as they are ineffective in inhibiting ovarian oestrogen production.[9]

Anastrozole is now listed on the Schedule of Pharmaceutical Benefits as an alternative to tamoxifen for treating hormone-dependent early breast cancer in postmenopausal women in whom tamoxifen is contraindicated or who are intolerant of tamoxifen. In this update, we review the trials of the aromatase inhibitors in early-stage disease, along with management strategies for common side effects.

The role of tamoxifen in early breast cancer

Tamoxifen is a non-steroidal anti-oestrogenic agent that binds to the oestrogen receptor. Since 1988, when the first overview of randomised trials of the adjuvant use of tamoxifen showed reduced mortality in early breast cancer,[10] tamoxifen has been widely used in the adjuvant setting. A 2000 update of 15 000 women at 15 years' follow-up confirmed a 31% reduction in mortality in women with ER-positive disease who received tamoxifen for 5 years, regardless of menopausal or nodal status, and a 39% reduction in the incidence of contralateral breast cancer.[11] Tamoxifen causes significantly more hot flushes (46% v 29%) and a higher incidence of vaginal discharge (12.4% v 4.5%) than placebo. Less common toxicities include cataracts, endometrial cancer and venous thrombosis and pulmonary embolism. Tamoxifen acts as an oestrogen in bone, and is protective against bone fracture.[12]

Sydney Cancer Centre, Royal Prince Alfred Hospital, Sydney, NSW.
Ilona C Nordman, MB BS, Medical Oncology Registrar;
Andrew J Spillane, BM BS, MD, FRACS, Visiting Medical Officer in Surgery; Anne L Hamilton, MB BS, FRACP, Medical Oncologist; and Senior Lecturer, University of Sydney.
Reprints will not be available from the authors. Correspondence: Dr Anne L Hamilton, Sydney Cancer Centre, Level 6 Gloucester House, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050. anne.hamilton@cs.nsw.gov.au

Aromatase inhibitors as a new option in early breast cancer

Seven trials of aromatase inhibitors in the adjuvant setting have been reported to date (Box 1). All restricted eligibility to postmenopausal women with early breast cancer, and targeted those with ER-positive or PR-positive disease. In all trials, tamoxifen was given at 20 mg/day, anastrozole at 1 mg/day, letrozole at 2.5 mg/day, and exemestane at 25 mg/day.

The ATAC (Arimidex, Tamoxifen Alone or in Combination) trial accrued 9366 women and compared anastrozole therapy with tamoxifen therapy, and with the combination of tamoxifen plus anastrozole over 5 years, employing a double-blind design. Findings were first reported at a median follow-up of 33.3 months and most recently at 68 months. The first analysis showed improved disease-free survival in patients receiving anastrozole, but no difference between combination therapy and tamoxifen alone.[15] Anastrozole maintained an advantage in disease-free survival at the final analysis (81.4% v 79.0%; $P = 0.01$).[16] Importantly, however, the disease-free survival curves do not convincingly separate until the third year of therapy (at which time the absolute difference in disease recurrence is 1.7%), and no significant difference in distant disease-free survival is seen until the 68-month report. No analysis has shown any difference in overall survival between anastrozole and tamoxifen.

BIG 01-98 (Breast International Group) randomly allocated 8028 women to receive tamoxifen for 5 years, letrozole for 5 years,

1 Efficacy of aromatase inhibitors in adjuvant trials

Trial and aromatase inhibitor	Years of tamoxifen therapy	No. of (evaluable) women	Median follow-up (months)	Absolute difference		
				Disease-free survival	Overall survival	Contralateral breast cancer
Aromatase inhibitor versus placebo						
MA-17 (Letrozole)[13,14]	5	5157	30	2.4%*	nr	0.4%
Aromatase inhibitor versus tamoxifen						
ATAC (Anastrozole)[15,16]	0	6186	68	2.4%*	0.3%	0.5%*
BIG 01-98 (Letrozole)[17]	0	8010	26	1.9%*	0.7%	0.3%
ABCSG/ARNO (Anastrozole)[18]	2	3224	28	2.4%*	nr	0.3%*
ITA (Anastrozole)[19]	2	426	24	7.1%*	nr	1.3%
IES (Exemestane)[20]	2–3	4742	31	3.5%*	0.6%	0.4%*

MA-17 = a trial sponsored by the National Cancer Institute of Canada Clinical Trials Group; ATAC = Arimidex, Tamoxifen Alone or in Combination trial; BIG 01-98 = Breast International Group; ABCSG/ARNO = Austrian Breast Cancer Study Group and German Adjuvant Breast Cancer Group trials; ITA = Italian Trial of Anastrozole; IES = International Exemestane Study; nr = not reported. Note: Numbers greater than zero indicate a numerical advantage to aromatase inhibitor. * Difference statistically significant, in favour of aromatase inhibitor.

or alternate sequencing of the two agents. The first analysis, reporting only the letrozole versus tamoxifen results at a median follow-up of 25.8 months, revealed disease-free survival of 91.2% v 89.3%; $P = 0.004$). There was no difference in overall survival.[17]

The ABCSG-8 (Austrian Breast Cancer Study Group) and ARNO-95 (German Adjuvant Breast Cancer Group) trials both assessed a switch to anastrozole after 2 years of adjuvant tamoxifen therapy in women who did not receive chemotherapy. In a combined analysis of 3224 women with a median follow-up of 28 months, recurrence-free survival favoured the switch to anastrozole (95.2% v 92.8%; $P < 0.0018$).[18]

The ITA trial (Italian Trial of Anastrozole) randomly allocated 426 patients with node-positive disease after 2 years of tamoxifen therapy to either continue taking tamoxifen or switch to anastrozole, to a total of 5 years of therapy. At a median follow-up of 24 months, event-free survival favoured anastrozole (95.2% v 88.1%; $P = 0.006$).[19]

The MA-17 trial, coordinated by the National Cancer Institute of Canada Clinical Trials Group, enrolled 5187 women who had completed 4.5–6 years of adjuvant tamoxifen therapy and randomly allocated them to receive either letrozole or placebo, for an additional 5 years. It was first reported at a median follow-up of 26.8 months, and most recently at 2.5 years. The first analysis showed a statistically significant difference in disease-free survival favouring letrozole.[13] At the latest analysis, the advantage in disease-free survival was maintained (96.4% v 94.0%; $P = 0.0004$). The intention-to-treat analysis showed no survival benefit, but a statistically significant survival advantage (relative risk [RR], 61%; $P = 0.04$) has emerged in the node-positive subgroup. The absolute magnitude of this survival benefit has not yet been presented.[14]

The International Exemestane Study (IES) enrolled 4742 women after 2–3 years of adjuvant tamoxifen therapy. Patients were randomly allocated to receive either exemestane or tamoxifen. At a median follow-up of 30.6 months, those receiving exemestane showed a 4.7% absolute benefit in disease-free survival (92.3% v 88.8%; $P = 0.001$). There was no difference in overall survival.[20]

Comparative toxicities of tamoxifen and the aromatase inhibitors

The three aromatase inhibitors have similar toxicity profiles (Box 2). They are associated with higher rates of hot flushes, arthralgia, myalgia, and osteoporosis, and less vaginal bleeding than placebo. Compared with tamoxifen, they are associated with fewer hot flushes, less endometrial toxicity and venous thromboembolism, but more arthralgia, myalgia and bone fracture. The relevance of an excess of non-breast cancer deaths (1.4% v 0.9%) in the letrozole arm of BIG 01-98 is as yet unclear.

2 Toxicity of aromatase inhibitors in adjuvant trials

Trial and aromatase inhibitor	No. of women	Hot flushes	Vaginal discharge/ bleeding	Endometrial cancer	Thromboembolic events	Cardiac/ Vascular events	Arthralgia/ myalgia	Bone fracture/ osteoporosis
Aromatase inhibitor versus placebo								
MA-17 (Letrozole)[13,14]	4299	47% v 41%†	4.3% v 6.0%*	nr	nr	4.1% v 3.6%	33 v 9.5†	5.8 v 4.5†
Aromatase inhibitor versus tamoxifen								
ATAC (Anastrozole)[16]	6186	36% v 41%*	8.9% v 23%*	0.2% v 0.8%*	2.8% v 4.5%*	6.1% v 6.2%	36 v 29†	11 v 7.7†
BIG 01-98 (Letrozole)[17]	8010	34% v 38%	3.3% v 6.6%	0.2% v 0.4%	0.8% v 2.0%*	9.9% v 9.4%	nr	5.8 v 4.1†
IES (Exemestane)[20]	2362	42% v 40%	4.0% v 5.5%	nr	1.0% v 1.9%*	nr	39 v 33†	7.4 v 5.7

MA-17 = a trial sponsored by the National Cancer Institute of Canada Clinical Trials Group; ATAC = Arimidex, Tamoxifen Alone or in Combination trial; BIG 01-98 = Breast International Group; IES = International Exemestane Study; nr = not reported. * Difference statistically significant, in favour of aromatase inhibitor. † Difference statistically significant, in favour of comparator.

Discussion

The ATAC and BIG 01-98 trials support the use of aromatase inhibitors as alternatives to tamoxifen as initial adjuvant hormonal therapy in postmenopausal women with ER-positive breast cancer (Box 3). The Australian Pharmaceutical Benefits Scheme (PBS) currently reimburses anastrozole for such women in whom tamoxifen is contraindicated, or who are intolerant of tamoxifen. Availability of these agents as alternatives to tamoxifen is appropriate, although:

- ATAC and BIG-98 show no advantage of using aromatase inhibitors rather than tamoxifen in the first 2–3 years, and no survival advantage over tamoxifen in the first 5 years of therapy;
- the clinical impact of the long term side effects of the aromatase inhibitors (specifically osteoporosis) are not yet well defined; and
- tamoxifen "priming" before aromatase inhibitors may be important, both in terms of preventing disease recurrence, and protection from osteoporosis.

The ITA, ABCSG/ARNO, MA-17, and IES studies all support switching from tamoxifen to an aromatase inhibitor in the adjuvant setting, although the optimal timing of the switch and duration of therapy are as yet uncertain. Longer follow-up of these studies, subgroup analyses by PR and human epidermal growth factor receptor-2 (HER-2) status, and data from other as yet unreported studies, will allow better modelling of relapse data. BIG 01-98 will give us the first data on the effects of reverse sequencing of tamoxifen and an aromatase inhibitor. The small survival advantage in the MA-17 trial should be discussed with patients with node-positive disease. Although aromatase inhibitors are not yet PBS-listed for use after 5 years of tamoxifen therapy, individuals with positive nodes may elect to purchase the drug.

The use of aromatase inhibitors is not recommended in premenopausal women, but phase II studies have shown efficacy in metastatic disease when used in combination with ovarian suppression by a luteinising hormone releasing hormone (LHRH) agonist.[21] This combination is now being compared in the adjuvant setting to the combination of LHRH agonist and tamoxifen, a commonly prescribed combination in metastatic disease.[22] The evidence for the use of aromatase inhibitors in male patients is even less robust, although case reports have been published.[23]

3 Hormonal therapy of early breast cancer

	Premenopause	Postmenopause
Year 1–5		
HR-positive	Tamoxifen	Tamoxifen or aromatase inhibitor
HR-negative	nil	nil
Year 6–10		
HR-positive/node positive	nil	Consider aromatase inhibitor
HR-positive/node negative	nil	nil
HR-negative	nil	nil

HR = hormone-receptor (oestrogen or progesterone).

Primary care of women on maintenance hormonal therapy for treatment of breast cancer

Current NBCC (National Breast Cancer Centre)/NHMRC recommendations for follow-up after treatment for early breast cancer include 3-monthly clinical review for the first year, 6-monthly review in the second to fifth years, and annual review thereafter. Annual mammography is recommended in all women who have retained one or both breasts after breast cancer.[24] These recommendations remain appropriate in women receiving aromatase inhibitors.

Hot flushes: Up to 50% of women receiving hormonal therapies for breast cancer will describe hot flushes, but placebo-controlled studies show that the hormonal therapy accounts for symptoms in only one in five affected women. Flushes usually reduce in frequency and severity over time, and there is a clear placebo response in clinical trials of therapeutic interventions. Hormone replacement therapy is not recommended in women with hormonally dependent breast cancer, because of its association with an increased risk of breast cancer in current users.[25] The safety of phyto-oestrogens (soy or clover) has not been established in breast cancer survivors. Selective serotonin reuptake inhibitors (SSRI) (eg, paroxetine) reduce the frequency of hot flushes in women taking tamoxifen, but are not recommended as their effect results from a pharmacokinetic interaction between SSRI and tamoxifen metabolites.[26] In general, hot flushes are best managed by layering clothing and bedding. Switching from tamoxifen to an aromatase inhibitor is recommended in highly symptomatic patients, and temporary or permanent discontinuation of hormonal therapy is occasionally required.

Gynaecological symptoms: Vaginal dryness is best managed by non-hormonal interventions. Glycerine or polycarbophil-based lubricant agents are commonly used.[27] Endometrial monitoring does not influence the outcome in women receiving hormonal therapy for breast cancer, and is not recommended. Thickening of the endometrial stripe on ultrasound, because of myometrial or endometrial changes, is a common finding in women taking tamoxifen and does not require further investigation. Women with any abnormal bleeding should be referred to a gynaecologist.[24]

Myalgia and arthralgia: Musculoskeletal pain can be problematic in women receiving aromatase inhibitors, although the mechanism is unknown. If simple analgesics do not control these symptoms, switching back to tamoxifen (if appropriate) may provide relief. Temporary or permanent discontinuation of hormonal therapy is occasionally required.

Osteoporosis and bone fractures: The clinical implications of the bone effects of aromatase inhibitors are not yet established, and no formal guidelines yet address bone density screening for women receiving these agents. The use of aromatase inhibitors is not yet an indication for bone density assessment under Australian Medicare. For women with established osteoporosis and a history of breast cancer, tamoxifen is the preferred hormonal agent, but if aromatase inhibitors are required, routine guidelines for managing osteoporosis should be followed.[28] Non-hormonal bone agents such as calcium, vitamin D and bisphosphonates are preferred in this setting. The use of hormone replacement therapy is not recommended in women with a history of ER-positive breast cancer. Raloxifene, a selective oestrogen receptor modulator with a similar mode of action to tamoxifen, may limit the efficacy of aromatase inhibitors if used in combination, as was seen with tamoxifen in the ATAC trial.

Prevention of venous thromboembolism: The association between tamoxifen and thromboembolic disease is greatest at

times of immobilisation, such as after major surgery or long-haul flights. Although no formal guidelines exist, based on tamoxifen's half-life of about a week, it has been suggested that it be withheld for one month before immobilisation, and recommenced once mobility is restored.[29]

Conclusion

The aromatase inhibitors are an acceptable alternative to tamoxifen in postmenopausal women with ER-positive early breast cancer. While generally well tolerated, the most common toxicities are hot flushes, myalgia and arthralgia, and bone fracture secondary to osteoporosis. Their optimal use in this setting will evolve over the next few years as data from completed clinical trials mature.

Competing interests

AstraZeneca (who make anastrozole) paid for Ilona Nordman to attend a conference as an honorarium for writing this article. AstraZeneca had no role in the content of the article.

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(Received 24 Jan 2005, accepted 3 May 2005) ❑