Time for a change in breast cancer therapy?

David Cameron

Taken together, recent studies make a powerful case for the licensing of aromatase inhibitors in the adjuvant setting, offering an alternative to tamoxifen which has long been the gold standard in breast cancer therapy in the prevention of recurrence.

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The first evidence has now appeared that the improvement in breast cancer recurrence rates can translate into a survival benefit for women with node-positive breast cancer treated with letrozole after tamoxifen (Goss et al, 2004) (*Table 1*).

Aromatase inhibitors (AIs) are established as first-line treatments in advanced metastatic disease, where they have been shown to be superior to, or at least as good as tamoxifen (Bonneterre et al, 2000; Mouridsen et al, 2001; Nabholtz et al, 2000; Paridaens et al, 2004a) (*Table 2*). At present there are limited licences in adjuvant treatment – anastrozole is licensed as an alternative to tamoxifen for the treatment of early breast cancer in postmenopausal women in whom tamoxifen is contraindicated, and letrozole is licensed for pre-operative therapy to facilitate breast surgery for large operable or locally advanced cancers.

TABLE 1.
The benefits of AIs vs tamoxifen in adjuvant breast cancer

	ATAC[1]	MA-17[2]†	IES[3]
Patient numbers	62421	5187	4742
Primary endpoint	DFS	DFS	DFS
Analysis	1st planned	1st interim	2nd interim
Median follow-up	47 months	28 months	31 months
Previous tamoxifen	Nil	4.5–6 years	2.4 years
Total no. events	885	207*	371
Benefit – total recurrences	413 *vs* 472	75 *vs* 132	144 *vs* 227
Benefit – contralateral recur	25 *vs* 40	14 *vs* 26	9 *vs* 20
Hazard ratio	0.86	0.57	0.68
DFS – absolute improvement	2%	6%	4.7%
OS – risk reduction	?	24% (NSS)	12% (NSS)

*Excludes deaths *n*=73 (31 vs 42); †Post 5 years tamoxifen; [1]Buzdar (2002); ATAC trialists' Group (2002); ATAC Trialists' Group (2003); [2]Goss et al (2003a); Goss et al (2003b); Goss et al (2004); [3]Coombes et al (2004). AI = aromatase inhibitor; ATAC = Anastrozole Tamoxifen Alone or in Combination; DFS = disease-free survival; IES = Intergroup Exemestane Study; MA-17 = National Cancer Institute of Canada MA-17 study; NSS = not statistically significant; OS = overall significance

This article will discuss data that suggest that AIs will give postmenopausal women, the largest group of patients with breast cancer, an even better outlook.

EVOLUTION OF ENDOCRINE THERAPY

The breast is clearly an endocrine-sensitive organ, undergoing significant changes in response to hormones during puberty, pregnancy and lactation. A significant proportion of breast cancers retain this endocrine sensitivity, for which the best predictor is the presence of detectable levels of the nuclear protein to which oestrogen binds, the oestrogen receptor (*Figure 1*).

Regression of advanced breast cancer following endocrine deprivation was described over a century ago (Beatson, 1896), with a second publication a few years later reporting that about one third of such cases in premenopausal women responded to surgical oophorectomy (Boyd, 1900). The main advantage of tamoxifen, when introduced around 30 years ago, was that it was much better tolerated than the surgical ablative procedures of hyphophysectomy, adrenalectomy and oophorectomy used to reduce the concentrations of oestrogenic steroids in patients with advanced breast cancer. The option of a daily tablet simplified endocrine treatment and made it more widely available. Endocrine-dependent breast cancer cells need oestrogen to proliferate and most endocrine therapies either block the hormone binding to the receptor or reduce serum and tumour concentrations of oestradiol.

At least a third of all breast cancers are oestrogen dependent and will regress with oestrogen deprivation (Miller, 1989). Over the past three decades tamoxifen has been the most widely used endocrine drug for the management of all stages of hormone-dependent breast cancer (Buzdar and Howell, 2001). It has been used irrespective of

menopausal status, and until recently was the standard first-line therapy for postmenopausal women with advanced breast cancer. Given for 5 years after potentially curative local treatment, it reduces the risk of recurrence by nearly a half (Early Breast Cancer Trialists' Collaborative Group, 1998), and clearly improves overall survival.

After the menopause, oestrogen production from the ovaries declines and takes place mainly in the peripheral tissues where aromatase catalyses the conversion of androgens to oestrogens (Buzdar, 1999). With the recognition that significant levels of aromatase activity were taking place outside the adrenal gland as well as in the tumour itself, the surgical approach to aromatase inhibition, adrenalectomy, although effective, was seen as inferior to the possibility of pharmacological inhibition (Roseman et al, 1997).

The first AI available for hormone-positive advanced breast cancer in postmenopausal women was aminoglutethimide, which was licensed in the 1980s. However, significant side effects with the standard dose of 1000 mg a day limited its use (Brodie and Njar, 1998). Second generation compounds, like formestane and fadrozole, were less toxic but their efficacy was not superior. The introduction of the third generation AIs letrozole and anastrozole as well as the so-called aromatase inactivator, exemestane, represented a step forward in the endocrine treatment of postmenopausal breast cancer (Lonning, 2001).

THREE HIGHLY POTENT AGENTS

There are currently three drugs that act on the aromatase enzyme: letrozole, anastrozole and exemestane. While aminoglutethimide and other second-generation compounds reduced oestrogen synthesis by 85–90%, these compounds effectively inhibit oestrogen synthesis by 97–99% (Brodie and Njar, 1998), often reducing circulating levels below the limit of detection by standard assays.

FIRST-LINE FOR ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN

All three of these potent AIs have been confirmed to be superior to the therapies previously used when tamoxifen had failed. They have all been directly compared with tamoxifen and are now challenging the superiority of this most widely prescribed anti-cancer agent (*Table 2*).

A study of over 900 women compared letrozole with tamoxifen (Mouridsen et al, 2001) as first-line therapy in postmenopausal women with metastatic breast cancer. In patients taking letrozole, time to disease progression was 41 weeks, compared to 26 weeks with tamoxifen. The AI was also superior in terms of time to treatment failure – 40 weeks compared to 25 weeks. Following the results of this study, the US and UK licensing authorities approved letrozole as a first-line treatment for metastatic breast cancer in January 2001.

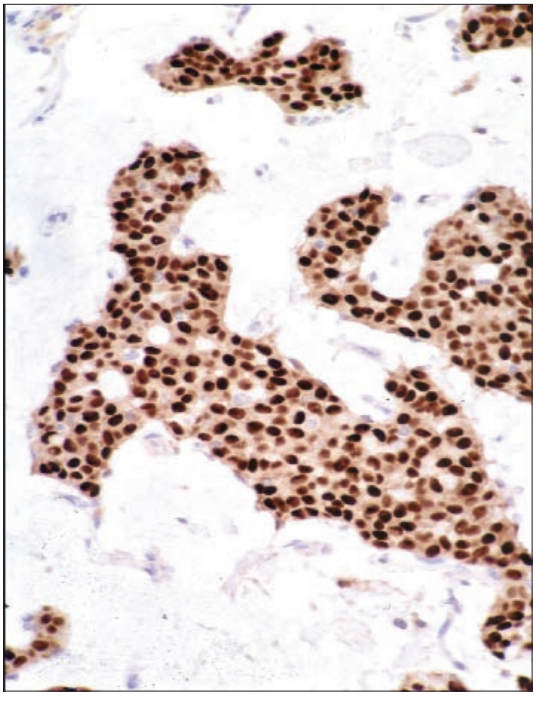

Figure 1. Oestrogen receptor positive (ER+) breast cancer.

A similar study involving anastrozole showed equivalence with tamoxifen in terms of efficacy as first-line therapy, but significant superiority for the AI in terms of thromboembolic events and vaginal bleeding (Bonneterre et al, 2000). A second, smaller study comparing the efficacy and tolerability of anastrozole *vs* tamoxifen as a first-line therapy in advanced breast cancer generated even more positive results for the AI, particularly as a higher proportion of patients were known to be oestrogen receptor positive (Nabholtz et al, 2000). The first phase III study comparing first-line treatment with the aromatase inactivator exemestane to tamoxifen in metastatic breast cancer was presented at the 4th European Breast

TABLE 2.
The benefits of AIs vs tamoxifen in advanced disease (first-line treatment of metastatic disease)

	Anastrozole 1mg*	Anastrozole 1mg*	Letrozole 2.5mg†	Exemestane 25mg‡
Patients (number)	353	668	907	382
Overall response rate (%)	21 *vs* 17	32.9 *vs* 32.6	30 *vs* 20 (*P*=0.0001)	44.2 *vs* 29.2
Clinical benefit (%)	59 *vs* 46 (*P*=0.0098)	56.2 *vs* 55.5	49 *vs* 38 (*P*=0.001)	
Time to progression (months)	11.1 *vs* 5.6 (*P*=0.005)	8.2 *vs* 8.3	9.4 *vs* 6 (*P*=0.0001)	10.9 *vs* 6.7
Time to failure (months)	7.6 *vs* 5.4	6.2 *vs* 6.0		

*Bonneterre et al (2000); †Mouridsen et al (2001); ‡Paridaens et al (2004a).
AI = aromatase inhibitor

Cancer Conference held in Hamburg in March 2004. The trial in 382 patients confirmed superiority for the aromatase inhibitor, compared with tamoxifen, with the medium progression-free survival for patients taking exemestane being 10.9 months compared with only 6.7 months for those taking tamoxifen (Paridaens et al, 2004b).

NEW HOPE FOR SUCCESSFUL BREAST-PRESERVING SURGERY

Tamoxifen has sometimes also been used to shrink tumours in women who are not eligible for breast-conserving surgery, and the potential for AIs to do this better has been explored.

Three hundred and twenty-four postmenopausal women with large, but non-metastatic tumours were given letrozole or tamoxifen for 4 months before surgery (Eiermann et al, 2001). Significantly more women taking letrozole went on to undergo breast-conserving surgery compared with tamoxifen (45% *vs* 25%). Following the adjustment for tumour size, nodal involvement and age, the number of planned mastectomies in the group was halved (Eiermann et al, 2001).

Subgroup analysis produced interesting data in the small group of tumours that depend on other pathways for growth. Tumours with high levels of the growth factor receptors epidermal growth factor receptor (EGFR) and Her-2/neu have a worse prognosis, and are probably less sensitive to tamoxifen. In the study of preoperative letrozole and tamoxifen, it was noted that 88% of patients in this subgroup (EGFR and/or HER-2/neu positive) responded to letrozole, compared to just 21% of those treated with tamoxifen (Ellis et al, 2001).

TABLE 3.
Adjuvant aromatase inhibitor trials

Trial	Arms of trial
ATAC	Tamoxifen 5 years
	Tamoxifen and anastrozole 5 years
	Anastrozole 5 years
ARNO	Tamoxifen 5 years
	Tamoxifen 2–2.5 years then anastrozole 3 years
MA-17	Tamoxifen 5 years then placebo 5 years
	Tamoxifen 5 years then letrozole 5 years
BIG 1.98	Tamoxifen 5 years
	Letrozole 5 years
	Letrozole 2.5 years then tamoxifen 3 years
	Tamoxifen 2.5 years then letrozole 3 years
ICCG study 96	Tamoxifen 5 years
	Tamoxifen 2–3 years then exemestane rest of 5-year period
NSABP B33	Tamoxifen 5 years then placebo 5 years
	Tamoxifen 5 years then exemestane 5 years
Team EXE	Tamoxifen 5 years
	Exemestane 5 years
EXEM 027	Exemestane 2 years
	Placebo 2 years

ARNO = Arimidex-Nolvadex, Jakesz et al (2004); ATAC = Arimidex Tamoxifen Alone or in Combination, ATAC Trialists' Group (2002, 2003); BIG 1-98 = Breast Inter-Group 1-98, results not yet presented; EXEM 027 = 2 year exemestane vs placebo trial, Geisler et al (2004); ICCG Study 96 = International Cancer Collaboration Group (ICCG) Study 96, Coombes et al (2004); MA-17 = National Institute of Canada MA-17 Study, Goss et al (2003b); NSABP B33 = National Surgical Adjuvant Breast and Bowel Project, no longer happening; TEAM EXE = Team Exemestane, results not yet presented.

ADJUVANT THERAPY WITH AIS

Following demonstration of its efficacy in advanced breast cancer, a series of trials has convincingly shown that up to 5 years of tamoxifen in women who have had potentially curative surgery for early breast cancer significantly reduces mortality from breast cancer. However, not all women benefit, and tamoxifen has been associated with an increased risk of both thromboembolic events and endometrial cancer (Miller, 1989). Nonetheless, 5 years of tamoxifen has become a standard of care, but the advantages of AIs in advanced disease have led to a number of trials challenging this gold standard of 5 years' tamoxifen for early breast cancer (*Table 3*).

The ATAC study (Arimidex or Tamoxifen alone or in Combination) randomized 9300 postmenopausal women with early stage breast cancer to treatment with anastrozole, tamoxifen or a combination of both. At 33 months the absolute difference in disease-free survival between those treated with the AI as opposed to tamoxifen was 1.5%, while at 47 months the absolute difference was 2.4% (ATAC Trialists' Group, 2002, 2003) with no benefits for giving the combination. The authors predict that differences in efficacy are likely to continue with further follow up. Both letrozole and exemestane have also been compared with 5 years of tamoxifen, in the Femara-Tamoxifen Breast International Group (BIG FEMTA or BIG1-98) and Tamoxifen and Exemestane Adjuvant Multi-centre (TEAM) trials respectively. The data are not yet ready for reporting, but are expected in the next few years.

EXTENDED ADJUVANT THERAPY WITH AIS

The development of resistance to tamoxifen is a significant problem in patients with breast cancer, such that many patients with advanced breast cancer will receive AIs after tamoxifen. This concept has also been tested in the adjuvant setting, and recently two trials have reported that the use of tamoxifen followed by an AI is superior to 5 years of single agent tamoxifen.

While data show that the postoperative administration of tamoxifen for 5 years reduces the risk of

recurrence by 47% and the risk of death by 26% (Fisher et al, 1989; Early Breast Cancer Trialists' Collaborative Group, 1998), a trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP) found that women who continued to use tamoxifen beyond 5 years had worse outcomes than those who had discontinued use at 5 years (Fisher et al, 1996, 2001). These results led the National Cancer Institute (1995) to recommend that outside clinical trials tamoxifen treatment should be limited to 5 years. However, approximately one-third of women with oestrogen receptor-positive breast cancer experience a recurrence and over half of these recurrences occur more than 5 years after surgery, leaving many women feeling vulnerable as they are no longer pharmacologically protected against recurrence once their tamoxifen ceases (Early Breast Cancer Trialists' Collaborative Group, 1998).

The National Cancer Institute of Canada MA-17 trial suggests that letrozole may have an important role to play in providing further protection for these women (Goss et al, 2003a, 2003b, 2004). In this pivotal phase III study, 5187 postmenopausal women with primary breast cancer, who had already completed approximately 5 years of adjuvant tamoxifen, were randomized to receive letrozole (2.5 mg) or placebo orally daily for 5 years.

The latest analysis presented at the 40th American Society of Clinical Oncology meeting in June 2004 revealed a 39% decrease in mortality for node-positive women randomized to letrozole compared to those receiving placebo at a median follow up of 2.5 years (Goss et al, 2004). This was statistically significant at the P=0.035 level and of particular note as these were the first data to show survival advantages for any AI outside the metastatic setting.

There was a also significant (P=0.002) 40% reduction in the rate of distant metastases in women receiving letrozole compared to those receiving tamoxifen, irrespective of nodal status. As node-positive women have a greater risk of dying from breast cancer earlier in the course of their disease, it is anticipated that in time, when there have been more events among node-negative women, that a survival advantage will become apparent for women without involved axillary nodes given letrozole after 5 years' tamoxifen.

That these gains are achieved without significant added toxicity was confirmed in data reported from the MA-17 trial at the 26th San Antonio Breast Cancer Symposium (Goss et al, 2003a). The data reviewed eight quality of life domains – physical health, role function, bodily pain, general health, vitality, social function, role function and mental health – in 3582 women. Investigators found deterioration in scores with time comparable between women taking letrozole and placebo in five domains, and only marginally worse for women taking letrozole in bodily pain, general health and vitality.

However, up to 10 years of adjuvant therapy is a long time for women to be taking medication, particularly while the long-term bone and other organ toxicities remains unclear. Furthermore, because of the significant advantage seen for the women given letrozole, almost all the patients in the study who originally received the placebo have now been given letrozole, so that the actual advantage of a full 5 years' treatment with letrozole after tamoxifen cannot be assessed from this group. Therefore the Intergroup Exemestane Study (IES) 031 trial (Coombes et al, 2004) was designed, in which 4742 women were randomized to switch to exemestane after around 2.5 years of tamoxifen or to continue to the full standard of 5 years of tamoxifen. The study showed that women switching to exemestane reduced their risk of breast cancer recurrence by 32% as compared to those continuing to take tamoxifen. Similar results were obtained in the much smaller Italian Tamoxifen Arimidex (ITA) study, which showed in 448 patients that those randomized to anastrozole after 2–3 years had 64% fewer relapses than those staying on tamoxifen for the full 5 years (Boccardo et al, 2003).

It is hoped BIG 1-98, expected to report in early 2005, will provide answers to the unresolved question of whether it is better to start upfront with an AI or switch from tamoxifen half way through. More than 8000 women have been enrolled in this phase III adjuvant trial which compares four treatment arms: 5 years of letrozole, 5 years of tamoxifen, 2 years of letrozole, followed by 3 years of tamoxifen and 2 years of tamoxifen followed by 3 years of letrozole.

Thus, we now have three studies demonstrating that 5 years of tamoxifen is less good for disease control than AIs or aromatase inactivators being used either instead of or in sequence with tamoxifen, and for the first time a study shows that one of these AIs (letrozole) produces benefits translating into increased survival for women with early breast cancer. It is hoped that survival advantages will soon follow for women with node-negative disease and the other AIs.

POSSIBILITY FOR PREVENTION

Given that elevated plasma oestrogen concentrations are a risk factor for breast cancer, AIs might also have a role to play in preventing breast cancer occurring in some postmenopausal

women. A further finding of the MA-17 trial, of a reduction in the frequency of new primary tumours in the contralateral breast of 46% in those taking letrozole (Goss et al, 2003b), adds weight to the use of AIs in prevention.

The International Breast Cancer Intervention Study (IBIS II), which started recruitment in October 2003, is a 10-year study designed to test the benefit of taking anastrozole in order to reduce the risk of developing breast cancer in healthy women considered at high risk. It follows the earlier IBIS I trial where 7152 women considered at increased risk of breast cancer were randomized to receive tamoxifen 20 mg/day or placebo for 5 years. This study found that while tamoxifen reduced the risk of breast cancer by 32%, similar to the benefit seen in the US NSABP P-1 prevention trial, there was an excess of thromboembolic events and deaths in the tamoxifen group that were considered unacceptable (IBIS Investigators, 2002). However, it is hoped that IBIS II will show that using AIs in place of tamoxifen can lower the risk of breast cancer further with a more acceptable level of side effects.

DO AIS DIFFER IN EFFICACY?

Clinical data suggest that the two non-steroidal AIs, letrozole and anastrozole, have similar efficacy (Bonneterre et al, 2000; Mouridsen et al, 2001). However, data are emerging to show there may be differences between the two, at least in terms of aromatase activity and side effects.

A study published in 2002 looked at how effective each therapy was at suppressing oestrogen levels in 12 postmenopausal women with advanced breast cancer (Geisler et al, 2002). Results showed that letrozole was a more powerful inhibitor of the body's capacity to produce oestrogen, with plasma oestrogen levels significantly lower than when patients were treated with anastrozole. However, the extent to which these biochemical differences impact on clinical efficacy is unclear.

More useful information for the practising clinician is provided in a UK patient preference study. The single blind study looked at 72 women with hormone-positive postmenopausal breast cancer. Half of the women were started on letrozole and the other half on anastrozole, for a 1-month period. The following month, treatments were changed over between the groups, and continued for a further month. Following completion of the trial, women were asked which treatment they would prefer to carry on with. Over twice as many women chose to take letrozole over anastrozole, 68% compared to 32% (Thomas et al, 2002). Significant differences were found between the two drugs in terms of lethargy, headache, joint pains, abdominal discomfort, nausea and poor appetite. Perhaps as interesting for clinicians involved in designing oncology trials, 92% of women welcomed the chance to choose which treatment to carry on with after an initial trial of both.

CHALLENGES FOR THE FUTURE

Experience with tamoxifen has shown it confers significant benefits in terms of recurrence and overall survival when used as an adjuvant therapy, and therefore it is in this same setting that one might expect to see the most important role for the AIs. Further results from trials using these new therapies in the adjuvant setting, both as monotherapy and in combination or sequential regimens, are eagerly awaited.

The lack of cross-resistance between tamoxifen and AIs in advanced disease means that sequential therapies offer a real possibility. The hope that more women with hormone-receptor positive tumours could be made eligible for breast-conserving surgery has already been suggested by studies with letrozole.

One issue remaining is whether oestrogen deficiency resulting from the use of AIs might be associated with menopausal osteoporosis and whether anastrozole and letrozole increase bone resorption. Data from the ATAC study suggest more fractures occurred in women in the anastrozole group as opposed to tamoxifen: 5.9% *vs* 3.7% respectively, $P<0.0001$ (ATAC Trialists' Group, 2002, 2003). The Zometa-Femara Adjuvant Synergy Trial (Z0-fast in Europe and Z-fast in the US) is currently underway to assess whether bone loss can be reduced by the addition of a bisphosphonate. In the study, 500 patients in Europe and 900 in the US are being treated for up to 5 years with letrozole and randomized to one of two bisphosphonate arms, receiving either an upfront infusion of zoledronic acid every 6 months from day one or delayed infusions. If differences in bone mineral loss are found, this may lead to a treatment paradigm where cancer therapy and bone loss prevention are provided together.

Finally, research showing that receptor status, beyond simple oestrogen receptor positive or negative status, is important opens up the possibility that anti-tumour regimens could be effectively tailored for maximum impact on the disease. HM

Conflict of interest: Dr Cameron has attended scientific conferences and presented at lectures for various pharmaceutical companies including AstraZeneca, Novartis Oncology, Pfizer and Roche.

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KEY POINTS

- There are currently three licensed drugs that act on the aromatase enzyme: letrozole, anastrozole and exemestane.
- Aromatase inhibitors (AIs) are already established as first-line treatments in advanced metastatic disease, when they have been shown to be superior to, or at least as good as, tamoxifen.
- Five years of adjuvant tamoxifen has become a standard of care but the advantages for AIs in advanced disease have led to a number of trials challenging this gold standard of 5 years' tamoxifen for early breast cancer.
- Approximately one third of women with oestrogen receptor-positive breast cancer experience a recurrence and over half of these recurrences occur more than 5 years after potentially curative surgery.
- The National Cancer Institute of Canada MA-17 trial has revealed that taking letrozole after 5 years of tamoxifen gives a 39% decrease in mortality for node-positive women, a 40% reduction in the rate of distant metastases and a 43% reduction in distant and local relapse, as well as the incidence of new tumours, for node-positive and node-negative patients. This suggests that letrozole may have an important role to play in providing further protection for these women.
- Breast Inter-Group 1-98 (BIG 1-98) results, expected in early 2005, will provide answers to the question whether it is best to start up front with an AI or switch from tamoxifen half way through 5 years of adjuvant treatment.
- For the first time there is a study to show that one of the AIs (letrozole) produces benefits translating into long-term survival advantages.