ABC of breast diseases

Medical treatment of early breast cancer. II: endocrine therapy

Ian E Smith, Susan Chua

Choice of adjuvant treatment depends on risk of relapse, potential benefits of different treatments, oestrogen receptor status, age of the patient, and acceptability of treatment to the patient. The risk of relapse relates to known prognostic factors, and these can be used to define risk groups. Age and menopausal status are important factors that influence the choice of adjuvant treatment.

Endocrine treatment

Until recently tamoxifen was the most commonly used hormonal agent in the adjuvant setting in premenopausal and postmenopausal women. A major development in adjuvant treatment for early breast cancer in postmenopausal women has been the emergence of the so called third generation aromatase inhibitors (anastrozole, letrozole, and exemestane), with increasing evidence of their superiority to tamoxifen.

These drugs act by blocking the synthesis of oestrogen (which is mediated through the aromatase enzyme), in contrast to tamoxifen (which is an oestrogen receptor antagonist). Their efficacy has been established in postmenopausal women only. Anastrozole achieved a small but important disease free survival benefit (3.3% improvement at six years with a hazard ratio of 0.83 (95% confidence interval 0.73 to 0.94) in the hormone receptor positive group compared with tamoxifen or the combination in the large ATAC (Arimidex, tamoxifen, alone or in combination) trial. Patients treated with anastrozole also had a small but significant reduction (0.86, 0.74 to 0.99) in distant disease free survival, but the latest analysis at 68 months showed no overall survival difference. Data from the Breast International Group 1-98 (BIG 1-98) study compared letrozole with tamoxifen in 8028 women with a median follow-up period of 25.8 months, and showed that patients who received immediate treatment with letrozole rather than tamoxifen had an improved disease free survival (0.81, 0.70 to 0.93, $P=0.003$), a better breast cancer relapse rate (absolute benefit 3.4% at five years, $P=0.0002$), and a significant improvement in time to development of metastases (hazard ratio 0.73).

These results are similar to those with anastrozole. Letrozole is a more potent inhibitor of oestrogen synthesis than anastrozole, and results from these adjuvant trials are consistent with letrozole having a similar clinical efficacy to anastrozole. A problem identified in the BIG 1-98 study was a small, non-significant increase in the number of non-breast cancer deaths from stroke (7 *v* 1) and cardiac death (26 *v* 13) in women who had received letrozole. As tamoxifen reduces cholesterol levels and may reduce death rates from myocardial infarction, any excess of deaths with letrozole could be the result of a reduction in events with tamoxifen. In the ATAC and BIG 1-98 studies, women who had received anastrozole or letrozole had more fractures, fewer thromboembolic events, fewer endometrial cancers, and fewer other gynaecological problems.

The sequential use of exemestane treatment after two or three years of tamoxifen for the remainder of the five years showed a significant improvement over standard five years tamoxifen alone, with a reduction in events (0.68, 0.56 to 0.82), and an absolute disease free survival benefit of 4.7% at three

This article is adapted from the 3rd edition of the ABC of Breast Diseases (Blackwell Publishing), available from all good medical bookshops, including www.hammicksbma.com

Disease free survival in women with oestrogen receptor positive in the study of adjuvant anastrozole, tamoxifen, or the combination (ATAC). Curves are truncated at 42 months. Adapted from *Lancet* 2002;359: 2131-9

Updated analysis (December 2004): probability of recurrence in hormone receptor positive (HR+) population in the ATAC study. Numbers indicate number of events in hormone receptor positive population and intention to treat (ITT) analysis. Adapted from Howell A, on behalf of ATAC trialists' group *Lancet* 2005;365:60-2

Toxicity profile update of ATAC study. Adapted from Howell A, on behalf of ATAC trialists' group, Annual San Antonio Breast Cancer Symposium 2004

years. A small but non-significant (at the predefined level of significance) excess of myocardial infarcts in the exemestane group raised concerns about the relative effects of tamoxifen and aromatase inhibitors on the cardiovascular system. None the less, there were fewer deaths in women who switched to exemestane, although this difference in favour of exemestane does not yet reach statistical significance ($P=0.08$). Combined results of two trials—the ABCSG 8 (Austrian breast and colorectal cancer study group 8) trial and the German Adjuvant Breast Cancer Group's ARNO 95 (Arimidex-Novaldex (tamoxifen) 95 trial)—have shown that a switch to anastrozole after two years of tamoxifen therapy also improves event free survival (0.60, 0.44 to 0.81).

The ATAC study indicated that anastrozole showed greater benefit than tamoxifen in women who had not received prior adjuvant chemotherapy; other studies have not shown this. Indeed, the BIG 1-98 trial showed the main benefit was in women who had received adjuvant chemotherapy. The ATAC study also indicated greater benefit for anastrozole in tumours that were oestrogen receptor positive but progesterone receptor negative; results from other studies have not shown a greater advantage for aromatase inhibitors in this group of women.

The Canadian led MA17 trial showed letrozole further decreased the risk of cancer recurrence compared with placebo when given as extended adjuvant treatment to women who remain in remission after five years of tamoxifen, with a predicted absolute gain of 6% four years after randomisation. Benefit was seen in women with node positive and node negative tumours. In the final updated analysis, the hazard ratios for disease free, distant disease free, and overall survival in node negative patients are 0.45 (95% CI 0.27 to 0.75), 0.63 (0.31 to 1.27), and 1.52 (0.76 to 3.06) respectively. In node positive patients the hazard ratios are 0.61 (0.45 to 0.84), 0.53 (0.36 to 0.78), and 0.61 (0.38 to 0.98), respectively. The significant survival advantage in node positive patients indicates that letrozole, after five years of tamoxifen in oestrogen receptor positive postmenopausal patients, will become standard of care for all but very low risk women. A further randomisation in this trial after 10 years of adjuvant therapy will compare a further five years of letrozole and placebo.

The MA17 trial has reminded doctors that as many breast cancer recurrences develop 5-15 years after diagnosis and

Event free survival from the ABCSG trial 8 and the ARNO 95 study in which patients were randomised to continue tamoxifen or switch to anastrozole after two or three years of tamoxifen. Adapted from Coombes R, et al. Annual San Antonio Breast Cancer Symposium 2004;88:S1

Overall survival in breast cancer patients receiving adjuvant letrozole and placebo after five years of tamoxifen (median follow up 2.5 years) in the National Institute of Canada clinical trials group's MA17 study. Adapted from Goss P, et al. *J Natl Cancer Inst* 2005;97:1262-71

Adjuvant breast cancer trials with aromatase inhibitors

	No of patients	Follow up (months)	Median age (years)	Node positive (%)	Hormone receptor positive (%)	Chemotherapy given	Hazard ratio	
							Disease free survival	Survival
ATAC immediately after operation*	6241	68	64	34	84	21	0.83†	0.96
BIG 1-98 immediately after operation‡	8028	26	61	41	99.8	25	0.81†	0.86
IES (international exemestane study) after 2-3 years of tamoxifen§	4742	37.4	64	50	84.5	32	0.73†	0.83
ABCSG 8 and ARNO after two years of tamoxifen¶	3123	26	63	27	100	0	0.6†	0.76
MA17 after five years of tamoxifen**	5187	30	62	46	100	46	0.58†	1.52 node negative 0.61† node positive

*ATAC compared five years of tamoxifen with five years of anastrozole

†Indicates statistically significant difference over tamoxifen or placebo, $P<0.05$

‡BIG 1-98 compared immediate letrozole with immediate tamoxifen

§IES compared switching to exemestane with continuing tamoxifen after 2-3 years of tamoxifen

¶ABCSG 8 and ARNO 95 compared switching anastrozole with continuing tamoxifen after two years of tamoxifen

**MA17 compared five years of letrozole with no therapy after completion of five years of tamoxifen

treatment as in the first five years, and the trial showed that five years of adjuvant hormonal therapy with tamoxifen is unlikely to be optimal. So far, the NSABP B14 (national surgical adjuvant breast and bowel project B14) trial has failed to show any further benefit in extending tamoxifen use after five years and has shown a small detriment with this approach. Two large trials—ATTOM (adjuvant tamoxifen treatment after more) and ATLAS (adjuvant tamoxifen longer against shorter)—investigating the use tamoxifen beyond five years continue, and should provide insight into the optimum duration of this drug.

Ongoing trials

One of the most important of the adjuvant aromatase inhibitor trials is the BIG 1-98 trial, which compared five years of tamoxifen or letrozole alone with sequential therapy of either two years' tamoxifen followed by three years' letrozole or two years' letrozole followed by three years of tamoxifen. The TEAM (tamoxifen and exemestane adjuvant multi-centre) trial is also investigating the question of whether first line treatment with aromatase inhibitors, in this case exemestane, is better than tamoxifen for two years followed by exemestane. A Canadian study will compare the steroidal aromatase inhibitor exemestane with the non-steroidal drug anastrozole. Finally, the important question of what the optimum duration of treatment with aromatase inhibitors should be needs to be looked at.

All trials of adjuvant aromatase inhibitor showed a reduction in the rate of contralateral breast cancers, and a reduction in new breast cancers in the treated but conserved breast. These observations have led to studies of the use of aromatase inhibitors in preventing breast cancer development in high risk postmenopausal women.

In premenopausal women, treatment options include tamoxifen alone or tamoxifen combined with ovarian ablation, most commonly using a gonadotrophin releasing hormone analogue, such as goserelin. The addition of tamoxifen to goserelin in younger premenopausal women seems to improve survival in women with oestrogen receptor positive disease. What is not yet clear is the optimal duration of ovarian suppression and whether benefit is gained from adding goserelin to tamoxifen.

Further reading

- Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of randomised trials. *Lancet* 2005;365:1687-717
- ATAC Trialists Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131-9
- Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two or three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;350:1081-92
- Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349:1793-802
- Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003;348:2431-42
- Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005;353:2747-57

Ian Smith is professor of cancer medicine, Royal Marsden Hospital, London, and Susan Chua is a medical oncologist, Melbourne, Australia.

The ABC of Breast diseases is edited by J Michael Dixon, consultant surgeon and senior lecturer in surgery, Edinburgh Breast Unit, Western General Hospital, Edinburgh.

Competing interests: Michael Dixon has received reimbursement for attending symposiums, fees for speaking, and educational grants from AstraZeneca, Novartis, and Pfizer. Ian Smith has received honoraria for lecturing, research grants, and fees for attending advisory boards from several companies involved in drugs for early breast cancer, including Novartis, AstraZeneca, Aventis, Pfizer, Eli Lilly, GlaxoSmithKline, and Roche

BMJ 2006;332:101-3

An unexpected response

A recent *BMJ* article exploring the reasons for doctors to consider leaving UK medicine reminded me of a lunchtime conversation in an Edinburgh hospital cafeteria several decades ago. In 1981 my wife, then a senior medical student, and I were on a month-long study leave from our work at McGill University.

At lunch one day with various house officers, senior registrars, and junior faculty, the conversation drifted on to the subject of what we would all do "when we grew up." The fellow from China wanted to return home and had come to the UK to see, among other things, "an imperialistic civilisation in decay." Another chap, born closer to Bow Bells, wanted to go to America, and a Scottish registrar intended to move to Australia. I was fascinated by the fact that virtually all of our dozen lunch mates were planning to leave the Sceptred Isle at the end of their studies.

Asked where we were "off to," my wife and I explained that we were planning to go back to Canada and then in a few years emigrate to Israel (which is what we did).

"Oooh, isn't it dangerous there?" one of our companions asked, obviously concerned for our safety—even in those days of sporadic violence. No, we explained, while bombs and war were real concerns in Israel, the likelihood of a particular individual being hurt was actually quite small.

One fellow, a taciturn junior house officer who had not yet joined in the fray, turned to me and said, "Actually, I agree with you. Individual or even mass terrorism is not the real danger."

"And what is?" we asked, intrigued by the sudden shift in the conversation.

"Nuclear war," he dolefully explained. "As soon as this job is over next month, my wife and I and our two small children are leaving the UK for good. We have made a careful study of the places in the world where a thermonuclear war is least likely to occur and, with the prevailing winds and tides, are most likely to be safe from fallout. This is the spot where humankind may just survive the coming conflagration."

All of us around the table were intrigued by his approach and interested in learning where this safe haven was.

"A few small islands about 400 km off the coast of South America," he offered. Asked to be more specific, he told us where he and his family were off to—a lovely and isolated spot not many of us had yet heard of, the Falkland Islands.

A Mark Clarfield *head of geriatrics, Soroka Hospital, Ben Gurion University of the Negev, Beer-Sheva, Israel (markclar@bgu.ac.il)*