Use of aromatase inhibitors in the adjuvant treatment of breast cancer

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Abstract
The value of endocrine treatment of early breast cancer has been illustrated by the antioestrogen, tamoxifen, which has now been available for nearly 30 years. However, if the recognised side effects and pharmacological properties of tamoxifen are taken into consideration, it is possible that other endocrine treatments that are now available can provide equal or superior efficacy, along with improved tolerability. One such group of agents is the aromatase inhibitors specifically the new-generation triazole aromatase inhibitors, such as anastrozole and letrozole, which have both shown tolerability and efficacy advantages over standard treatments in postmenopausal women with advanced breast cancer. There are convincing reasons why the new generation of aromatase inhibitors have advantages over tamoxifen. For instance, from their agonist properties, the effects on the endometrium and tumour stimulation seen with tamoxifen would not be expected, nor would the visual disturbances that have been associated with the triphenylethylene compounds, including tamoxifen. A number of aromatase inhibitors, for instance, anastrozole, letrozole and exemestane, are currently being investigated for treatment of early breast cancer. The results of the trials of aromatase inhibitors and tamoxifen will, in the next few years, define whether or not the new-generation aromatase inhibitors have a role to play in the treatment of postmenopausal women with early breast cancer.

Introduction
The value of endocrine treatment of early breast cancer has been illustrated by the antioestrogen, tamoxifen, which has now been available for nearly 30 years. Consequently, there is a wealth of clinical experience of the use of tamoxifen for both early and advanced breast disease. The most convincing evidence to date on the effectiveness of this drug for the adjuvant treatment of early breast cancer comes from the recently published meta-analysis of breast cancer trials conducted by the Early Breast Cancer Trialists’ Collaborative Group (1998). Based on an overview of 37,000 women in 55 randomised controlled trials, it was shown that 5 years of adjuvant treatment with tamoxifen significantly reduced the recurrence rate and mortality rate in women with estrogen receptor (ER)-positive and ER-unknown tumours, a benefit that was largely irrespective of age and menopausal status.

However, when the recognised side effects and pharmacological properties of tamoxifen are taken into consideration, it is appropriate to speculate whether other endocrine treatments that are now available may provide equal or superior efficacy, along with improved tolerability. The good tolerability of tamoxifen is well recognised, with a rare incidence of serious adverse events and a treatment withdrawal rate of less than 5% (Jaiyesimi et al. 1995). It is now known that tamoxifen cannot be considered as a simple antioestrogen; indeed, the partial agonist effects of the drug are thought to be related to some of its originally unforeseen benefits, in addition to some potentially adverse events. There is evidence that tamoxifen reduces serum cholesterol and may reduce the incidence of ischaemic heart disease (Dewar et al. 1992, Love et al. 1992), and, in addition, it protects against bone mineral loss in postmenopausal women (Love et al. 1994, Powles et al. 1995). It is the same agonist properties that provide the beneficial effect that, in part, limit its usefulness as an antioestrogen. Tamoxifen has been associated with an increased risk of endometrial cancer (Early Breast Cancer Trialists’ Collaborative Group 1998), and, based on in vivo experiments with breast cancer cells, where clones of cells can become dependent on tamoxifen, it is theoretically possible that the late
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failure of, or de novo resistance to, adjuvant tamoxifen might be related to these observations (DeFriend & Howell 1994, Katzellenbogen et al. 1994). Thus, notwithstanding the undoubted value of tamoxifen, there is a need for new agents that will replace and improve upon it in the treatment of early breast cancer, while avoiding the possible adverse effects. One such group of agents is the aromatase inhibitor class of drugs, specifically the new-generation triazole aromatase inhibitors such as anastrozole and letrozole.

The use of aromatase inhibitors in the treatment of breast cancer

The usefulness of aromatase inhibitors in the effective treatment of advanced breast cancer in postmenopausal women was initially demonstrated by the non-steroidal aromatase inhibitor, aminoglutethimide (Gale et al. 1994). While proving effective in the management of advanced breast cancer, the associated toxicity (Johannesen & Lonning 1992) and dosing regimen (4×250 mg daily standard dose with concomitant hydrocortisone) did not lend itself to long-term dosing in the adjuvant situation. Indeed, adjuvant trials with aminogluthethimide in the 1980s had to be terminated for toxicological reasons (Coombes et al. 1987). Following on from aminogluthethimide, the next aromatase inhibitor to be developed was the steroidal compound 4-hydroxyandrostenedione (formestane); formestane was also shown to be effective in the treatment of advanced breast cancer (Perrez Carrion et al. 1994), but again the dosing regimen (intramuscular injection every 2 weeks) (Coombes et al. 1992) did not lend itself to long-term administration in the adjuvant setting.

The major reasons for the success of tamoxifen as a breast cancer treatment are its efficacy, route and mode of administration (oral route, once or twice daily) and its good tolerability. It is against these important properties that alternative agents will have to be judged. There is now compelling evidence that the new-generation aromatase inhibitors anastrozole and letrozole may well fulfill these basic requirements. They have shown efficacy benefits over the previously established second-line agents in the treatment of advanced breast cancer in postmenopausal women, with anastrozole showing a significant survival advantage over megestrol acetate (Buzdar et al. 1997). In addition, the once-daily dosing regimen and good tolerability make them good candidates for use in the adjuvant setting. In addition to fulfilling these fundamental needs, based on the mode of action (reduction in endogenous oestrogen levels) and the lack of intrinsic hormonal activity (non-steroidal with no effect on hormone receptors), there is convincing evidence that the new-generation aromatase inhibitors will have advantages over tamoxifen. For instance, the effects on the endometrium and tumour stimulation resulting from its agonist properties would not be expected, nor would the visual disturbances associated with triphenylethylene compounds, including tamoxifen (Tang et al. 1997).

Aromatase inhibitors in the adjuvant setting

The non-steroidal inhibitors, anastrozole and letrozole, and the steroidal orally active agent, exemestane, are currently being investigated in adjuvant breast cancer trials. Aromatase inhibitors are being compared directly with tamoxifen as initial adjuvant therapy, or given sequentially after 2-3 years of adjuvant tamoxifen versus tamoxifen alone. The design of the Femtja/BIG trials encompasses a two-arm study of either tamoxifen (20 mg daily) or letrozole (2.5 mg daily) for 5 years and a four-arm study comprising 5 years of either tamoxifen or letrozole and tamoxifen for 2 years followed by letrozole for 3 years and the reverse sequence of letrozole for 2 years followed by tamoxifen for 3 years. The ATAC (arimidex, tamoxifen, alone or in combination) trial is the most advanced study and is unique in including a combination arm of tamoxifen plus an aromatase inhibitor (anastrozole).

The ATAC trial

The ATAC trial is a randomised double-blind trial comparing anastrozole alone with tamoxifen alone and with anastrozole plus tamoxifen in combination as adjuvant treatment in postmenopausal women with early breast cancer. The trial is designed to compare efficacy (time to recurrence, time to distant recurrence, incidence of new breast primaries and survival) and safety of tamoxifen with that of anastrozole and of tamoxifen versus the combination of tamoxifen and anastrozole, the primary end point being time to recurrence and safety (Baum & Houghton 1998).

A unique feature of the ATAC trial is the inclusion of the anastrozole/tamoxifen combination arm, allowing investigation of whether maximal endocrine blockade (oestrogen withdrawal+oestrogen antagonism) provides additional benefit over oestrogen antagonism alone. The inclusion of the combination arm was justified on the basis of findings of a small pilot study on postmenopausal women with early breast cancer, in which the effects of anastrozole on tamoxifen pharmacokinetics were investigated as the primary end point. A further end point was to see whether the degree of oestriadiol suppression observed with anastrozole alone was affected by the presence of tamoxifen. In summary, it was observed that anastrozole had no significant effect on serum tamoxifen levels and
furthermore that the oestradiol suppression seen with anastrozole alone (Fig. 1) was unaffected by tamoxifen (Dowsett et al. 1997, 1999).

Although the effect of tamoxifen on plasma anastrozole levels was not investigated in this particular trial, given the suppression of oestradiol seen, if such an effect did in fact exist, it was insufficient to reduce the oestradiol-suppressive effects of anastrozole. The effects of tamoxifen on blood anastrozole levels will be investigated in one of the subprotocols of the ATAC trial. In addition to the lack of interaction with tamoxifen, further pharmacokinetic studies have shown that anastrozole does not affect, and in turn is not itself affected by, a number of drugs that may impact upon liver metabolism. For instance, anastrozole did not affect the pharmacokinetics of antipyrine or warfarin, both of which are metabolised by the liver, and anastrozole itself was not affected when co-administered with cimetidine, a non-specific inhibitor of liver cytochrome P450 (Dowsett et al. 1998). For a drug such as anastrozole, which will, in the first instance, be given for up to 5 years to postmenopausal patients, in whom concomitant drug treatment is not uncommon, lack of interaction with other drugs is an important property. As mentioned above, in addition to its efficacy in breast cancer, tamoxifen has beneficial effects on the cardiovascular system and bone mineral density in postmenopausal women as the result of its partial agonist activity. Theoretically, as the new-generation aromatase inhibitors are potent suppressors of oestrogen, and lack the partial agonist effects of tamoxifen, it is possible that these new agents may have adverse effects on bone mineral density and the cardiovascular system. Conversely, however, the proliferative effect of tamoxifen on the endometrium would not be expected with the new-generation aromatase inhibitors. As the success of any drug is based on the balance between its clinical efficacy and side effects, it was important that a number of subprotocols should be initiated as part of the ATAC trial. The subprotocols are assessing the effects on bone, blood lipids, endometrium, quality of life and pharmacokinetics, and will ultimately provide essential information on the use of anastrozole.

The ATAC trial is still recruiting patients, and is expected to complete recruitment by the end of 1998, when approximately 7500 patients will have been entered. This rapid recruitment reflects both the need for improvements in breast cancer treatment and the expectation that the new-generation aromatase inhibitors will improve efficacy, tolerability and/or quality of life.

**Sequential treatment trials**

As mentioned above, a different approach to adjuvant treatment of breast cancer, which is currently being investigated, is to use the new-generation aromatase inhibitors sequentially to initial tamoxifen treatment.
Typical of this type of trial design is the ARNO (ARimidex-NOlvadex) trial being carried out by the German Breast Cancer Group. Patients are initially given 2 years of adjuvant tamoxifen, after which they are randomised either to stay on tamoxifen for a further 3 years or to receive an aromatase inhibitor for 3 years. As mentioned above, the Femta/BIG trial has side arms with a similar design but employing letrozole. The MA17 trial randomises patients after 5 years of tamoxifen to a further 5 years on the drug or 5 years of letrozole. There is also a trial in which patients are randomised to receive either exemestane or a continuation of adjuvant tamoxifen. The results of these trials will be very useful in determining whether the use of an aromatase inhibitor, after initial tamoxifen treatment, can delay the onset of breast cancer recurrence or modify the effects of tamoxifen on the endometrium, bone and lipids.

Conclusions
The direct head-to-head and sequential trials of aromatase inhibitors and tamoxifen will, in the next few years, define whether the new-generation aromatase inhibitors have a role to play in the treatment of postmenopausal women with early breast cancer. Despite the success of tamoxifen, there is a need for new agents to replace or improve upon this ‘original’ antioestrogen. With the establishment of large-scale multicentre collaborative groups, the clinical efficacy and utility of the new-generation aromatase inhibitors will be evaluated in perhaps half the time it took to appreciate the value of tamoxifen.

References
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