Breast cancer: preliminary results from the ATLAS study show extended adjuvant tamoxifen reduces breast cancer recurrence and mortality

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Preliminary results from the ATLAS study show a reduction in breast cancer recurrence and mortality from extending adjuvant tamoxifen to 10 years compared with stopping it at 5 years in women with oestrogen-receptor (ER)-positive disease. There was, however, an increased incidence of endometrial cancer and pulmonary embolism. Longer follow-up of ATLAS (and a meta-analysis of other ongoing extended tamoxifen treatment trials) are needed to fully assess the benefits and risks. Current NICE guidance on the use of the aromatase inhibitors for adjuvant treatment of early ER-positive invasive breast cancer in post-menopausal women remains valid.

Overview and current advice

Tamoxifen has a long established role in the adjuvant treatment of oestrogen-receptor (ER)-positive invasive breast cancer, and current practice is to give tamoxifen for up to 5 years.¹ The aromatase inhibitors (anastrozole, exemestane and letrozole) are alternative options for postmenopausal women. For adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women, the NICE clinical guideline on early and locally advanced breast cancer from 2009 recommends the following:

- Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.
- Offer an aromatase inhibitor, either exemestane or anastrozole, instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low risk and who have been treated with tamoxifen for 2 to 3 years.
- Offer additional treatment with the aromatase inhibitor letrozole for 2 to 3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years.
- Offer the aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women.
- The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and the side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.

See the NICE Evidence topic page on breast cancer for a general overview of the condition. The NICE Pathway – Early and locally advanced breast cancer brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

**New evidence**

Five years of adjuvant tamoxifen has already been shown to reduce the risk of relapse and mortality in women with ER-positive breast cancer. The Adjuvant Tamoxifen: Longer against Shorter (ATLAS) trial is an international study which aims to assess the potential benefits and risks of continuing tamoxifen to 10 years compared with stopping it at 5 years.

The study recruited 12,894 women with early breast cancer who had completed a median of 5 years of tamoxifen treatment. Women were randomised to continue tamoxifen to 10 years or to stop it at 5 (control group). This was an open control study; no placebo was given to the control group. These preliminary results from ATLAS report on data obtained up to August 2012 (an average of 7.6 woman-years of follow-up after entry into the study). Longer-term follow-up is continuing.

Of the 12,894 women, 6846 (53%) had ER-positive disease and 6048 (47%) had negative or unknown ER status. The main analysis on recurrence and breast cancer mortality only included the 6846 women with ER-positive disease. All 12,894 women were included in the analyses on side effects. After entry into the study, yearly follow-up forms recorded any recurrence, second cancer, hospital admission or death.

In women with ER-positive disease, continuing tamoxifen to 10 years reduced the risk of breast cancer recurrence compared with stopping it at 5 years (617/3428 recurrences in women continuing tamoxifen versus 711/3418 recurrences in controls; rate ratio [RR] 0.84, 95% confidence interval [CI] 0.76 to 0.94; p=0.002). Breast cancer mortality (331 deaths versus 397 deaths; RR 0.83 95% CI 0.72 to 0.96 p=0.01) and overall mortality (639 deaths versus 722 deaths; RR 0.87 95% CI 0.78 to 0.97 p=0.01) were also reduced.

With regard to the potential increased risk of side effects from extending tamoxifen treatment to 10 years, an increased incidence (hospitalisation or death) of endometrial cancer (RR 1.74 95% CI 1.30 to 2.34, p=0.0002) and pulmonary embolism (RR 1.87 95% CI 1.13 to 3.07, p=0.01) were seen. No increase in stroke incidence was seen and a decrease in ischaemic heart disease was noted (RR 0.76 95% CI 0.60 to 0.95, P=0.02).
The increased risk of endometrial cancer is a concern for postmenopausal women, and the authors estimated that the cumulative risk of this during years 5 to 14 (year 5 being entry into the study) was 3.1% (mortality 0.4%) for women continuing tamoxifen compared with 1.6% (mortality 0.2%) for controls. However, they suggest that this is outweighed by the decrease in breast cancer recurrence (and mortality) in women with ER-positive disease, which was estimated to be 21.4% (12.2%) for women continuing tamoxifen versus 25.1% (15.0%) for controls over the same time period.

As the decrease in breast cancer mortality produced by 5 years of tamoxifen persists for at least a decade after treatment ends, trials of 10 years of tamoxifen will need to be followed up for at least 15 years from diagnosis (which will be at least 10 years after entry into the study).

Longer follow-up of ATLAS (and a meta-analysis of other ongoing extended tamoxifen treatment trials) are needed to fully assess the benefits and risks of extending adjuvant tamoxifen treatment to 10 years. In addition, as discussed in an accompanying editorial, if the findings from this study are confirmed, it will potentially raise questions on the best treatment options for postmenopausal women. There are no data available on the use of aromatase inhibitors for more than 5 years, or data comparing aromatase inhibitors with tamoxifen treatment extended to 10 years.

**Commentary**

Commentary provided by Medicines and Prescribing Centre

Deaths attributable to breast cancer continue for decades after the diagnosis and initial treatment. Indeed, at no point after diagnosis does the standardised survival curve achieve parallelism with the community curve. The goals of treatment are local control of disease, elimination of micrometastases and prevention of recurrence (including the development of second primaries). For women with high-risk or advanced disease, achieving long-term survival is an increasingly achieved goal. Many of the benefits of therapeutic advances during the last 20 years have their greatest proportional impact on the 10-year survival, rather than the traditional 5-year point, and it is very probable that even longer-term advantages will emerge from trial cohorts in time.

In this context, the use of long-term adjuvant therapy to prevent recurrence is likely to have long-lasting benefits, and the longer the duration of treatment, the longer the benefits are realised. Of course, the potential for long-term side effects to counterbalance the benefits exists. Therefore, large, long-term randomised trials are required to expose the risk/benefit ratio.

Extending the duration of endocrine therapy in localised breast cancer is already enshrined in many guidelines, as is a trend towards the use of aromatase inhibitors rather than tamoxifen in postmenopausal women at higher risk of recurrence (based on factors such as tumour size and number, and histological grade). In women at lower risk of recurrence, the benefits of longer-term therapy may be just as real, but harder to demonstrate.

These preliminary results from the ATLAS study show a further benefit of a second 5 years of tamoxifen therapy at a risk likely to be acceptable to most patients. Confirmation from other studies and longer-term follow-up are required to help determine the place of extended endocrine therapy, but the general direction seems clear.

For postmenopausal women, current practice favours aromatase inhibitors over tamoxifen where the risk of breast cancer recurrence is higher than average. Future analysis might explore whether 10 years of tamoxifen is better value than 5 years of an aromatase inhibitor or 5 years of tamoxifen followed by 2 or 3 years of an aromatase inhibitor. For these women at higher risk, 5 years of an aromatase inhibitor followed by a period of tamoxifen use might also be an option worth exploring. Women at lower risk might well also benefit from an extension of their tamoxifen therapy.
What is clear is that a new generation of long-term studies of breast cancer management is being opened up for women with ER-positive disease using agents which offer proven benefit at modest or lowcost, and acceptable and well-defined risk profiles. For now, pending further information from ongoing studies, current NICE guidance remains valid, but recruitment to trials of longer periods of endocrine therapy should be encouraged.

Study sponsorship

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References


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