Breast cancer

ATTOM AND ATLAS COMBINED DATA

Caroline Lohrisch, MD, FRCP, Medical Oncologist, Vancouver Cancer Centre; Chair, Breast Cancer Systemic Therapy Committee, British Columbia Cancer Agency

TRIAL SUMMARY: Longer tamoxifen reduces recurrence and breast cancer mortality in ER+ disease


In estrogen receptor-positive (ER+) early breast cancer, 5 years of tamoxifen reduces breast cancer death rates by about a third throughout years 0 to 14. It has been uncertain how 10 years of tamoxifen compares with this.

Between 1991 and 2005, 6953 women with ER+ (n=2755) or ER-untested (4198; estimated 80% ER+ if status known) invasive breast cancer from 176 UK centres were randomized to stop tamoxifen after 5 years or continue the drug to year 10. Annual followup recorded compliance, recurrence, mortality and hospital admissions.

Allocation to continue tamoxifen reduced breast cancer recurrence (580/3468 vs 672/3485; p=0.003). This reduction was time dependent: rate ratio (RR) 0.99 during years 5–6 (95% CI 0.86–1.15); 0.84 (0.73–0.95) during years 7–9; 0.75 (0.66–0.86) later. Longer treatment also reduced breast cancer mortality (392 vs 443 deaths after recurrence; p=0.05), RR 1.03 (0.84–1.27) during years 5–9 and 0.77 (0.64–0.92) later, as well as overall mortality (849 vs 910 deaths; p=0.1), RR 1.05 (0.90–1.22) during years 5–9 and 0.86 (0.75–0.97) later. Non-breast cancer mortality was not significantly affected (457 vs 467 deaths, RR 0.94 [0.82–1.07]). There were 102 vs 45 endometrial cancers, RR 2.20 (1.31–3.24; p<0.0001) with 37 (1.1%) vs 20 (0.6%) deaths (absolute hazard 0.5%; p=0.02). Combining the similar results of aTTom (Adjuvant Tamoxifen Treatment — Offer More?) and its international counterpart ATLAS (Adjuvant Tamoxifen: Longer Against Shorter; Davies C, Pan H, Godwin J et al. Lancet 2013;381:805-16) enhances statistical significance of recurrence (p<0.0001), breast cancer mortality (p=0.002) and overall survival (p=0.005) benefits.

The aTTom trial confirms that, in ER+ disease, continuing tamoxifen to year 10 further reduces recurrence from year 7 on, and breast cancer mortality after year 10. Taken together with the reduction in breast cancer deaths seen in trials of 5 years of tamoxifen vs none, these results indicate that 10 years of adjuvant tamoxifen, compared to no tamoxifen, reduces breast cancer mortality by about one third in the first 10 years following diagnosis and by a half subsequently.

COMMENTARY: The aTTom and ATLAS trials, described above, provide further evidence of survival and recurrence benefit for more than 5 years of hormone therapy compared with 5 years only, a concept first demonstrated by the MA.17 trial comparing 5 years of tamoxifen to 5 years of tamoxifen followed by 5 years of letrozole. These 3 large trials make a compelling argument for longer hormone therapy. However, several questions remain unanswered or are only partially answered by the available data.

The first is the strength of the evidence for younger women, who make up the largest population likely to consider 10 years of tamoxifen. While it is reassuring that many trials show similar proportional benefits of tamoxifen in young and older women, only 9% of the ATLAS study population and an unspecified portion of the aTTom study were premenopausal at enrolment. Women who are menopausal at initial diagnosis or at the 5-year mark are much more likely to switch to an aromatase inhibitor (AI), based on data showing an earlier recurrence-free survival benefit for this approach than has been demonstrated for 10 years of tamoxifen. However, tamoxifen remains the only option for premenopausal women.

A second knowledge gap is in distinguishing cancers still at risk of relapse beyond year 5 from those almost certain never to relapse, and confining exposure to continued therapy, with its attendant side effects, to the still at-risk population. The 24% and 19% event rates in the ATLAS and aTTom control arms suggest that in an unselected population, between 75% and 80% of patients will not benefit from extended therapy because they are not at risk for relapse in the first place. Using population databases, recurrence patterns more than 5 years from diagnosis for tumours grouped according to stage, grade, patient age at diagnosis, strength of ER expression and so on, can be constructed to help clinicians estimate ongoing risk for individual women, and whether there is potential benefit of longer hormone therapy. More elusive at present is distinguishing cancers that will avoid relapse due to longer therapy from those that will relapse in spite of it. Tissue-based microarrays and careful examination of disease and patient characteristics in the extended therapy trials may provide some clues.

The final and largest conundrum arises from the routine use of AIs in the first 5 years of therapy, as recommended for menopausal women by 2004 ASCO guidelines. The only trials of extended hormone therapy with results to date enrolled women who had completed 5 years of tamoxifen.
The disease-free survival benefit of longer therapy is in the order of 3% — the same as observed when an AI is substituted for some (or all) of the treatment in the first 5 years (compared with 5 years of tamoxifen). Given this, there is no guarantee that continuing therapy beyond 5 years will reduce recurrence rates further if an AI has been used in the first 5 years. While it is tempting to conclude that there will be benefit, particularly in women with high risk at diagnosis who are coming to an end of 5 years of hormone therapy, we will have to rely on the results of ongoing trials such as National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 (randomizing women to 5 years of letrozole or placebo after 5 years of hormone therapy that comprised at least 2 years of an AI) and others for definitive answers. Perhaps a missed opportunity here is trialing the reverse sequence of MA.17: many menopausal women are coming to the end of 5 years of an AI, and if there is a benefit to longer therapy in this setting, it might be maximized by switching to tamoxifen at year 5 rather than continuing with the same AI. However, this is not being examined in a large-scale trial.

Regardless of the outstanding questions, aTTom adds to presently available data and provides some definitive answers and guidelines for lengthening hormone therapy in ER+ breast cancer. Once the results of trials of NSABP B-42 type design are available, we may be able to develop a more comprehensive algorithm outlining who should have longer therapy and what that therapy should be. Certainly, telling all new patients to anticipate between 5 and 10 years of hormone therapy seems appropriate based on what we already know, with the expectation that knowledge gaps described above may be filled by the time we have to make the 5-year decision for these women.

Disclosure
Dr. Lohrisch reports no conflict of interest relevant to this article.

References: