The ATLAS trial: Tamoxifen for a longer duration for early breast cancer

The long-awaited results of the ATLAS (Adjuvant Tamoxifen Long Against Short) trial were presented at the San Antonio Breast Cancer Conference in December 2012 as well as pre-published online in the Lancet on 5 December 2012.¹ For many years, 5 years of adjuvant tamoxifen was considered as standard of care in patients with oestrogen receptor (ER)-positive breast cancer; this practice was based on many studies including the results of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis.² Questions have been asked as to whether the use of adjuvant tamoxifen beyond 5 years could further reduce recurrence and death but there were no answers. The results of a previous smaller National Surgical Adjuvant Breast and Bowel Project (NSABP) trial did not show any benefit of extending tamoxifen beyond 5 years.³ However, controversy was reopened when the results of the MA-17 trial showed that sequential hormonal treatment comprising tamoxifen and letrozole beyond 5 years reduced recurrence and death.⁴–⁶ The ATLAS trial was initiated by investigators from Oxford University in 1995.

The study included patients with early breast cancer who had completed 5 years of tamoxifen. These patients, if disease-free, were then randomly allocated to further 5 years of tamoxifen or no tamoxifen. A large number (12 894) of patients were randomized over a 10-year period from 32 different countries, thus making it the largest international trial in breast cancer. India joined in 1997 and recruited about a quarter of patients (nearly 3000). The results that were pre-published in the Lancet relate to the efficacy in 6846 ER-positive patients but toxicity and side-effects were reported in all 12 894 patients who included many ER-unknown and ER-negative patients. As expected, there was no benefit of continuing tamoxifen in 1248 ER-negative patients and an intermediate benefit was seen in 4800 ER-untested patients, many of whom would have been ER-positive. The longer duration of tamoxifen significantly reduced the risk of recurrence of breast cancer (617 recurrences in 3428 women allocated to continue tamoxifen v. 711 among 3418 controls, p=0.002), reduced breast cancer mortality (331 v. 397 deaths, p=0.01) and reduced overall mortality (639 v. 722 deaths, p=0.01). The authors estimated that 10 years of adjuvant tamoxifen will reduce the risk of relapse by 39% (p<0.0001) and breast cancer mortality by 36% (p<0.0001). Moreover, a carry over benefit of tamoxifen was seen beyond 10 years indicating that with further follow-up continued benefit beyond 15 or even 20 years could be seen in patients who took tamoxifen for longer periods. Hence, there is a need for continued follow-up of patients included in the ATLAS trial. The adverse fall out of extended use of tamoxifen was the cumulative risk of endometrial cancer in 3.1% v. 1.6% and mortality in 0.4% v. 0.2%, meaning an absolute increase in mortality of 0.2% among those receiving a longer duration of tamoxifen. The full results of a trial similar to the ATLAS trial being done in the UK, called the aTTOM trial (which is also a large trial), are expected in 2014.⁷ It was also observed in the ATLAS trial that only 60% of patients allocated to receive tamoxifen for a longer duration were actually taking it at 10 years, indicating that the benefit might have been more had all patients been taking tamoxifen for 10 years.

So, what are the implications of these results? The most profound change will be in ER-positive pre-menopausal patients where the options are limited because aromatase inhibitors are not used in this group. The findings of this study will influence clinicians to recommend 10 years of tamoxifen for this group of patients. The implications on post-menopausal patients are less clear because these days many patients are preferentially being given aromatase inhibitors and the results of the ATLAS trial using tamoxifen cannot be extrapolated to these drugs simply because the side-effects and efficacy of aromatase inhibitors used for 10 years are still unknown. The results establish for the first time that 10 years of tamoxifen is safe.

Indian investigators have the satisfaction of having contributed in a major way to this study and this trial reinforces India’s capacity to participate in good international studies and to provide good quality data. This should be seen against the current backdrop of negative publicity about clinical trials in India. India should not and ought not to shut the door on clinical trials as is being suggested in some quarters but should try to improve the governance issues related to clinical trials.⁸
REFERENCES


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