Commentary on "aTTom": long-term effects of continuing adjuvant Tamoxifen to 10 years

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Introduction

For more than two decades, five years of adjuvant Tamoxifen remained a standard of care in women with estrogen-receptor-positive (ER+) early breast cancer (EBC). According to the most recent Oxford's group meta-analysis of 20 trials (n=21,457), five years of Tamoxifen substantially reduced recurrence by 39% and breast cancer mortality by 30% in the treated patients (1). Nevertheless, over 50% of all recurrences in these patients will still occur after completion of five years of adjuvant Tamoxifen, denoting that late relapses are a considerable problem in luminal subtypes of breast cancer (2). Earlier studies extending Tamoxifen course beyond five years have yielded inconclusive results, with two trials reporting a detrimental effect of the longer Tamoxifen treatment [the Scottish Adjuvant Tamoxifen trial (3) and NSABP B-14 (4)] and a 3rd smaller study showing a trend for improved DFS in patients receiving extended Tamoxifen (ECOG study) (5).

The first report on a real significant beneficial effect of extended adjuvant endocrinal treatment in EBC was provided by the MA.17 trial (5,187 patients). This large, double-blind, placebo-controlled phase III study, investigated whether extended adjuvant therapy with letrozole following completion of five years of Tamoxifen could prolong disease-free survival (DFS) in postmenopausal women with ER-positive or receptor-unknown EBC. The very early results of MA.17 trial, at a median follow-up of 2.5 years, showed that letrozole significantly reduced the risk of recurrence by 42% regardless of the patient's nodal status or receipt of prior chemotherapy (6). Importantly, mortality was reduced by 39% in letrozole treated patients, among the approximately 2,500 women with node-positive disease randomized in the study. Exploratory analyses based on longer follow-up (64 months) and adjusting for subsequent treatment crossover suggested that extended adjuvant letrozole was superior to placebo in DFS, and overall survival (7). Nevertheless, the chapter on the potential benefit of longer Tamoxifen use was never closed, as a final answer was still waiting for the long term results of two much larger studies ATLAS and aTTom, which had been initiated more than 20 years ago and collectively recruited around 14,000 women with EBC. Recently the ATLAS study (6,846 patients) has shown that extended Tamoxifen treatment significantly reduced both recurrence rate by 25% and breast cancer mortality by 29%, compared with stopping Tamoxifen at five years. Of note, these results were reported at eight years of follow-up (13 years from initial diagnosis of EBC) (8).

aTTom trial in brief

During the ASCO 2013 plenary session, Dr. Gray and his co-worker from the University of Oxford, United Kingdom, presented the updated results of the aTTom trial (Abstract 5). The aTTom study included 6,953 from women 176 UK centers, who had completed 4+ years of adjuvant Tamoxifen. All patients had invasive breast cancer (53% node negative, 31% node positive, 16% node status unspecified), with only 39% of them reported to have ER+ disease (ER was untested in 61% of the cases) (9). These patients were randomized between continuing Tamoxifen treatment for another five years or no further treatment. The first report of the aTTom (at a median follow-up of 4.2 years) was presented during the ASCO 2008, which did not show a significant benefit of extended Tamoxifen over

no treatment in terms of recurrence rate [RR =0.94, 95% CI: 0.81-1.09; P=0.4] (10). However the updated results after nine years of follow-up could demonstrate that the longer-treatment group compared with the 5-year treatment group had a significantly fewer breast cancer recurrences (28% *vs.* 32%; P=0.003), which is translated as a 15% reduction in the risk of recurrence [relative risk (RR) 0.85, 95% CI (0.76, 0.95); P=0.003]. Longer treatment was also associated with a non-significant (as yet) reduction of breast cancer mortality compared with five years of treatment (21% *vs.* 24%; P=0.06). The aTTom investigators believed that, the benefit of Tamoxifen in their trial may be even greater than reported, as 61% of enrolled patients had an unknown ER status (estimated 30% of such patients were ER-negative and did not benefit from Tamoxifen). As expected the longer duration of Tamoxifen increased the risk for endometrial cancer, with 102 versus 45 cases of endometrial cancers in the 10- and 5-year treatment groups, respectively (rate ratio 2.20, P<0.0001), and more deaths from endometrial cancer (1.1% and 0.6% respectively, P=0.02).

In fact, the results of the aTTom study almost mirrored those of the ATLAS trial. In both studies the relapse risk reduction was time dependent, with practically no benefit at all seen with longer treatment on years 5-9, followed by an abrupt significant improvement on year 10 and subsequent years. In the ATLAS the recurrence rate ratio (RR) was 0.90 (95% CI: 0.79-1.02) during years 5-9 and 0.75 (0.62-0.90) in later years; while breast cancer mortality RR was 0.97 (0.79-1.18) during years 5-9 and 0.71 (0.58-0.88) in later years. Similarly, in the aTTom the RR was 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) in later years. A pooled analysis of patients enrolled in aTTom and ATLAS showed a 9% reduction in the risk of death after patients received 10 versus 5 years of Tamoxifen for the entire follow-up period [RR 0.91, 95% CI (0.84, 0.97); P=0.008]; the relative risk reduction increased to 16% starting at year 10 [RR 0.84, 95% CI (0.77, 0.93); P=0.0007].

How can we interpret the data of the ATLAS and aTTom?

The analysis of both trials would tell us that the benefit of longer Tamoxifen treatment is real but definitely "modest and delayed". As such the magnitude of benefit of extended adjuvant treatment using letrozole as reported by the MA 17 would favor aromatase inhibitors (AIs) over Tamoxifen use for ten years in postmenopausal women. Importantly the benefit of letrozole was seen throughout the study period starting as early as the first year, which was not the case in both ATLAS and aTTom (6,7). In line with MA 17 results, similar DFS beneficial effects of extended adjuvant therapy using other AIs, following five years of Tamoxifen have been reported in two smaller trials (NSABP B-33 and ABCSG6a) (11,12). Accordingly, we strongly believe that for most postmenopausal women, who finished Tamoxifen for five years, switching to an AI especially letrozole should be a better choice rather than to keep them on Tamoxifen for a longer duration. It should be emphasized that, the current practice in postmenopausal women entails an early use of AIs either upfront or after 2-3 years of Tamoxifen, therefore, the benefits of ten years of Tamoxifen as reported by the ATLAS and aTTom trials, can not be fully applied to these women. Nevertheless, we suggest that postmenopausal women who have completed five years of adjuvant AIs, may be good potential candidates to begin Tamoxifen for five more years. In these patients the risk of endometrial cancer will be certainly less than that reported by the aTTom, while the protective effects of Tamoxifen on bone and lipid metabolism will be able to partially offset the deleterious effects of the prior AIs use (13). Of note, the role of extending AIs beyond five years has not been proved yet. The results of an ongoing trial 'NSABP B-42" which is randomizing 3,966 post menopausal women to five years of letrozole or placebo after five years of hormone therapy that comprised at least two years of an AI, will be of a great help to answer such question (14). Whether further extended hormonal treatment beyond ten years will be needed is not known at the present time, The re-randomization of MA.17 patients to an additional five years of letrozole versus no treatment will provide further insights into the benefits and side effects of such a very long-term endocrinal treatment.

For younger women who are still pre/perimenopausal at the time of completion of five years of Tamoxifen, the results of ATLAS and aTTom are extremely encouraging. A longer duration of Tamoxifen seems to emerge as a new standard of care, especially in node positive cases, who are known to have a higher risk of late relapses. In these women the benefit of longer Tamoxifen treatment, in terms of lives saved from breast cancer should be weighed against the adverse events of treatment (fertility issues, menopausal syndrome, bone health, sexual and cognitive dysfunction). Importantly, premenopausal women treated with Tamoxifen have no known increased risk of uterine cancer and hence they require no specific gynecologic monitoring beyond routine care (15).

Conclusions

Since patients with ER+ EBC are known to have a considerable risk of relapse after completing five years of adjuvant endocrinal therapy, hence the need to protect against late relapse is clear. AIs especially letrozole could unequivocally offer a good approach to treating these women. The recent data provided by ATLAS and aTTom has added Tamoxifen as a further useful agent for such patients. In postmenopausal women, we believe that the results of extended adjuvant treatment using Letrozole may be more convincing, compared to longer Tamoxifen treatment. However, the results of ATLAS and aTTom are particularly useful in premenopausal women and those postmenopausal women who can not tolerate the long term use of AIs.

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