Reducing the Risk of Late Relapse in Postmenopausal Women with Hormone-sensitive Breast Cancer – Extended Adjuvant Letrozole

a report by

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DOI: 10.17925/EOH.2006.0.2.28

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Risk of Late Recurrence

The risk of breast cancer recurrence continues even after primary management with surgery and/or chemotherapy. In postmenopausal women with oestrogen receptor-positive tumours, adjuvant therapy with the anti-oestrogen tamoxifen for five years significantly reduces the risk of recurrence and for many years has been the standard therapy in this adjuvant setting.[1,2] Despite the efficacy of tamoxifen in the adjuvant setting, its use beyond five years is not recommended as it has not been shown to add further benefit, and serious side effects such as uterine malignancies and thromboembolic events have been shown to accumulate with on-going treatment.[3] Yet several studies confirm that there is a significant and on-going risk of recurrence of breast cancer that continues on in years 5–10 post-surgery.[4,5] The Oxford overview meta-analyses from the Early Breast Cancer Trialists' Collaborative Group analysed a study population of patients who were at years 5–10 following successful completion of five years of tamoxifen. The analysis showed the overall breast cancer recurrence risk to be approximately 3% per annum; 2% per annum in node-negative patients, and 4% per annum in node-positive patients during the study period. Thus, women who have remained disease-free after initial adjuvant tamoxifen therapy are still at substantial clinical risk for a late relapse event.[1,2] An unmet need for a new agent and treatment paradigm to address this risk of recurrence was needed. Due to the substantial risk of late recurrence and the time-dependent efficacy limitation of adjuvant tamoxifen therapy, the third-generation aromatase inhibitors (AIs) anastrozole, letrozole and exemestane were investigated as potential therapy in the time period following adjuvant tamoxifen known as the extended adjuvant treatment setting. AIs prevent oestrogen-mediated breast cancer stimulation through suppression of oestrogen biosynthesis rather than by blocking activation of the oestrogen receptor, as tamoxifen does. AIs have been shown to be effective alternatives to tamoxifen, both as first-line treatment of hormone receptor-positive advanced breast cancer and as treatment following failure of first-line tamoxifen therapy in postmenopausal women.

Efficacy of Letrozole in the Extended Adjuvant Setting

Of the three AIs, letrozole is the more pharmacodynamically potent, suppressing oestradiol to a greater extent than anastrozole.[6,7] Letrozole is also the only AI to show a significant improvement in time-to-progression (TTP) and a survival advantage over tamoxifen in the first-line setting.[8] Together, these data suggested that letrozole may be effective in preventing recurrences when given after five years of tamoxifen therapy. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.17 trial investigated whether extended adjuvant therapy with letrozole could effectively address the risk of late recurrence. This large, randomised, multicentre, multinational, double-blind, placebo-controlled trial evaluated the efficacy of five years of letrozole therapy versus placebo in postmenopausal women who had completed 4.5 – 6 years of tamoxifen therapy. The primary end-point of the trial was disease-free survival (DFS), which was defined as the time to recurrence of the original cancer (either locally, in regional nodes, or as distant metastases) or to the occurrence of a new primary cancer in the contralateral breast. Secondary end-points included overall survival (OS), quality of life (QoL) and long-term safety.

The DFS benefit of extended adjuvant letrozole therapy when compared with placebo was so great that the clinical trial was unblinded at the very first interim analysis. The early unblinding of the MA.17 trial was recommended by the data monitoring and safety committee because a highly statistically significant improvement in the primary end-point of DFS was observed in the letrozole arm.[9] The final data analysis, at 30 months of follow-up, showed a significant 42% improvement in DFS in patients receiving letrozole and pre-specified sub-group analysis found the benefit of extended adjuvant letrozole was not influenced by nodal status.[10]

In the MA.17 trial, distant metastatic events were the most common type of recurrence, both in the

node-positive and node-negative patients. In node-negative patients, at least 50% of the recurrences occurred in distant metastatic sites and the remaining were distributed between local in-breast recurrences, regional lymph node and soft tissue recurrences, and ipsilateral and contralateral new primary tumours. In node-positive patients, distance metastatic occurrences were even more common and accounted for considerably greater than 50% of sites of disease recurrence.[9,10] The sites of disease recurrence are important, as distant metastases are associated with higher mortality and lower 10-year survival rates. In the overall population, extended adjuvant therapy with letrozole significantly reduced the risk of distant metastases by 40% and also significantly improved OS in patients with node-positive disease who comprised approximately 50% of the 5,187 MA.17 participants.[10]

To be eligible for enrollment into MA.17, women had to be within three months of completing five years of tamoxifen. Consequently, extended therapy with letrozole had only been approved for use within this time interval. However, following unblinding of the MA.17 trial, women on the placebo arm were offered the opportunity to take letrozole.[13] Of those originally randomised to receive placebo, 1,655 women switched to letrozole and 613 patients decided to receive no treatment. Women who began letrozole therapy anywhere from 1–5 years following completion of tamoxifen, significant benefits in reduction in breast cancer recurrence (DFS), reduction in distant metastases (DDFS) and improvement in OS were all observed compared with those who elected no further treatment.[14] The publication of more detailed analyses is eagerly awaited, but these first results are exciting and promise to change clinical practice.

Despite the efficacy of tamoxifen in the adjuvant setting, its use beyond five years is not recommended as it has not been shown to add further benefit.

The recurrence rates in the placebo arm of the MA.17 trial also confirm that there is a substantial on-going risk of late recurrence.[11,12] Prior to the results of the NCIC CTG MA.17 study there was no further treatment option for women with hormone receptor-positive breast cancer who had completed five years of tamoxifen. These women were still vulnerable to considerable cumulative risk of late local and distant recurrences, and lacked any intervention to further protect against those late events.

The results from the MA.17 trial led to the approval of letrozole for the use in the extended adjuvant setting worldwide, offering women a new treatment paradigm to further protect themselves against recurrence. Several guidelines recommend the use of extended adjuvant therapy and, thus, this treatment option should be discussed with all women completing five years of adjuvant tamoxifen. However, in the clinic there are always exceptions, and for some women with very small, favourable tumours or with toxicity contrain-dications, extended adjuvant letrozole therapy may not be needed.[11]

Although the MA.17 trial was unblinded early, a small number of study participants had completed five years of letrozole after tamoxifen. A cohort study analysed the benefits of extended letrozole, looking at both hazard rates and hazard ratios between the placebo and letrozole arms of the trial. This afforded an opportunity to evaluate the benefit of on-going therapy over each year of therapy.[15,16] Results of this analysis showed that each 12-month period of letrozole therapy, after completing five years of tamoxifen, conferred additional benefit to women. It is suggested with statistical confidence that there continues to be on-going and increasing benefit with longer durations of extended adjuvant letrozole therapy through to at least four years.[16]

Safety of Letrozole in the Extended Adjuvant Setting

When compared with placebo, extended adjuvant letrozole therapy was well tolerated and did not adversely affect QoL.[10,17] Concern has been expressed regarding the potential consequences to women's health in general of lowering oestrogen to ultra low levels with aromatase inhibition in postmenopausal

women. Multiple organs and multiple organ functions are known to be under the control of oestrogen, and may potentially be adversely affected. Therefore, and as expected, safety evaluations found the principle adverse events associated with extended adjuvant letrozole therapy to be symptoms associated with oestrogen deprivation and menopause, including hot flashes, musculoskeletal discomfort and arthralgia, and an increase in the incidence of self-reported diagnosis of osteopenia and osteoporosis, as well as a small trend towards an increased clinical fracture risk, albeit not significant.[9,10] At the recent 29th International San Antonio Breast Cancer Symposium (SABCS), the MA.17 trialists presented results which indicated that extended adjuvant letrozole therapy is as effective in the elderly (i.e. women over the age of 70 years) as in younger postmenopausal women.[18] Thus, extended adjuvant letrozole therapy should not be withheld from elderly women, who are increasingly vulnerable to competing causes of non-breast cancer death.

Recently, particular attention has been focused on the potential affects of aromatase inhibition on serum cholesterol and other lipid levels, and consequently on cardiovascular events. To date, no adjuvant AI trial has shown firm evidence of adverse effects on lipid levels or cardiovascular events. The MA.17 trial, a placebo-controlled trial of 5,187 patients, showed that letrozole and placebo had similar effects on serum cholesterol levels, and cardiovascular health.[10,19] The MA.17 lipid substudy, looking at fasting lipid levels in trial participants, also showed no evidence of an effect on serum lipid levels.[19] Thus, while differences in incidences of hypercholesterolaemia and cardio-vascular events have been demonstrated in those trials comparing an AI to tamoxifen, no differences have been observed when compared with placebo. The current thinking is that AIs may lack the lipid-lowering, cardioprotective effects of tamoxifen. The AIs, however, do not have a detrimental effect on lipid profiles or cardiac health. The incidence of cardiac events seen in the AI arms of these adjuvant trials are similar to those seen in age-matched women in the general population.[20,21]

The NSABP B-33 Trial

Also of note, a second trial initiated around the time of the MA.17 trial, the NSABP B-33 trial, randomised patients completing approximately five years of adjuvant tamoxifen to exemestane or placebo in a double-blinded, controlled fashion.[22] As a consequence of the results of the MA17 trial, the NSBAP B-33 trial was discontinued early after only half the intended number of patients had been enrolled (1,598) and unblinded to study participants. All patients receiving placebo were offered exemestane and 44% of such patients chose to cross over to exemestane.[22] The first results from the intent-to-treat analysis from this trial, with 30 months of follow-up, were recently presented at the 2006 SABCS.[22]

The data clearly indicate that patients who received exemestane after five years of tamoxifen were significantly less likely to have a relapse of breast cancer (56%) than those who received placebo. Thus, these results from a smaller, intent-to-treat analysis further corroborate the effectiveness of extended adjuvant AI therapy.

Discussion

For women with hormone receptor-positive early stage breast cancer, >50% of relapses will occur after completing five years of tamoxifen therapy.[2] The optimal duration of tamoxifen therapy remains unresolved and two trials, ATLAS and ATTOM, to be reported soon, will address this question. Currently, extending tamoxifen beyond five years is not recommended, as it has not been shown to add further benefit, and is associated with an increased risk of serious adverse events, such as uterine malignancies and thromboembolic events.[3]

Several trials have now confirmed the benefits of using AIs in the extended adjuvant setting, including the MA.17 trial and the NSABP B-33 trial. However, to date, only letrozole has been fully investigated in a phase III, double-blind, placebo-controlled trial of over 5,000 patients, has fully published efficacy and safety data and is the only AI approved by regulatory authorities for use in the extended adjuvant setting.

Future investigations, such as the recently amended MA.17R trial, will address the question over whether greater than five years of adjuvant AI therapy is beneficial, and will help to define the optimal duration and the benefit-to-risk ratio of greater than five years of AI therapy. Those results are eagerly awaited and may also further change clinical practice.

Currently, it is clear that this new extended adjuvant treatment paradigm now offers women the opportunity to continue living relapse-free once they have completed adjuvant tamoxifen and should be discussed with all patients who are finishing adjuvant tamoxifen. Furthermore, results from the MA.17 post-unblinding analysis show that patients may still experience benefit from extended adjuvant letrozole even if some time has elapsed since treatment with tamoxifen (up to five years).[14] Thus, late extended adjuvant letrozole therapy should also be discussed with all patients. ■

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