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ANTI-TUMOUR TREATMENT

Beyond tamoxifen: Extended and late extended endocrine therapy in postmenopausal early breast cancer

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Summary Breast cancer is a leading cause of cancer death among women worldwide. The majority of cases are oestrogen receptor- or progesterone receptor-positive and, therefore, potentially sensitive to endocrine therapy. A significant risk of recurrence and death persists following initial diagnosis, with over one half of all recurrences and two thirds of breast cancer-related deaths reported to occur following completion of standard adjuvant tamoxifen therapy. There is a need for effective protection against recurrence beyond the initial 5 years of adjuvant treatment for women with hormone-responsive cancer. Extended adjuvant endocrine therapy with letrozole following completion of adjuvant tamoxifen treatment is well tolerated and reduces recurrence risk by 42% and the risk of developing distant metastases by 40% when compared with placebo. Extended adjuvant letrozole therapy confers protection against late relapses and should be considered for women completing adjuvant tamoxifen therapy. The MA.17 trial was unblinded early because of a statistically significant benefit in disease-free survival with letrozole, and patients receiving placebo were allowed to receive letrozole. MA.17 post-unblinding results show that women originally randomised to placebo who then chose to receive letrozole at the time of trial unblinding experienced a significant improvement in all outcomes (disease-free survival and distant disease-free survival), including a significant survival advantage when compared with women in the placebo arm who chose to continue with no further treatment. Physicians should consider late extended adjuvant therapy for women who have been off tamoxifen for some time, as it may offer benefit in outcomes, and this option should be discussed.

Introduction

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among women

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worldwide.[1,2] Breast cancer accounted for 27.4% of all incident cancer cases and 17.4% of cancer deaths among women in Europe in 2004.[2] Even following initial surgery, a significant risk of recurrence and death remains for many, meaning that a definition of a ''cure'' from breast cancer remains problematic.[3]

Tamoxifen is effective therapy in post-menopausal women. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reviewed a total of 194 randomised trials of various systemic adjuvant therapies to determine effects on recurrence and mortality at 10- and 15-year follow-up among post-menopausal women diagnosed with early-stage breast cancer. Treatment with tamoxifen for 5 years following initial diagnosis was found to reduce breast cancer recurrence by 41% and mortality by 34%.[4]

The use of tamoxifen is now being displaced by the third-generation aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane, which have demonstrated superior disease-free survival (DFS) benefits over tamoxifen in several trials and are now recommended as adjuvant therapy in post-menopausal women with hormone-sensitive breast cancer by the St. Gallen, American Society of Clinical Oncology (ASCO), and National Institute for Health and Clinical Excellence (NICE) guidelines (Table 1).[5–15] It was stated that post-menopausal women requiring endocrine therapy may benefit from: (1) an AI alone (anastrozole or letrozole) for 5 years; (2) tamoxifen for 2–3 years followed by an AI (anastrozole or exemestane) to complete 5 years of therapy; or (3) an AI (letrozole) following completion of 5 years of tamoxifen.[12,13]

Notably, over 50% of recurrences and deaths occurred after 5 years of adjuvant therapy,[3,4] demonstrating the need for an effective therapy beyond the initial 5 years of adjuvant treatment.[3,4] Although the results from a number of extended tamoxifen trials are awaited, the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, evaluating the efficacy of extending tamoxifen therapy beyond 5 years in patients with oestrogen receptor-positive (ER+) tumours and negative axillary lymph nodes,[16] found that continued treatment with tamoxifen beyond 5 years did not confer a DFS or an overall survival (OS) advantage and, therefore, treatment beyond 5 years was not recommended. As the AIs have a different mechanism of action than tamoxifen, they were hypothesised to be effective following adjuvant tamoxifen use. This review discusses late recurrence risk and summarizes the current data supporting the use of EA therapy.

Risk of early versus late recurrence

A number of studies have shown a peak hazard of recurrence during the first few years following surgery. One study showed a peak at year 2, followed by declining rates of recurrence until year 5, with an annual average hazard of recurrence 5 years after initial treatment of 4.3%.[3] In the Strathfield Breast Centre, a total of 456 (18%) of patients experienced a local, regional, or distant recurrence, with 58% of these occurring within the first 3 years following surgery and 79% within the first 5 years.[17] This was also seen in the PROFARE study ($N = 1550$), where over 40% of the patients experienced relapse or death during the first few

Table 1 Efficacy of aromatase inhibitors in the adjuvant setting

Trial	Follow-up	Comparator	Disease-free survival	Reduction in distant metastases	Overall survival
Initial adjuvant					
Arimidex, Tamoxifen, Alone or in Combination[5]	68 mo	Anastrozole vs tamoxifen	HR = 0.83, $p = 0.0049$[a]	HR = 0.84, $p = 0.06$[a]	HR = 0.97, p = ns[a]
Breast International Group 1–98[6]	25.8 mo	Letrozole vs tamoxifen	HR = 0.81, $p = 0.003$	HR = 0.73, $p = 0.001$	HR = 0.86, $p = 0.155$
Breast International Group 1–98 subset monotherapy analysis[7]	51 mo	Letrozole vs tamoxifen	HR = 0.82, $p = .007$	HR = 0.81, $p = 0.03$	HR = 0.91, $p = 0.35$
Switch adjuvant					
Intergroup Exemestane Study[8]	55 mo	Exemestane vs tamoxifen	HR = 0.75, $p = 0.0001$[a]	HR = 0.83, $p = 0.03$[a]	HR = 0.83, $p = 0.05$[a]
Austrian Breast and Colorectal Study Group trial 8; Arimidex-Nolvadex 95 trial[9]	28 mo	Anastrozole vs tamoxifen	HR = 0.60, $p = 0.0009$[b]	HR = 0.54, $p = 0.0016$[c]	NR, $p = 0.16$
Austrian Breast and Colorectal Study Group trial 8; Arimidex-Nolvadex 95 trial; Italian Tamoxifen Anastrozole trial meta-analysis[10]	30 mo	Anastrozole vs tamoxifen	HR = 0.59, $p < 0.0001$	HR = 0.61, $p = 0.002$	HR = 0.71, $p = 0.04$
Italian Tamoxifen Anastrozole trial[11]	52 mo	Anastrozole vs tamoxifen	HR = 0.42, $p = 0.0001$	HR = 0.57, $p = 0.06$	HR = 0.52, $p = 0.1$

HR, hazard ratio; NR, not reported; ns, not significant.
[a] Value reported in hormone receptor-positive population.
[b] Event-free survival.
[c] When looking at distant metastases first events only.