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Breaking the 5-year barrier: Results from the MA.17 extended adjuvant trial in women who have completed adjuvant tamoxifen treatment

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ARTICLE INFO

Article history:
Received 10 April 2006
Received in revised form
23 April 2006
Accepted 26 April 2006

Keywords:
Hormone-receptor-positive breast cancer
Extended adjuvant therapy
Letrozole
Placebo
Tamoxifen
Postmenopausal women
Recurrence
Disease-free survival
Aromatase inhibitor

ABSTRACT

The selective estrogen-receptor modulator, tamoxifen, has been the mainstay of adjuvant endocrine therapy for several decades, significantly improving outcomes for numerous women with hormone-receptor-positive (HR+) early breast cancer. However, tamoxifen is associated with acquired resistance: efficacy appears to decrease gradually with prolonged use, whereas the incidence of troublesome adverse events, such as thromboembolic disease and endometrial cancer, persists. Hence, long-term exposure to tamoxifen is associated with an unfavorable risk:benefit profile, limiting adjuvant tamoxifen therapy to 5 years. The majority of breast cancer recurrences and deaths occur more than 5 years after surgery, demonstrating the need for new treatment strategies for women who have completed tamoxifen therapy. Furthermore, the risk of late relapse is particularly high among women with HR+ disease, who are thus ideal candidates for further endocrine therapy.

In 2003, the first interim analysis of the MA.17 trial was published, identifying letrozole as the first agent to significantly reduce the risk of recurrence in women who had completed standard adjuvant tamoxifen therapy. Over 5000 women with HR+ breast cancer were randomized to receive either letrozole or placebo within 3 months of stopping tamoxifen therapy. The trial was unblinded at the first planned interim analysis because of a highly significant ($p = 0.00008$) 43% reduction in the relative risk of recurrence at a median follow-up of 28.8 months. The final analysis (median follow-up 30 months) confirmed these findings, with letrozole reducing the relative risk of recurrence by 42%, equating to an absolute reduction in the risk of relapse of 4.6% at 4 years. The beneficial effect of letrozole was seen regardless of nodal status, previous chemotherapy or duration of tamoxifen treatment (>5 years or $\leqslant$5 years), and increased with duration of therapy. Letrozole also reduced the risk of distant recurrence, and significantly improved overall survival in patients with node-positive, but not node-negative disease, becoming the first aromatase inhibitor to improve survival compared with standard treatment in early-stage breast cancer.

Letrozole therapy was well tolerated: no significant detrimental effects were seen on the cardiovascular system (5.8% vs 5.6% $p = 0.76$), lipid metabolism (16% vs 16% $p = 0.79$) or global quality of life scores compared with placebo. Musculoskeletal side effects, including patient-reported new osteoporosis, were more common in patients taking letrozole. Patient-reported new osteoporosis was not associated with an increased fracture risk.

Letrozole is the first agent shown to reduce the risk of late relapse after completion of tamoxifen therapy, in what is now known as the extended adjuvant setting. Letrozole is,

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1359-6349/$ - see front matter
doi:10.1016/j.ejcsup.2006.04.137

therefore, a highly effective and well-tolerated endocrine therapy that significantly improves outcomes for women with HR+ early breast cancer. Letrozole has improved treatment options for women with early breast cancer, extending the duration of adjuvant therapy to at least 10 years.

1. Introduction

Endocrine therapy is an important systemic adjuvant treatment in patients with hormone-receptor-positive (HR+) early-stage breast cancer. Approximately 75% of invasive breast cancers are estrogen-receptor-positive (ER+) and/or progesterone-receptor-positive (PgR+). Adjuvant tamoxifen given for 5 years, which has been the standard adjuvant therapy in postmenopausal women with HR+ early breast cancer for many years, has had a major impact on patient outcome, reducing the risk of recurrence by 47%, and the risk of death by 26%.[1] In ER+ breast cancer, 5 years of adjuvant tamoxifen therapy reduces the annual breast cancer death rate by 31%, and improvements in disease-free survival (DFS) and overall survival (OS) continue for at least 15 years from diagnosis.[2,3] However, continuation of tamoxifen for more than 5 years has been shown to be associated with worse outcomes compared with women who stop therapy after 5 years; the balance between acquired resistance and the incidence of problematic adverse events changes over time.[4]

Although tamoxifen reduces the risk of breast cancer recurrence, and may have beneficial effects on serum lipids and the cardiovascular system, tamoxifen increases the risk of endometrial cancer, stroke and pulmonary emboli, so its use requires careful assessment of the potential benefits and risks.[5,6] Furthermore, despite the benefits of tamoxifen therapy, substantial rates of relapse and new primary tumors are seen, which are associated with a continuing need for local and systemic anti-cancer therapy, and risk of mortality.[7] Most recurrences and deaths occur more than 5 years after surgery,[3] that is, after completion of tamoxifen. The risk of late relapse is higher in HR+ than in HR− disease, making patients with HR+ breast cancer candidates for further endocrine therapy after completion of 5 years of tamoxifen.[7]

The aromatase inhibitors (AIs) have a different mechanism of action from tamoxifen, preventing estrogen biosynthesis by inhibiting aromatase, the cytochrome P450 enzyme that catalyzes the conversion of androgens to estrogens in peripheral tissues and in breast tumor and peritumoral tissue.[8,9] The third-generation AIs, anastrozole, letrozole and exemestane, have been extensively investigated in first- and second-line treatment of HR+ advanced breast cancer,[10–17] and have been shown to be equivalent, or superior, to the standard of care. These studies, and the efficacy of these agents in the neoadjuvant setting,[18–20] have provided the rationale for the use of AIs in the adjuvant setting.

The MA.17 trial was the first large-scale study to compare an AI (letrozole) with placebo in women who had received 5 years of tamoxifen. MA.17 was a randomized, double-blind, placebo-controlled, phase III trial comparing letrozole (2.5 mg orally once daily) with placebo, given for a period of 5 years. The primary endpoint was DFS; secondary endpoints included overall survival (OS), safety, and quality of life (QoL).[21] It was hypothesized that, if the micrometastatic cells that are the source of breast cancer recurrences in tamoxifen-treated women become resistant to, or dependent on, tamoxifen by virtue of becoming estrogen hypersensitive, they might be particularly sensitive to AIs. Letrozole was investigated in this setting because of its substantial benefits in clinical studies as neoadjuvant therapy,[18,22] and in women with metastatic breast cancer, including those with disease progression while on tamoxifen.[13]

2. The MA.17 trial

2.1. *Study design*

The MA.17 trial recruited postmenopausal women with primary breast cancer treated for approximately 5 years with tamoxifen. Patients were randomly assigned using the minimization method to oral letrozole or placebo once daily for 5 years, and were stratified according to tumor hormone-receptor status (HR+ or unknown), lymph node status (negative, positive or unknown) and previous adjuvant chemotherapy (yes or no). Eligibility criteria included previous adjuvant tamoxifen for 4.5–6 years, histologically confirmed primary breast cancer, an ER+ and/or PgR+ tumor (defined by 10 fmol/mg protein or a positive result on immunohistochemical analysis of ER or PgR), discontinuation of tamoxifen therapy less than 3 months before enrollment, an ECOG (Eastern Cooperative Oncology Group) performance status of 0, 1, or 2, life expectancy of more than 5 years, and postmenopausal status. Exclusion criteria included the concurrent use of investigational drugs, a history or presence of another type of cancer (except skin cancer or carcinoma in situ of the cervix), concomitant treatment with a selective ER modulator, and concomitant systemic hormone replacement therapy.

The primary endpoint, DFS, was defined as the time from randomization to the recurrence of primary disease (in the breast, chest wall, or nodal or metastatic sites) or the development of a new primary breast cancer in the contralateral breast. Secondary endpoints included OS (defined as the time to death from any cause), annual incidence of contralateral breast cancer, QoL, and long-term safety. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0). QoL was assessed using the Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36) and the Menopause-Specific QoL (MENQOL) questionnaire. Distant DFS was a secondary endpoint defined in the final analysis, calculated as the time from randomization to the first observation of distant metastasis.

2.2. Patient and disease characteristics

Of the 5187 patients enrolled in the trial, 5170 (letrozole $n = 2583$; placebo $n = 2587$) were included in the analyses, with 17 (letrozole $n = 10$; placebo $n = 7$) excluded due to non-compliance with good clinical practice guidelines. Twenty-one patients (letrozole $n = 7$; placebo $n = 14$) did not receive the study medication and were excluded from the safety analyses: 5 patients randomized to letrozole received placebo and one randomized to placebo received letrozole, therefore, the safety analyses included 5149 patients (letrozole $n = 2572$; placebo $n = 2577$). The two arms were well balanced for baseline patient characteristics, tumor characteristics, and prior therapy for breast cancer (Table 1). The median time from initial diagnosis of breast cancer and random assignment in the study was 64.3 months.

Table 1 – Baseline[a] characteristics

Characteristic	Letrozole no. (%)	Placebo no. (%)
Number	2583	2587
Age (years)		
<70	1901 (74)	1946 (75)
⩾70	682 (26)	641 (25)
Median	62 years	62 years
Menopausal status[b]		
Postmenopausal (⩾50 years)	1964 (76)	1961 (76)
Postmenopausal (<50 years)	617 (24)	624 (24)
Missing	2 (<1)	2 (<1)
Axillary lymph node status		
Negative	1292 (50)	1276 (49)
Positive	1171 (45)	1189 (46)
Unknown	113 (5)	113 (5)
Missing	7 (<1)	9 (<1)
Hormone receptor status[c]		
Positive	2516 (97)	2519 (97)
Negative	2 (<1)	6 (<1)
Unknown	45 (2)	46 (2)
Missing	20 (1)	16 (1)
Duration of tamoxifen treatment		
⩽5 years	1160 (45)	1208 (47)
>5 years	1420 (55)	1374 (53)
Median	5.0	5.0
Missing	3 (<1)	5 (<1)

a Assessments made at the time of randomization.
b At the start of tamoxifen treatment.
c Positive refers to positivity for the estrogen receptor, progesterone receptor or both.

2.3. Interim efficacy analysis

The interim analysis was based on data received by August 2003, at a median follow-up of 28.8 months when a predetermined number of events (171 recurrences or new primary tumors) had occurred. At this time, 207 breast cancer events (40% of the events required for the final analysis) and 73 deaths had occurred, and 384 patients had been followed for 40 months.[21] The trial was stopped approximately 1 year earlier than anticipated, in October 2003, at the recommendation of the independent Data and Safety Monitoring Committee of the National Cancer Institute of Canada Clinical Trials Group. The trial was stopped because the first protocol-prespecified interim efficacy analysis revealed a highly significant, 43% relative reduction in DFS (local or metastatic recurrence or new contralateral breast cancer), the primary endpoint (hazard ratio [HR] 0.57, 95% confidence interval 0.43–0.75, $p = 0.00008$). The estimated 4-year DFS was 93% for letrozole and 87% for placebo, and letrozole was at least as effective in women with node-negative disease (HR 0.47, $p = 0.005$) as in those with node-positive disease (HR 0.60, $p = 0.003$).[21]

In addition to a significant improvement in DFS, a substantial reduction in the rate of distant metastasis was seen in patients treated with letrozole. The death rate due to breast cancer was reduced by almost 50%, and letrozole was also associated with a trend towards a reduction in overall mortality (estimated 4-year OS: 96% for letrozole, 94% for placebo), although this was not statistically significant.[21]

2.4. Final efficacy analysis

The final analysis, updated to the time of unblinding (9 October 2003) confirmed the results of the interim analysis. At a median follow-up of 30 months, 247 breast cancer events and 113 deaths had occurred; 1115 and 503 patients had been followed for 40 and 48 months, respectively.[23] Letrozole achieved a statistically significant improvement in DFS in women who had received standard adjuvant tamoxifen for 5 years, with substantial reductions in local, distant, and contralateral events, and a significant improvement in OS in women with node-positive but not node-negative disease.

In the analysis of DFS, 92 events had occurred in patients treated with letrozole and 155 in patients treated with placebo. Letrozole achieved a 42% reduction in the risk of disease recurrence (HR 0.58, 95% CI 0.45–0.76, $p < 0.001$) compared with placebo; 4-year DFS was 94.4% and 89.8% in patients treated with letrozole and placebo, respectively, equating to an absolute reduction in risk of recurrence of 4.6% in patients treated with letrozole (Fig. 1A). The stratified log-rank test for the difference in DFS, adjusted for receptor status, lymph node status, and prior adjuvant treatment at randomization, was statistically significant ($p < 0.001$). The treatment effect remained statistically significant after adjustment for two additional potential prognostic factors (menopausal status at the start of tamoxifen treatment and duration of tamoxifen therapy) in a stratified Cox model (adjusted HR 0.59, 95% CI 0.45–0.76).

Letrozole also significantly improved distant DFS, reducing the risk of distant recurrence by 40% compared with placebo (HR 0.60, 95% CI 0.43–0.84, $p = 0.002$). The incidence of contralateral breast cancer, expressed as the annual rate per 1000 patients, was 4.8 for placebo and 3.0 for letrozole (difference of 1.8 per 1000, 95% CI −1.3 to 4.9 per 1000). A non-significant relative risk reduction of 37.5% was seen with letrozole for time to contralateral breast cancer (HR 0.63, 95% CI 0.18–2.21, $p = 0.12$).

Fewer deaths occurred in the letrozole arm than the placebo arm (letrozole $n = 51$; placebo $n = 62$), although this did not reach significance (HR 0.82, 95% CI 0.57–1.19, stratified log-rank $p = 0.3$). The 4-year OS rate was 95.4% for letrozole and 95.0% for placebo, an absolute increase of 0.4% (Fig. 1B).

In a pre-planned subgroup analysis, letrozole was superior to placebo for DFS in all patient subgroups, except for those with unknown hormone receptor or lymph node status; however, both these groups contained very few patients (Fig. 2A). Letrozole significantly improved OS compared with placebo in patients with node-positive disease (HR 0.61, 95% CI 0.38–0.98, $p = 0.04$) (Fig. 2B), but not in patients without nodal involvement. Letrozole is the only AI to date to demonstrate an OS advantage in the adjuvant setting.

2.5. *Safety*

The MA.17 trial is arguably more informative about the safety profile of AIs than other studies in the adjuvant setting because of its unique design, comparing an AI with placebo in a population of women who were well and free from recurrent cancer at the start of letrozole therapy. The caveat is that all women had survived and completed a period of 5 years of tamoxifen and, therefore, women with significant co-morbid disease may be excluded from the MA.17 patient population. The results from the final analysis demonstrated that letrozole was well tolerated: most adverse events were mild to moderate (grade 1 or 2).[23] Hot flushes, alopecia, arthralgia, myalgia, and anorexia were significantly more common in

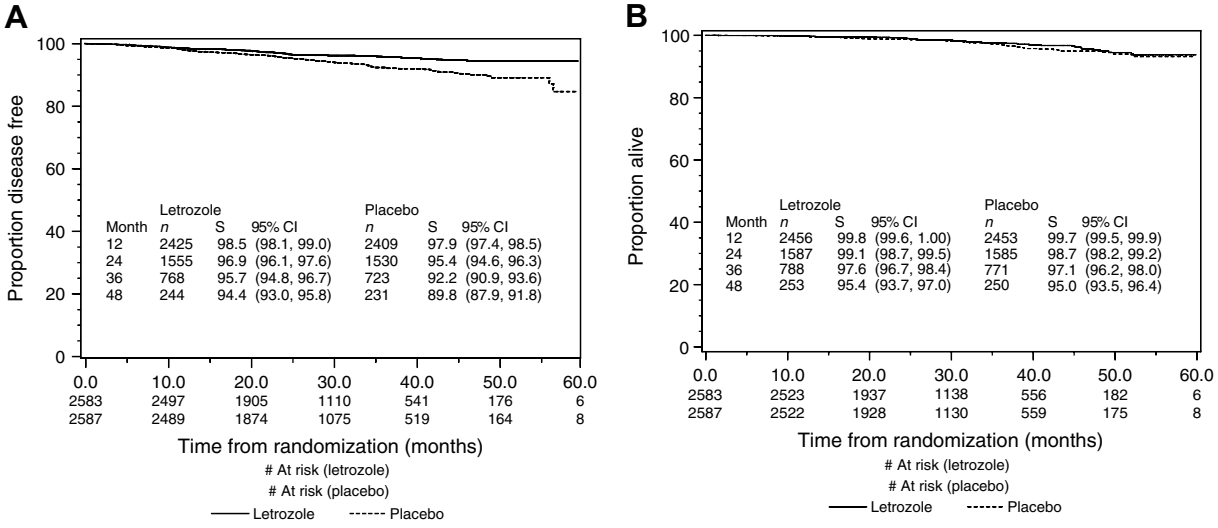

Fig. 1 – Kaplan–Meier estimates of DFS (A) and OS (B) in the final analysis (Acknowledge Journal of the National Cancer Institute and by permission of Oxford University Press).

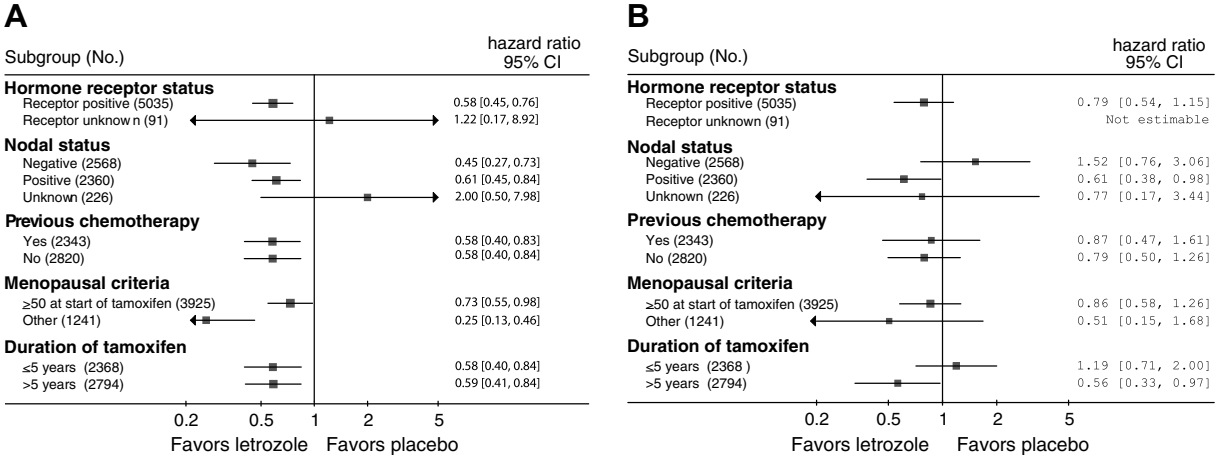

Fig. 2 – Forest plots of the treatment effect (letrozole vs placebo) for DFS (A) and OS (B) in subgroups defined by hormone receptor status, lymph node status, previous chemotherapy, menopausal criteria and duration of tamoxifen treatment. For each subgroup, the hazard ratio for recurrence or contralateral breast cancer (A) or for death from any cause (B) is plotted as a solid square, and the area of the square is proportional to the variance of the estimated effect. The length of the horizontal line through the square indicates the 95% CI. The arrow at the end of the horizontal line indicates that the CI is larger than the scale of the figure (Acknowledge Journal of the National Cancer Institute and by permission of Oxford University Press).

patients treated with letrozole, whereas vaginal bleeding was more common in patients treated with placebo.

More patients treated with letrozole than with placebo had a fracture or a new diagnosis of osteoporosis, but only the incidence of self-reported new osteoporosis was significantly different from placebo (letrozole $n = 209$ [8.1%], placebo $n = 155$ [6.0%], $p = 0.003$). There was no difference between the two treatment groups in the incidence of cardiovascular events (letrozole $n = 149$ [5.8%]; placebo $n = 144$ [5.6%], $p = 0.76$) or hypercholesterolemia (letrozole $n = 418$ [16%]; placebo $n = 411$ [16%], $p = 0.79$).[23] Closer examination of serum lipids in the MA.17L lipid substudy (total-, low-density lipoprotein- and high-density lipoprotein-cholesterol, lipoprotein[a] and triglycerides evaluated at baseline, 6 months, 12 months and annually thereafter) showed that letrozole does not significantly alter serum lipids compared with placebo in non-hyperlipidemic postmenopausal women.[24]

2.6. *Quality of life*

Of the 5187 patients included in the trial, 3612 (70%) participated in a QoL substudy (letrozole $n = 1813$; placebo $n = 1799$), making this the largest QoL substudy in an adjuvant AI trial to date.[25] Letrozole had no adverse effect on overall QoL after 36 months of treatment, although small effects were observed in some domains, consistent with a minority of patients experiencing QoL changes due to estrogen deficiency. There were no differences in the SF-36 physical and mental component summary scores at any timepoint between the two treatment arms. Small (<0.2 standard deviations) but statistically significant differences in mean change scores from baseline were seen in patients treated with letrozole for the SF-36 domains of physical functioning (12 months), bodily pain (6 months) and vitality (6 and 12 months), and the MENQOL vasomotor (6, 12 and 24 months) and sexual domains (12 and 24 months). In the response analysis, there was a significant difference between placebo and letrozole in the percentage of patients reporting a worsening of QoL for bodily pain (placebo 47%, letrozole 51%, $p = 0.009$) and the vasomotor domain (placebo 22%, letrozole 29%, $p = 0.001$).[25]

3. Discussion

Breast cancer recurrences can occur many years after diagnosis and even women with node-negative disease have a significant risk of eventual relapse.[2] Although adjuvant tamoxifen therapy is effective in patients with HR+ early breast cancer, studies have shown that there is no additional benefit in continuing treatment for longer than 5 years. This 5-year period of therapy reflects an artificial barrier in the treatment of HR+ early breast cancer and there is an important clinical need for effective endocrine therapy that can be given for longer periods. Letrozole is the first treatment to achieve a significant reduction in the risk of recurrence of breast cancer in patients who have completed 5 years of tamoxifen therapy, in what has now become known as the extended adjuvant setting. Preliminary results from a small, open label study comparing 3 years of anastrozole with no treatment, after 5 years of tamoxifen or tamoxifen plus aminoglutethimide, suggest that anastrozole is also effective in the extended adjuvant setting.[26]

The MA.17 trial demonstrated that extended adjuvant therapy with letrozole is effective and well tolerated in the treatment of HR+ early breast cancer. DFS was significantly improved, with an absolute reduction in recurrence of 4.6% at 4 years. Letrozole achieved substantial reductions in local, contralateral and distant events, with a relative reduction in risk of disease recurrence or the development of contralateral breast cancer of 42% ($p < 0.001$), and a 40% reduction in the risk of distant recurrence. The benefit with letrozole was seen irrespective of nodal status or previous exposure to chemotherapy, suggesting that extended adjuvant letrozole is equally effective in higher- and lower-risk disease. To date, letrozole is the only AI to demonstrate an OS advantage in the adjuvant setting.

Unlike tamoxifen, there is currently no evidence that AIs should not be used for treatment periods longer than 5 years. An extension study to the MA.17 trial, MA.17R, is being conducted, in which patients remaining disease-free after completing 5 years of treatment with letrozole (either in the MA.17 trial or in the community) are randomized to either a further 5 years of letrozole or 5 years of placebo. This extension study will enable the optimum duration of treatment to be determined in terms of efficacy and tolerability.

In view of the evidence from recent clinical trials, national and international guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the St. Gallen International Expert Consensus now recommend the use of an AI in the extended adjuvant setting.[27–29] Letrozole is the only AI approved for extended adjuvant therapy in postmenopausal women with HR+ breast cancer following 5 years of adjuvant tamoxifen treatment.[27–29] It is, thus, clearly established that treatment with letrozole after completion of adjuvant tamoxifen therapy provides a continuing clinical benefit compared with no further treatment.

In conclusion, the results of the MA.17 trial have changed clinical practice and established the benefit of extending adjuvant endocrine therapy for HR+ breast cancer in postmenopausal women beyond 5 years. In addition, letrozole has shown a survival advantage in the extended adjuvant setting in patients with node-positive disease. Extended adjuvant letrozole treatment should now be considered for all postmenopausal women completing standard adjuvant tamoxifen therapy.

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