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Review

Extended adjuvant endocrine therapy – A standard to all or some?

Domen Ribnikar [a, 1], Berta Sousa [b, *], Tanja Cufer [c, 2], Fatima Cardoso [b]

[a] Princess Margaret Cancer, Toronto, Ontario, Canada
[b] Champalimaud Clinical Center, Lisbon, Portugal
[c] University Clinic Golnik, Slovenia

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ABSTRACT

Patients with estrogen receptor-positive (ER +) early breast cancer (EBC) are at a continuous risk for distant relapse despite 5 years of standard endocrine therapy, even after 10–15 years after primary diagnosis. Hence, large randomized clinical trials were conducted to evaluate the role of extended endocrine treatment (ET) with the primary goal to prevent or at least delay distant relapse. Two very large trials of extended tamoxifen (TAM), the ATLAS and the aTTom trial, proved the efficacy of prolonged TAM particularly important after 10 years due to the carry-over effect of the five initial years. Additionally, the extended use of AIs after 5 years of tamoxifen, also proved to be efficacious in preventing late distant relapses. For letrozole (LET) it was shown in the MA.17 trial that it also improves overall survival (OS) in node-positive BC patients.

There are many options and still unanswered questions related to extended ET, which are discussed in this review. The most important issue in deciding prolonged duration of ET is undoubtfully how to identify ER+ patients who benefit most from this approach. With this purpose, not only classical pathological factors have been studied, but also molecular profiles of individual tumors, which might help us in the near future to better tailor ET. Not only efficacy, but also toxicity of such prolonged treatment is essential for optimal use, particularly maintained compliance in a routine clinical practice. These issues are discussed in this review.

1. Introduction

New evidence about the duration of adjuvant ET for ER+ early breast cancer has evolved in recent years derived from longer follow-up of patients included in clinical trials of extended ET with TAM and aromatase inhibitors (AIs).

The rational for these trials was based on the known natural history of breast cancer with an annual rate of death of approximately 5% for at least 15 years, even after 5 years of TAM therapy [1]. ER+ disease is characterised by a constant risk of relapse beyond 5 years in contrast to estrogen receptor negative (ER-) disease, which has an hazard rate of recurrence around 5.2% for years 5–8, and around 4.6% more than 8 years after diagnosis [1]. Furthermore, the EBCTCG reveals that 50% of relapses and breast cancer deaths occur after 5 years of diagnosis [2,3].

Similar findings occur when patients receive 5 years of AIs, as it was shown in the 10 years follow-up data of the ATAC trial [4].

Current guidelines [5,6] recommend 10 years of adjuvant ET for the majority of pre- and postmenopausal patients, unless there are characteristics of a very low risk disease. In premenopausal patients this treatment can be tamoxifen for 10 years. Ovarian suppression during the first years should be considered for high risk patients based on the results of SOFT and TEXT trials [7]. The inclusion of AIs in the first 5 years of ET have shown positive impact on survival in postmenopausal patients, reducing 10-year breast cancer mortality rates by about 15% when compared to 5 years of tamoxifen, at a cost of increased fracture rates (5-year risk 8.2% vs 5.5%) [3,4]. Extended treatment with AIs after 5 years of tamoxifen has shown a relative decrease by 32–56% of disease free survival (DFS) or relapse free survival (RFS) events [8–10], while in the largest MA.17 trial, an overall survival (OS) benefit was confirmed where letrozole was given for 5 years after 5 years of tamoxifen [10]. Only a trend for improvement was seen in other two studies [8,9], a fact that is maybe related to a premature closure and high cross-over rate of patients to the extended AI, after the release of positive results of MA.17.

* Corresponding author. Av. de Brasília, s/n, 1400-038, Lisbon, Portugal.
E-mail address: berta.sousa@fundacaochampalimaud.pt (B. Sousa).
[1] Tel.: +1 416 946 4501x3248.
[2] Tel.: +386 42456 499.

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The main challenge for clinicians today is how to choose the best sequencing of ET, especially in extended treatment and how to appropriately select patients who could be spared extended ET. In this paper we review the current evidence for extended endocrine treatment.

2. Extended adjuvant therapy with tamoxifen

Adjuvant treatment with 5 years of tamoxifen is associated with significant reduction of breast cancer recurrence rates and more importantly mortality, as data shown by the EBCTCG overview [2]. This patient-level meta-analysis assessed long-term outcomes among 21.475 women with EBC that were included in trials comparing 5 years of tamoxifen to observation or placebo. The relative reduction in breast cancer mortality was about a third throughout the first 15 years with relative risk (RR) 0.71 during years 0–4, 0.66 during years 5–9, and 0.68 during years 10–14 ($p < 0{\cdot}0001$). The benefit was seen if positive or marginally positive ER+ disease, and was independent of age, nodal status, tumor grade or size, and the use of chemotherapy. Tamoxifen treatment was associated to a non-significant increase in mortality due to thromboembolic events (stroke and pulmonary embolism) and uterine cancer. The rate for this last event was higher in older women: 10-year mortality of less than 0.1% in women younger than 55 years old and 0.6% in women older than 55.

Longer follow-up of tamoxifen trials revealed that half of recurrences occur beyond 5 years after diagnosis in patients treated with tamoxifen or not. For that reason extended tamoxifen treatment studies were initiated. Results are now available from three main prospective trials that included the largest number of patients: NSABP-B14 [11], aTTom trial [12] and ATLAS trial [13]. They had a similar design, ie after 5 years of treatment with tamoxifen patients were randomized to additional tamoxifen treatment versus placebo, and are described in Table 1.

NSABP B- 14 [11] included 1172 patients with node negative and ER+ disease. After 7 years of follow-up there was no statistical difference in DFS and OS between groups, with a slight advantage for patients in the placebo arm (OS at 7 years 94% for women receiving tamoxifen 5 years and 91% if received extended therapy, $p = 0.07$). These results led to discontinuation of the trial at the 3rd interim analysis (4 were planned). The main criticism for this trial, in terms of meaningful results, is the observed low event rate, which is expected in the node negative only population, and shorter follow up time taking into account the natural history of ER+ disease (breast cancer recurrences 34 and 47 in the placebo and tamoxifen respectively; number of deaths 106 and 137). Long follow up is also determinant to identify results, due to the known carryover effect of 5 years of ET.

Two other trials aTTom and ATLAS, left no doubt about the advantage of extending treatment. In the ATLAS trial [13] 12 894 women with ER positive, negative or unknown ER status were randomized after completing 5 years of tamoxifen, to continue treatment to 10 years or observation. There were 1328 recurrence events and 2860 deaths. Extended treatment with tamoxifen reduced significantly breast cancer recurrence rates and mortality in the ER+ subgroup of patients. This effect was mainly seen after the first decade (HR = 0.75, 95%CI [0.62–0.90]), while only a small decrease occurred in the first 10 years (HR = 0.90, 95%CI [0.79–1.02]). Similar findings were found for BC mortality with a RR of 0.97 (95%CI, 079–1.18) during years 5–9 and 0.71 (95%CI, 0.58–0.88) and non-breast cancer mortality was not affected. In addition, no benefit was seen in ER negative disease, and an intermediate one occurred if unknown ER status. No other predictive factors were identified.

The aTTOM trial [12] randomized 6953 patients in the UK and had a similar design. The ER status positivity was confirmed in 2755 patients, while it was untested in 4198 patients (80% of these were estimated to be ER+). Ten years of tamoxifen was associated with significant reductions in breast cancer recurrence and breast cancer/overall mortality which was again only apparent in the second decade. For breast cancer mortality RR was 1.03 (95%CI, 0.84–1.27) during years 5–9 and 0.77 (95% CI, 0.64–0.92) after the first decade. Taken together these trials show that 10 years of tamoxifen reduces breast cancer mortality by about one third in the first decade and by half during the second decade after the diagnosis.

The results from aTTOM and ATLAS clearly show the carryover effect of 5 years of treatment (Fig. 1) and the crucial role of longer follow-up. If and for how long 10 years of Tamoxifen also have a carryover effect needs further follow-up.

A meta-analysis of the five trials of extended tamoxifen treatment [14] was recently published showing no significant reduction in the risk of BC recurrence or deaths with recurrence in the overall population, but a trend for this effect after 10 years of observation was seen. A significant benefit of BC recurrence was seen after 10 years and in lymph node positive disease. It included data from the trials discussed above plus 2 additional smaller trials: the Scottish trial [15] (342 patients) and the ECOG E4181/ES181 (193 patients) [16]. The total number of patients was 21.554, the majority being postmenopausal (87%). A significant heterogeneity among studies was found and it was only feasible to evaluate results with the use of a random effects modeling. This meta-analysis has several limitations: trials included had different follow-up times; some trials had short follow up time (i.e. less than 10 years); there was no access to ER status in a large proportion of patients and the fact that it is not derived from individual patient level data as the EBCTCG overview.

Extended tamoxifen treatment had an expected increase of the incidence of endometrial cancer from 2.3 fold with 5 years of treatment to about 4-fold with 10 years [2,11,13]. The reported event rate ratios were 2.0 (0.7–6.6), 1.74 (1.30–2.34) and 2.20 (1.31–2.34) in NSABP-B-14, ATLAS and aTTOM trials [11–13] respectively. This risk was higher in women older than 55 years old (absolute increase 2.6% [SE 0.6], 95% CI 1.4–3.8) [2]. Although there was an increase in the incidence rate of endometrial cancer, the associated mortality was low (about a tenth of the incidence rate) and lower than the benefit seen in reducing breast cancer

Table 1
Prospective randomized trials evaluating more than 5 years of tamoxifen.

Trial	Population (n)	mFU	Previous treatment	Randomization	HR for DFS (p value)	HR for OS (p value)
NSABPB-14	1172 ER+, N–	7 ys	5 ys TAM	- TAM 5 ys - PLAC 5 ys	1.3 (p = 0.03)	NR (p = 0.07)
ATLAS	6846[a] ER+, any N	8 ys	5 ys TAM	- TAM 5 ys - no further th	0.84 (p = 0.002)	0.71 (p = 0.01)
aTTom	6953 ER+ (39%), any N	9 ys	4-5 ys TAM	- TAM 5 ys - no further th	0.86 (p = 0.003)	0.91 (p = ns)

PLAC- placebo; TAM- tamoxifen; th- treatment.
[a] Only ER+ included into analysis.