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Extended Adjuvant Endocrine Therapy After Breast Cancer: "Longer Is Better"

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Abstract:

Recent evidence supports the use of extended adjuvant endocrine therapy (EAET) with either Tamoxifen (TMX) or an Aromatase Inhibitor (AI) after five years of initial adjuvant TMX to reduce BC recurrence and mortality in women with hormone-receptor positive early-stage breast cancer. This manuscript wants to give a brief overview of published data and ongoing studies concerning extended adjuvant endocrine therapy.

Premenopausal women should be treated with 10 years of Tamoxifen. Current strategies for postmenopausal women include initial adjuvant AI therapy, sequential AI therapy after 2 to 3 years of tamoxifen, or extended AI use after 5 years of TMX. However, data from trials looking at prolonged AI therapy beyond 5 years are required to determine the optimal total duration of AI therapy. In cases of recommending extended endocrine therapy with AI, Letrozole is first line treatment; Exemestane and Anastrozole still require research. Future studies are required; emphasis should be laid on who should use which drug, and for how long.

Keywords: ***Aromatase inhibitors; Drug therapy; Breast cancer; Recurrence; Tamoxifen.***

INTRODUCTION

Hormone receptor (HR)–positive, especially estrogen-receptor (ER) expression, in breast cancer (BC) patients, is an essential and required criterion for adjuvant treatment. HR–positive early-stage BC patients have a better early prognosis, an initially lower recurrence risk compared to HR–negative ones, but higher rates of late recurrence. Late recurrence is the biggest risk for HR-positive BC [1].

Despite those five years of mandatory hormonal therapy, half recurrences occur beyond five years since primary diagnosis [1,2], recurrence risk continues increasing up to at least fifteen years later (2% of the annual rate of relapse fifteen years after diagnosis) [3]. Mortality is also reduced in this group of patients, but the magnitude still continues increasing to 30% over a fifteen-year period [2]. These are main reasons why several trials had evaluated endocrine therapy beyond five years in HR–positive BC [4], in order to avoid late recurrences (up to 5 years).

Recent evidence supports the use of extended adjuvant endocrine therapy (EAET) with either Tamoxifen (TMX) or an Aromatase Inhibitor (AI) after five years of initial adjuvant TMX to reduce BC recurrence and mortality [4]. The most important factor deciding the hormonal therapy is the menopausal status. Extended therapy is more beneficial for women who remain premenopausal after their first five years of TMX [4], the St. Gallen International Breast Cancer Conference Expert Panel, considered extended TMX for all patients who remain premenopausal after their first 5 years of endocrine therapy. For patients who are premenopausal at diagnosis but who are found to be postmenopausal at the time of completion of their first 5 years of tamoxifen, the panelists recommended treating with an additional 5 years of tamoxifen or 5 years of an AI are both valid strategies (Table 1) [4]. Despite these conclusions of an expert panel, the optimal duration, which regimen of adjuvant hormonal therapy suits better and to whom (including postmenopausal patients), as well as the ideal timing of sequencing from TMX to an AI in HR-positive early-stage BC is still unclear [1,4]. This manuscript wants to give a brief overview of published data and ongoing studies concerning EAET.

TAMOXIFEN BEYOND FIVE YEARS

Tamoxifen (TMX) is the most widely used therapy. TMX is a Selective Estrogen Receptor modulator (SERM), with a non-steroidal anti-estrogen effect in the breast, but estrogenic for the bones, the uterine endometrium and the regulation of circulating cholesterol. TMX effect is cytostatic, so it suggests that indefinitely maintenance will be benefit from recurrence [3,5].

Though initial studies, like NSABP B-14 (The National Surgical Adjuvant Breast and Bowel Project, protocol B14) did not show that 10 years of tamoxifen therapy had greater

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benefit than 5 years of tamoxifen therapy [2,4,5]. Currently, there is robust evidence for the benefit of adjuvant endocrine therapy up to ten years in both pre- and postmenopausal women [4]. Current evidence recommends that premenopausal women should be treated with 10 years of tamoxifen [5]. Most important clinical trials were ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) study and aTTom (Adjuvant Tamoxifen—To Offer More?) trial; which obtained that maximal reduction in recurrence and death from BC was not until year 10 of TMX therapy [4]. BC women with extended TMX use obtained significant reductions in recurrence, mortality, and overall survival [5-8].

In ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial, after continuing 5 years of TMX, a reduction in mortality only emerged after completion of 10 years of tamoxifen, a total estimated relapse risk reduction of 39% ($p < 0.0001$) and risk reduction of BC mortality of 36% ($p < 0.0001$) [3]. The results of the aTTom (Adjuvant Tamoxifen: To Offer More?) randomized trial were quite similar to the ATLAS [8]. Longer treatment also reduced breast cancer mortality in a time-dependent way, with a relative risk of 1.03 during years 5 to 9 and 0.77 later (10-14 years), so that maximum benefit was obtained up to 10 years of continued treatment [8].

AROMATASE INHIBITORS BEYOND FIVE YEARS

Aromatase inhibitors (AIs) are only used in the management of BC for postmenopausal women. In postmenopausal women, AIs have further improved outcomes either as an alternative to TMX for 5 years or given as initial TMX therapy [1]. AIs are contraindicated as monotherapy for premenopausal patients [3, 6] unless ovarian function has been suppressed [5].

The St. Gallen expert panel advocates ovarian suppression in women under the age of 40, combined with TMX rather than as monotherapy or in combination with an AI [4], but it does not indicate for how long. A potential advantage with the use of AI plus ovarian function suppression (OFS) could be jeopardized by suboptimal estrogen suppression, especially in obese or overweight patients [8]. OFS utilizes luteinizing hormone-releasing hormone (LHRH) agonists (Goserelin or Leuprolide, usually depot each 3 months) [6]. Data on ovarian suppression with TMX, chemotherapy, or both showed no significant reduction in recurrence or death rates, instead of AI [6, 8]. It is also unclear if OFS will provide a carryover effect. SOFT and TEXT trials require longer follow-up for a complete understanding of benefits and risks of treatment. Patients with a higher risk for recurrence could be offered TMX plus OFS or AI plus OFS for 3-5 years. For now, prolonged indication of OFS-based strategies is not recommended until more evidence [8].

Although, there is no direct comparative data between extended TMX compared with an AI; indirect evidence suggests that an AI may have increased efficacy, due to a menopausal status. In premenopausal women, studies evaluating the longer duration of AI treatment are in progress [5].

In EBCTCG (Early Breast Cancer Trialists Collaborative Group) meta-analysis, published in 2010, concluded that adjuvant initial endocrine therapy with AIs in postmenopausal women produces significantly lower recurrence rates compared with TMX, either as initial monotherapy or after 2 to 3 years of tamoxifen [9]. In the comparison of first 5 years of endocrine therapy with AI versus 5 years of TMX (EBCTCG meta-analysis), recurrence rate favored AI significantly during first 5 years, but not thereafter. The first 5 years of an AI therapy reduces 10-year BC mortality rates by about 15% compared with 5 years of TMX, and about 40% compared to no endocrine treatment [10].

ATENA (Adjuvant post-TMX Exemestane versus Nothing Applied), and EBCTCG (Early Breast Cancer Trialists Collaborative Group) meta-analysis, confirmed that EAET with AI was associated with a decreased absolute risk of BC recurrence (2.9%, $p < 0.0001$) and mortality (0.5%, $p = 0.11$). Authors had concluded that EAET with an AI after 5 years of TMX further reduces the risk of recurrence and improves survival in postmenopausal women, at least in those with node-positive disease [3].

The NCIC-CTG (Canadian Cancer Trials Group) MA.17 trial compared the effectiveness of Letrozole daily for 5 years prior 4 to 6 years of TMX to no further treatment in postmenopausal women with primary BC [7,11]. The trial found a 6% absolute improvement in 4-year disease-free survival in the Letrozole group compared with placebo [8]. MA.17 demonstrated a survival advantage with Letrozole in extended therapy compared to placebo in women with axillary lymph node-positive (but not lymph node-negative), ER-positive BC. No survival benefit was obtained in women at initial adjuvant therapy with an AI versus first-line TMX [6], but a 40% risk-reduction in metastatic disease was obtained [11].

Based on the results of MA.17, Letrozole was approved in the EAET of HR-positive BC [7,11]. Premenopausal patients, who have become postmenopausal after TMX, benefit more from EAET with Letrozole than those postmenopausal at diagnosis [7]. The NSABP-B42 trial will determine whether extended Letrozole will improve disease-free survival in ER-positive postmenopausal women after 5 years of initial hormonal therapy with an AI. The “estrogen

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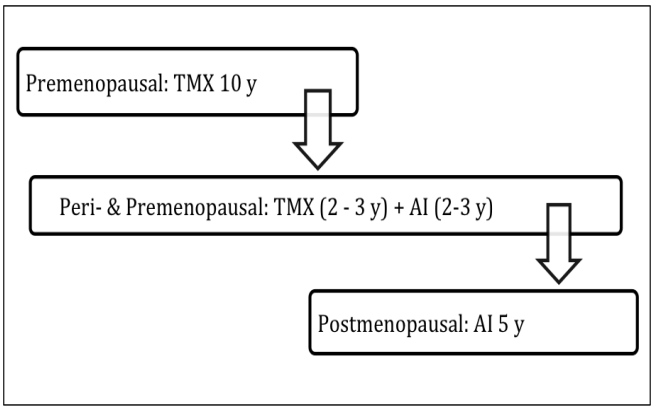
purge" concept is now being integrated into trials of EAET [2]. The SOLE (The Study of Letrozole Extension) trial is comparing a continuous versus an intermittent regimen of extended Letrozole after an initial 5 years of adjuvant tamoxifen [7]. The trial employs "an intermittent anti-estrogen regimen" so that woman's own estrogens may periodically purge and kill the nascent sensitized BC cells that are developing [2].

Exemestane has become a secondary approach for extended adjuvant therapy in previous premenopausal o perimenopausal patients after 5 years of TMX and then become postmenopausal [8]. The ATENA (Adjuvant post-Tamoxifen Exemestane versus Nothing Applied) trial tested 5 years of Exemestane after previous TMX. The study was prematurely closed because of low recruitment [7]. Patients initially randomized to Exemestane had a borderline statistically significant improvement in 4-year disease-free survival and a significant improvement in 4-year relapse-free survival [7]. Research is required to validate its recommendation as a second line treatment.

The ABCSG (Austrian Breast and Colorectal Cancer Study Group 8) trial showed a protective effect on recurrence for 3 years of Anastrozole, in HR–positive BC premenopausal women (with OFS) and postmenopausal ones after 5 years of TMX. The DATA (Different durations of Anastrozole after TMX) trial, which is comparing shorter (3 years) versus longer (6 years) Anastrozole after 2-3 years of TMX is still recruiting patients and no preliminary data has been published [7]. Another trial ongoing is the SALSA (Secondary Adjuvant Long-term Study with Arimidex) trial, which is comparing 2 versus 5 years of extended Anastrozole therapy. So further research to have other therapeutic alternatives that Letrozole is required.

Figure 1. Summary scheme of recommended hormonal therapy for early-stage breast cancer, according to current evidence.



Acronyms: TMX – tamoxifen, AI – aromatasa inhibitor, y – years, & - and.

COMPLIANCE TO EXTENDED ADJUVANT ENDOCRINE THERAPY

There is a high rate of compliance and persistence in case of extended treatment was recommended, around 72 to 85%. In the case of discontinuation, related adverse effects were the main reason. The large majority of patients stopped therapy during the first year of EAET [11]. These patients consider themselves cured and the discontinuation of therapy is associated with a life that is no longer affected by a daily intake of a medication that reminds them of their cancer. It is rarely possible to convince these patients of the benefits of an extended therapy [11].

Management of adverse effects helps with compliance to long-term treatment for both Tamoxifen and AIs. Most Frequent side effects are:

- Tamoxifen has bone and heart protective effects, but adverse effects are dependence or resistance to estrogen-receptor in prolonged treatment, increased risk of endometrial cancer, thromboembolic events [3, 5]. Patients taking Tamoxifen should be clinically screened for thromboembolism and for endometrial cancer if abnormal bleeding occurs [5].

- AI adverse effects are osteoporosis and menopausal symptoms [3, 5]. Patients taking AIs should be screened for optimal bone health and pay careful attention to the management of other chronic health disorders [5].

QUESTIONS UNSOLVED ABOUT EXTENDED ADJUVANT ENDOCRINE THERAPY

How many patients who started an endocrine therapy were eligible for an EAET according to current guidelines? There is currently no published data, which attempted to quantify the group of women who are actually candidates. However, only a minority of the patients that started endocrine therapy, almost half (50.7%) are actually eligible for an extended approach [11].

Some risk factors in which it is actually recommended the hormone therapy are metastatic lymphatic nodes, large primary tumor size (T3) or according to gene expression profile of the tumor. In research, Platforms of genetic profiles are a future option to identify patients at risk of late recurrence [8]; and therefore, the indication of extended endocrine therapy. Likewise, the Hospital Universitario Vall d´Hebrón (Barcelona, Spain), is developing a phase III clinical trial (PLUTTO trial) seeking an association between the metastatic lymph node load determined by OSNA with survival prognosis in breast cancer. Their results are promising and may be a determinant of risk and a highly specific indicator of hormone therapy maintenance.

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- How many eligible patients for EAET are recommended to receive the treatment? A 64.5% is reported. Advanced age, favorable stage I disease, a low-risk category, and no previous chemotherapy were significant contributing factors where a recommendation for an EAET was not made [11].

- And who proposes the continuation of the adjuvant hormonal therapy? The fact is that physicians do not always recommend an extended therapy [11]. In most cases, physicians have not been adequately informed that endocrine therapy regimen has extended the indication beyond the usual "5 years of TMX", to 10 years. Many times, physicians are not able to adequately counsel patients and explain the reason for EAET so that the patient will not understand the purpose and refuses it. In addition, there is a risk of not adequately select patients, sometimes because doctors themselves are afraid or do not trust their indication when there is still not enough experience in its use [11].

Who benefits from prolonged treatment? Patients with medium to high risk of relapse, positive node status at diagnosis, large tumor size, molecular risk scores by clinicopathological and gene expression platforms, and positive hormone receptor. In a randomized ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, a multivariate analysis found node status and tumor size to be the only individual factors that added prognostic information in years 5 to 10. Estrogen-receptor and progesterone-receptor status proved to be significant prognostic variables for first 5 years [3, 7].

Table1. Recommendations from The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for adjuvant endocrine therapy for women with estrogen receptor-positive early-stage breast cancer

Recommended adjuvant endocrine therapy for women with ER-positive early-stage BC, according to ASCO / NCCN Clinical Practice Guidelines.	
Postmenopausal women at diagnosis	**Peri- & premenopausal women at diagnosis**

• Sequential treatment with AI therapy for 5 y.
• TMX for 2 – 3 y followed by one of the following options:
  ○ An AI to complete 5y; or
  ○ TMX followed by 5y of an AI.
• TMX alone for 5 y or up to 10 y is limited to those who decline or who have a contraindication to AIs.
	• Sequential treatment with AI therapy for 5y with OS.
	• 5 y of TMX with or without ovarian suppression.
	• After 5 y of initial endocrine therapy, for women who are postmenopausal at that time (including those who have become postmenopausal during the 5 y of TMX therapy), consider:
	  ○ EAET with an AI for up to 3 – 5 y; or
	  ○ Based on the data from the ATLAS trial: TMX for an additional 5 y or up to 10 y of TMX therapy.
	• EAET should have a total of 10 y of TMX.

Acronyms: ASCO - American Society of Clinical Oncology, NCCN - National Comprehensive Cancer Network, ER - estrogen receptor, BC – breast cancer, AI(s) – aromatasa inhibitor(s), TMX – tamoxifen, y – years, OS – ovarian supression, EAET – extended adjuvant endocrine therapy, & - and.

Future perspectives

EAET is a promising strategy to further reduce the risk of recurrence. Nonetheless, there is actually no strong evidence to support this in daily clinical practice, mainly AIs. Future studies are required; emphasis should be laid on who should use which drug, and for how long [1, 12]. Important challenges to clarify the benefit of EAET are still unsolved questions like:

- Which risk factors identify who will really benefit from EAET? Are platforms of genetic profiles a new future option to identify this group of patients?
- Who benefits from EAET? Adequately selection of patients would prevent overtreatment and side effects [12].
- How many years of extended adjuvant therapy? Should it be at least five?

To conclude, adjuvant endocrine therapy has made a significant impact in improving overall survival for women with hormone receptor-positive breast cancer. There is evidence that Tamoxifen for up to 10 years in pre- or perimenopausal patients and Letrozole for 5 years in postmenopausal women after 5 years of Tamoxifen should

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be recommended (Figure 1). Future research on identifying factors that predict who will benefit from extended endocrine therapy are required.

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