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Review

Optimizing adjuvant endocrine therapy for early ER+ breast cancer: An update for surgeons

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ABSTRACT

Introduction: The optimal duration of adjuvant endocrine therapy in early ER + breast cancer has been controversial. This article aims to provide an overview of the evidence.
Methods: A search of the literature was conducted via MEDLINE using appropriate keywords. Eligible studies were screened and relevant articles were selected for this report.
Results: Studies investigating the role of extended adjuvant tamoxifen beyond 5 years have revealed mixed results depending on the proportion of node positivity. In postmenopausal women, aromatase inhibitors (AIs) for 5 years are superior to tamoxifen. Extending the use of AIs beyond 5 years seem to reduce the risk of relapse in postmenopausal women with node positive disease. The addition of bisphosphonates to counteract AI-related osteopenia may further improve overall and disease-free survival. Women younger than 40 years seem to benefit from ovarian suppression combined with tamoxifen or exemestane.
Conclusions: An individualised approach is required for every patient. The adverse effects of endocrine therapy should be weighed against the potential benefits of extended therapy to better inform decision-making.

Introduction

The optimal duration of adjuvant endocrine therapy in patients with early estrogenic receptor (ER) positive breast cancer has recently been the subject of much debate and controversy. The issue has been complicated by the fact that this topic has been the focus of numerous publications revealing mixed results. Breast cancer surgeons who monitor their patients during follow-up after breast cancer treatment are often asked by their patients for their recommendations regarding when to stop adjuvant endocrine therapy. This article aims to provide a concise overview of the evidence. A simple evidence-based treatment algorithm based on this review is also presented.

Methods

A search of the English literature was conducted using a computerized search of MEDLINE (PubMed) and the following key words: (tamoxifen) AND (adjuvant) AND (randomized controlled trial) AND (5 years) AND (10 years) OR (meta-analysis) OR (review) OR (extended adjuvant tamoxifen) OR (aromatase inhibitors) AND (extended adjuvant). Eligible studies were screened and most relevant articles were selected for this report based on preapproved criteria.

Results

Studies investigating the role of extended adjuvant tamoxifen beyond 5 years have revealed mixed results with outcomes predicated on the presence of metastatic nodal disease in selected patients. In postmenopausal women, aromatase inhibitors (AIs) for 5 years or for 2–3 years after 2–3 years of tamoxifen are superior to 5 years of tamoxifen. Extending the use of AIs beyond 5 years seem to reduce the risk of relapse in postmenopausal women with node positive disease. The addition of adjuvant bisphosphonates to counteract the adverse impact of AIs particularly in women with reduced bone mineral density may further improve overall and disease-free survival. Women younger than 40 years seem to

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benefit from ovarian suppression combined with tamoxifen or exemestane.[1]

Extended adjuvant endocrine therapy is superior to 5 years in patients with high risk disease and should not be routinely recommended for patients at low risk of relapse. A multidisciplinary personalised approach is required for every patient. Genomic profiling can be added to standard pathological markers for more accurate risk stratification.

The long-term adverse effects of endocrine therapy such as thrombo-embolism, and secondary endometrial cancer in the case of tamoxifen and bony fractures and possibly cardiovascular disease in the case of AIs, and the impact of these treatments on patient quality of life should be considered when assessing the potential benefits of extended therapy in order to assist patients in making informed decisions.

Tamoxifen 5 versus 10 years

Towards the end of the last century 5 years treatment with tamoxifen was considered the gold standard in adjuvant hormonal therapy in early breast cancer. This was based on the findings of NSABP B-14 trial extension showed that five years of TAM was superior to ten years in terms of disease-free survival (DFS) (92% versus 86%, $p = 0.003$) and distant disease relapse-free survival (96% versus 90%, $p = 0.01$). Of note, the difference in overall survival (OS) in favour of five years Tam was not statistically significant.[2] A subsequent meta-analysis of adjuvant tamoxifen trials was conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) which included 55 clinical trials involving a total of 37,000 women for durations of one, two and five years of adjuvant tamoxifen.[3]

The risk of breast cancer recurrence and breast cancer specific mortality was lowest for five years of tamoxifen, with an observed risk reduction of 47% for recurrence ($p < 0.00001$) and 20% for breast cancer mortality ($p = 0.003$).[4] Consistent with B-14 trial, the Scottish adjuvant tamoxifen trial demonstrated no benefit of extended adjuvant tamoxifen.[3] These findings in addition to the known adverse effects of long term use of tamoxifen such as secondary endometrial cancer and thromboembolism, led to five years of tamoxifen being considered to be the optimal duration for hormonal adjuvant therapy.

In 2013, the worldwide ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial investigated the use of tamoxifen for 10 years compared with 5 years. The results showed superior OS and DFS in patients who took tamoxifen for 10 years, compared to 5 years.[5] The trial enrolled 12,894 women with early breast cancer who were randomly allocated (1:1) to continue TAM for 10 years or to stop after 5 years (open control) between 1996 and 2005. The cumulative risk of recurrence during years 5–14 was 21·4% for women allocated to continue versus 25·1% for controls; breast cancer mortality during years 5–14 was 12·2% for women allocated to continue versus 15·0% for controls (absolute mortality reduction 2·8%).[5]

In relation to adverse effects, the RR for pulmonary embolus was 1·87 (95% CI 1·13–3·07, $p = 0·01$ with a mortality rate of 0·2% in both treatment groups), for stroke 1·06 (0·83–1·36), ischaemic heart disease 0·76 (0·60–0·95, $p = 0·02$), and endometrial cancer 1·74 (1·30–2·34, $p = 0·0002$). The cumulative risk of endometrial cancer during years 5–14 was 3·1% with a mortality rate of 0·4% for women allocated to continue versus 1·6% with a mortality rate of 0·2% for controls (absolute mortality increases 0·2%). The trial however did not investigate the interaction between the benefit and various clinicopathological parameters in order to identify subgroups of patients who benefitted most from the additional 5 years of therapy. It is unlikely that all patient derived the same magnitude of benefit. For example, women with low risk disease such as node negative small low-grade tumours would not benefit from additional 5 years of tamoxifen but will be exposed to the additional risk of endometrial cancer (absolute additional risk of 1.5%) and thromboembolism (5).

The smaller aTTom (Adjuvant Tamoxifen—To Offer More) trial also reported a lower risk of breast cancer recurrence with a longer duration of tamoxifen therapy.[6] A meta-analysis of extended adjuvant tamoxifen trials found that extended adjuvant tamoxifen was not associated with a significant reduction in recurrence or a reduction in all-cause death in unselected patients.[7] The presence of a significant heterogeneity, the use of a fixed effect model and inability to pool individual patients' data represent significant limitations of this meta-analysis.

Of note, the eligible patients in the trials which demonstrated no benefit from extended adjuvant tamoxifen beyond 5 years were either all node negative or predominantly (77%) lymph node negative.[3] By contrast the two trials reporting reduced risk of breast cancer recurrence with extended adjuvant tamoxifen included a greater proportion of lymph node positive patients.[5,6]

Aromatase inhibitors (AIs)

AIs emerged as a new standard of care for adjuvant endocrine therapy in post-menopausal women in the early part of this century. Studies established that five years of AI or 2–3 years of AI after 2–3 years of TAM was superior to five years of TAM lead to a change in clinical practice.[8] A meta-analysis by the EBCTCG in 2015 showed that the 10-year breast cancer mortality was lower with AIs than with Tamoxifen (12.1% versus 14.2%, RR = 0.85, 0.75–0.96, 2p = 0.009). Furthermore, the risk of breast cancer recurrence was significantly reduced during the first four years of treatment but non-significantly thereafter. The use of AI for five years was superior to the use of Tam for 2–3 years and subsequent use of AI for 2–3 years in terms of breast cancer recurrence (RR = 0.79, 0.81–0.99, 2p = 0.045). However, the breast cancer mortality reduction was not significant.[9] There were fewer endometrial cancers with aromatase inhibitors than tamoxifen (10-year incidence 0·4% vs 1·2%; RR 0·33, 0·21–0·51) but more bone fractures (5-year risk 8·2% vs 5·5%; RR 1·42, 1·28–1·57); non-breast-cancer mortality was similar.[9] Although there is no direct comparison between 10 years of tamoxifen versus 5 years of AI, it appears however that the magnitude of additional benefit in relation to OS and DFS seen with 10 years of Tam is similar to that seen with 5 years AIs in postmenopausal women.

Five recently published studies have investigated whether extending AI after initial TAM/AI therapy adds further benefit (10). The results of these studies have been mixed. They failed to confirm that extended adjuvant therapy in all women with ER + diseases was beneficial. None of the studies was able to show an overall survival benefit. In select subsets of patients, such as patients with ER+ and progesterone receptor (PR+) breast cancer, or patients at higher risk such as N+, pT2 or larger tumours or women who had received prior chemotherapy, there seems to be benefit of extending the duration of adjuvant therapy with AI (10). More recently, Blok et al. found no difference in benefit of 5 years verses 2.5-year extension beyond an initial 5 years of endocrine therapy.[11]

In summary, post-menopausal women with ER positive early breast cancer AIs are considered the new standard of care, in women who have satisfactory bone mineral density. Taking AIs for longer than five years seems to be beneficial for post-menopausal women who have higher risk disease. It should be noted that presently, there remains conflicting data in literature with regards to the additional duration of therapy. Some studies showed reported a small benefit in terms of disease-free survival when comparing ten years with five

years while others showed that the use of AIs beyond seven years did not seem to lead to additional benefit.[12]

Ovarian suppression

The potential benefit of ovarian suppression has been the focus of a recent meta-analysis by Zhang et al.[13] The authors concluded ovarian suppression plays a beneficial role in premenopausal women aged 40 years or younger and advanced stage breast cancer. However, it is associated with an increase in hot flushes and vaginal dryness. There are currently insufficient data to recommend AIs over tamoxifen in this context with no evidence of difference in OS.[10,13]

According to Francis et al.,,premenopausal women with breast cancers that express estrogen receptor and are at high risk of recurrence, warranting adjuvant chemotherapy, should be considered for ovarian suppression for 2–5 years plus Tamoxifen or exemestane.[14] Ovarian suppression has been included in recent recommendations from ASCO, among others.[15]

Genomic profiling

The Recurrence Score (RS) based on a 21-gene assay is being used to guide therapeutic decision-making regarding chemotherapy and endocrine therapy in breast cancer. The RS differentiating patients into a high, middle and low risk groups. While recommendations for the high and low risk groups are clear, the decision-making for the middle group can be controversial.[16] More recently, Sparano et al. (TAILORx trial) reported that adjuvant endocrine therapy and chemo-endocrine therapy had similar efficacy in women with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who had a midrange (16–25) recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger.[17] Therefore, patients with RS greater than 25 should be considered for extended adjuvant endocrine therapy.

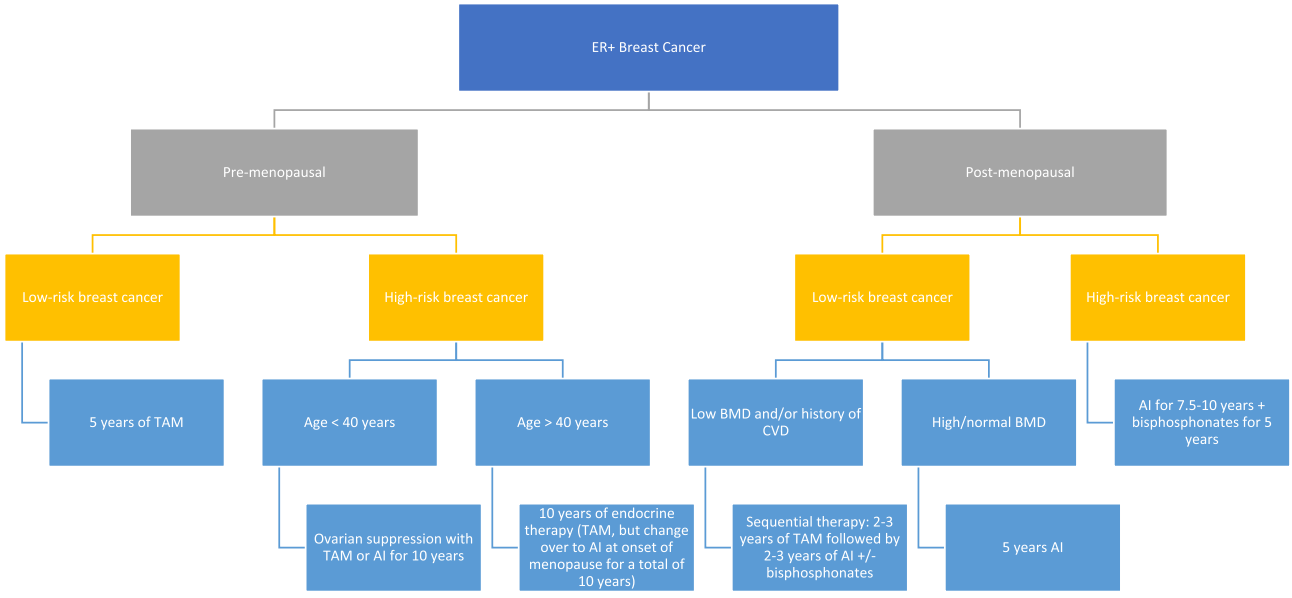
The Breast Cancer Index is a 7-gene assay applicable to cases of node negative, hormone receptor positive early breast cancer, which generates a 10-point Prognostic Score, which estimates the risk of late recurrence, and a Predictive Score, which stratifies patient into groups with low and high-likelihood of benefit from endocrine therapy.[18]

Other genomic profiling assays used in clinical practice include EndoPredict Clinical, and Mammaprint.[19] The former combines molecular profiling with pathological parameters and has been demonstrated to accurately identify those patients with a low 10-year risk of distant relapse after 5 years of adjuvant endocrine therapy[19] suggesting that such patients can avoid the additional adverse effects of extended therapy. However further studies investigating the impact of genomic profiling on optimising the duration of adjuvant endocrine therapy are warranted.

Conclusions & recommendations for clinical practice (Fig. 1)

Considering the above evidence, it would be reasonable to recommend Tamoxifen for ten years in most pre-menopausal women with early ER positive breast cancer. However, those with node negative small grade 1 or grade 2 tumours could opt to have Tamoxifen for five years only, particularly if genomic profiling shows the tumours to be at low risk of relapse within a 10-year period. For patients with node positive, grade 3 and/or large tumours, adjuvant tamoxifen for ten years should be the new standard of care. For post-menopausal women with node negative ER positive breast cancer 5 years of AIs should be sufficient. For those with node positive disease, high grade and/or large tumours, the duration of AI should be increased to 7.5–10 years.[20]

The stratification of risk can be objectively facilitated by the use of genomic profiling which accurately predicts the risk of relapse within 10 years in order to personalise the duration of adjuvant endocrine therapy.[19] Extended adjuvant endocrine therapy can be recommended if the molecular score suggests a higher risk of relapse within 10 years.



AI: aromatase inhibitors; BMD: Bone mineral density; CVD: Cardio-vascular disease; TAM: tamoxifen.

Fig. 1. Clinical algorithm summarising the recommendations regarding the use of adjuvant endocrine therapy in early ER + breast cancer.

Postmenopausal women with low risk disease and low bone mineral density can opt to have sequential therapy (Tam then AI). However, those with high risk tumour and low bone mineral density are best treated with AI upfront in addition to bisphosphonates. In addition to counteracting the adverse impact of AI on bone density, bisphosphonates have been recently reported to reduce the risk relapse and improve survival.[21]

Finally, the long-term adverse effects of endocrine therapy such as thrombo-embolism, and secondary endometrial cancer in the case of tamoxifen and bony fractures and cardiovascular disease[22] in the case of AIs, and the impact of these treatments on quality of life are extremely important aspects that should be an essential part of the discussion with the patient in order to make an informed choice.

These recommendations are presented in algorithmic form to aid in clinical decision making (Fig. 1).

Since genomic profiling has been shown to accurately identify patients at very low risk of distant recurrence after five years of adjuvant endocrine therapy,[20] such tools can be used to guide extended endocrine therapy decisions where patients with high risk scores can be advised to receive extended adjuvant endocrine therapy for 7–10 years and those with low risk scores can be adequately treated with five years of adjustment to adjuvant endocrine therapy alone.[23] Furthermore, the linear let relationship between these scores and disease outcome could allow us to fine tune the duration of endocrine therapy in order to maximize benefit and minimize adverse effects. Therefore, those with low scores can receive five years of therapy, whereas patients with moderate risk scores can receive seven years and high score patients can receive 10 years of treatment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

Wazir U and Mokbel K drafted the manuscript. Wazir A proofread the manuscript. Mokbel L made the diagrams.

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