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Choosing early adjuvant therapy for postmenopausal women with hormone-sensitive breast cancer: Aromatase inhibitors versus tamoxifen

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Abstract

Aims: The aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole have demonstrated superior disease-free survival (DFS) over tamoxifen in several trials. As the choice of adjuvant endocrine treatment for early breast cancer (EBC) is evolving from tamoxifen to the AIs, this review compares the AIs with tamoxifen to help surgeons choose a treatment plan that provides the greatest reduction of recurrence risk for their patients.
Methods: MEDLINE was searched to identify relevant literature on the adjuvant use of tamoxifen and AIs in EBC.
Results: Despite the use of adjuvant tamoxifen, recurrence is a persistent threat to women with hormone-sensitive EBC. Trials of the AIs versus tamoxifen have established that patients benefit from longer DFS, and in some cases distant DFS, after the use of an AI as initial adjuvant therapy, as switch therapy following 2–3 years of tamoxifen, or as extended adjuvant therapy following 5 years of tamoxifen. The AIs are well tolerated, with a different safety profile than that of tamoxifen in all these settings. Trials addressing the optimal regimen and treatment duration for AIs are also underway.
Conclusions: The advantage in DFS associated with AIs over tamoxifen use should prompt physicians and patients to consider the use of an AI as the initial adjuvant endocrine therapy or, alternatively, switching patients who currently take tamoxifen to an AI for the remainder of adjuvant endocrine therapy. Prolonging the period of adjuvant therapy with letrozole after 5 years of tamoxifen reduces recurrence and is associated with a survival advantage in node-positive patients.

Keywords: Early recurrence; Tamoxifen; Breast cancer; Letrozole; Distant metastases; Aromatase inhibitors; Adjuvant therapy

Introduction

Breast cancer is the most common female cancer in developed countries. In 2004, breast cancer was the most common cancer among women in Europe, with an estimated 370 100 new cases diagnosed, and the most common cause of cancer death in European women, with 129 900 deaths.[1] Even though most women now present with early-stage breast cancer,[2] there is an ongoing risk of disease recurrence.[3] The benefits of available adjuvant treatments need to be carefully weighed in order to reduce this risk, not least because therapies shown to reduce the risk of breast cancer recurrence are likely to have a significant beneficial effect on survival in patients with early breast cancer.[4,5] Five years of tamoxifen, the standard adjuvant, endocrine therapy,[3] is now known to be inferior to treatment with the third-generation aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole, which are approved for treatment in a variety of adjuvant settings. This review will discuss the use of AIs in comparison with tamoxifen in the different early adjuvant treatment settings that reduce breast cancer recurrence risk, to help surgeons choose a treatment plan that will provide the greatest protection for their patients.

Breast cancer recurrence risk

For most women with early-stage breast cancer who undergo surgery there is a constant, ongoing risk for recurrence, but effective adjuvant therapy reduces this risk. Studies have shown that for women receiving adjuvant therapy after surgery, the risk of recurrence peaks early, at about 1–3 years after primary therapy (Table 1), decreasing thereafter until 5 years; beyond 5 years, the risk persists and decreases

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Table 1
Hazard of recurrence by extent of disease, treatment, and yearly interval post surgery[6]

	Hazard of recurrence				
	Years 0–1	Years 1–2	Years 2–3	Years 5–6	Years 11–12
Group					
All breast cancer	7.7	13.3	11.9	4.5	1.6
Nodes					
0	5.9	7.1	7.3	1.9	0.0
1–3	4.3	7.9	9.5	3.7	0.6
4+	11.9	23.6	18.9	8.5	3.8
Treatment					
Chemotherapy	8.1	13.3	14.3	2.9	0.8
Chemotherapy + tamoxifen	7.0	15.4	12.7	5.9	4.3

slowly but never reaches zero.[6,7] Beyond the 5-year mark, recurrence is more of a problem in patients with oestrogen-receptor-positive (ER+) disease than in those with ER-negative (ER−) tumours.[8] Some predictors for early relapse include grade III tumours, low-positive ER status, and higher lymph-node involvement.[9] Importantly, the majority of these early relapses are distant metastases.[10,11] Because distant metastatic events are associated with worse overall survival (OS),[4] choosing therapies shown to reduce the risk of breast cancer recurrence, especially distant metastases, are likely to have a significant beneficial effect on survival in patients with early breast cancer.

Adjuvant tamoxifen treatment

Efficacy

Most ER+ breast cancers are dependent on oestrogen for growth, and the use of ER antagonist drugs such as selective oestrogen-receptor modulators and especially tamoxifen has to date dominated adjuvant treatment of early breast cancer.[3] In women with ER+ tumours, 5 years of adjuvant tamoxifen therapy significantly reduced the relative risk of breast cancer recurrence by 41% and mortality by 34%.[3] Five years of tamoxifen also significantly reduced the appearance of contralateral breast cancer by approximately 39%.[3,12] A troubling aspect of tamoxifen use as early adjuvant treatment is that some patients demonstrate de novo resistance and thus relapse during the first few years of the planned 5-year course of treatment.[13] An additional limitation of tamoxifen use is that therapy beyond 5 years has not been shown to be beneficial.[14]

Tamoxifen safety

The long-term safety profile of tamoxifen is well understood and undoubtedly limits its use. Almost two thirds (63%) of tamoxifen patients reported at least one adverse effect, with 23–40% of women in clinical trials stopping adjuvant tamoxifen because of tolerability issues.[15] Notably, older women (>80 years) are the most likely to stop therapy, putting themselves at risk of recurrence.[16]

Long-term adverse effects associated with 5 years of adjuvant treatment with tamoxifen can be significant and include venous thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, vaginal discharge, endometrial and uterine cancer and hysterectomy.[17–20] Recent studies have shown that an excess of the more serious adverse events occurs early in tamoxifen therapy.[21,22]

Improvement is needed from both a clinical efficacy and a side-effect profile standpoint for drugs used as early adjuvant therapy in women with ER+ breast cancer.

Adjuvant aromatase inhibitor treatment

AIs prevent oestrogen synthesis in postmenopausal women by inhibiting the aromatase enzyme, which converts androgens to oestrogen, primarily in peripheral fat. This mode of action is in contrast to that of tamoxifen, the net effect of which is to block oestrogen at the oestrogen receptor on breast cancer cells, but it continues to act as an oestrogen agonist in other tissues. The lack of oestrogen agonist activity accounts for the observation that AIs do not increase the risk of endometrial cancer or thromboembolic events.[23]

The third-generation AIs have demonstrated superiority over tamoxifen in clinical trials in terms of disease-free survival (DFS) in a variety of adjuvant settings, including initial adjuvant therapy, switch adjuvant therapy, and extended adjuvant therapy (Fig. 1).[17,24–26] It is important that the most effective adjuvant therapy is chosen. Yet, although the third-generation AIs are now approved as adjuvant treatment for breast cancer, there is still debate regarding the optimal use of AIs and tamoxifen in the management of postmenopausal women with ER+ breast cancer. A review of the current evidence provides insights into which treatment strategy is likely to be most effective at reducing early and late recurrences.

Comparing clinical trials

Several large clinical trials compare AIs with tamoxifen, but to date, there are no head-to-head comparisons of AIs in the adjuvant setting (Fig. 1). Comparisons between trials are fraught with difficulty, and evaluating the magnitude of any differences within trials can sometimes be obscured. When evaluating trial data, it is important to distinguish between absolute risk reduction and relative risk reduction (Table 2). Relative risk reduction, or risk ratio, refers to the risk of recurrence in the experimental group divided by the risk of recurrence in the control group; it is usually expressed as a percent and specifically describes patient benefits.[27] Absolute risk reduction refers to the risk of recurrence in the experimental group minus the risk of recurrence in the