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Short review

Start strong or switch? Adjuvant endocrine strategies for postmenopausal women with hormone-sensitive breast cancer

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Abstract

Women are at considerable risk of recurrence in the first few years following initial treatment for early breast cancer. To reduce the risk of recurrence, including distant metastases, those with hormone-sensitive breast cancer receive adjuvant endocrine treatment. Lymph node metastases are a predictor of high risk of early recurrence and distant metastases; however, a significant number of women with node-negative disease will also develop distant metastases. This is of concern, because the development of distant metastases is associated with a high risk of breast cancer death. Studies in postmenopausal women showed that an aromatase inhibitor (AI) as initial, upfront treatment reduces early recurrence, including distant metastases, compared with tamoxifen. The three available AIs (letrozole, anastrozole, and exemestane) are approved for adjuvant use. Upfront letrozole or anastrozole improved time to distant metastasis in patients included in the Breast International Group 1-98 and Arimidex, Tamoxifen, Alone or in Combination trials, respectively. Of note, the beneficial effects of letrozole on distant disease were already observed in the first report at 2 years of follow-up and confirmed in the updated results with 50 months of follow-up. Here, we discuss the available data for all AIs and strategies to be taken into account for patient management, with a special focus on the effects of available options on early recurrences and metastasis risk.

Keywords: Aromatase inhibitors; Letrozole; Anastrozole; Exemestane; Breast cancer

1. Introduction

Surveillance data show that, like women worldwide, European women are more likely to be diagnosed with breast cancer than any other cancer. In 2006 in Europe, the most common form of cancer was breast cancer (429,900 cases), accounting for 13.5% of all cancer cases; in women, breast cancer is the leading cause of cancer death (16.7%). Decreasing mortality has been noted in younger women, but mortality is still increasing in older women [1].

Following primary surgical treatment, long-term follow-up indicates that nearly one half (45%) of breast cancer patients will experience a recurrence, with the greatest risk among postmenopausal women. Recurrence risk peaks in the first few years after surgery [2]. In one study of postmenopausal women with breast cancer who received adjuvant tamoxifen therapy ($N = 4145$; 75% with estrogen receptor-positive disease [ER+]), the cumulative risk of distant metastases peaked to 3.2% at 2 years, and the overall cumulative recurrence rate was 4.2% at 2 years after successful surgery [3]. Recurrence events include both loco-regional, contralateral, and distant metastases, with the latter accounting for the majority of relapse events [4]. Compared with local recurrence, the appearance of distant metastases is associated with poorer survival [5].

Abbreviations: ABCSG, Austrian Breast and Colorectal Study Group; AIs, aromatase inhibitors; ARNO, Arimidex–Nolvadex; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG 1-98, Breast International Group 1-98; DFS, disease-free survival; ER+, estrogen receptor-positive; FACE, Femara Anastrozole Clinical Evaluation; GROCTA 4B, Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group; HR, hazard ratio; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Arimidex; ITT, intent-to-treat; OR, odds ratio; OS, overall survival.

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The selective estrogen receptor antagonist tamoxifen had been the mainstay, upfront adjuvant therapy in women with ER+ disease. Five years of tamoxifen therapy demonstrated a 41% decrease in the annual risk of recurrence and a 34% decrease in the risk of death in women with ER+ disease [6]. However, the approval of three third-generation aromatase inhibitors (AIs), anastrozole, letrozole, and exemestane, has expanded the choice of treatment for physicians and patients in this setting. Multicenter trials such as the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [7] or the Breast International Group 1-98 (BIG 1-98) study [8,9] report a significantly superior disease-free survival (DFS) benefit for anastrozole or letrozole, respectively, when compared with tamoxifen as initial upfront therapy. Switching treatment to an AI after 2–3 years of initial tamoxifen has also been demonstrated to be superior to continuing with tamoxifen for 5 years in terms of DFS [10,11]. It is not yet clear if one treatment strategy is superior to the other, or if one strategy is of particular benefit to specific subpopulations. Here we review the risk of early recurrence following primary surgery and how effective AIs and tamoxifen are at reducing this risk. This may assist physicians in discussing therapeutic options with their patients.

2. Early recurrence risk and the risk of distant metastases

There is a peak of recurrence early on at 2 years post surgery, but there is an ongoing risk of recurrence that persists for up to 15 years [2,6]. The average hazard of recurrence was 4.3% per year for the time between years 5 and 12 [2] (Fig. 1) [12,13]. Women with positive nodes [2] and higher-grade tumors were more likely to recur compared with women with negative nodes or lower-grade tumors. Positive nodal status also confers a greater risk for early recurrence (Fig. 1), as well as an increased risk of distant metastases.

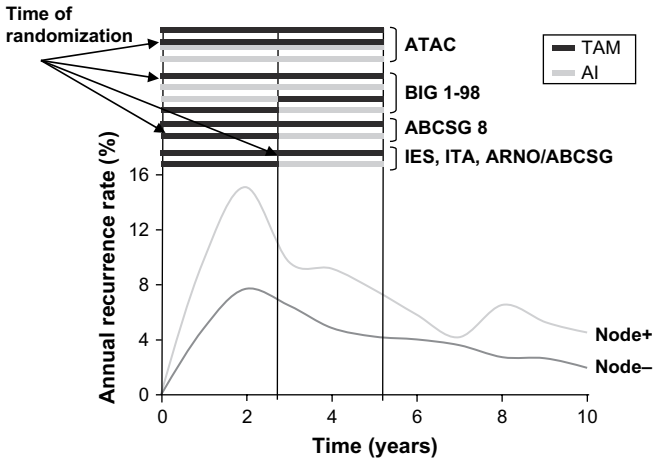

Fig. 1. Adjuvant aromatase inhibitor treatment strategies for reducing the early risk of relapse in postmenopausal women with hormone receptor-positive breast cancer [12,13]. ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG 1-98, Breast International Group 1-98; ABCSG 8, Austrian Breast and Colorectal Study Group 8; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Arimidex; ARNO, Arimidex–Nolvadex; TAM, tamoxifen; AI, aromatase inhibitor; node+, node-positive; node–, node-negative.

Distant metastases are the most common recurrence event. Using a cancer registration database, recurrence was computed in breast cancer patients diagnosed in 1996 and 1997 in the West Midlands. At a median follow-up of 70 months, 20.6% of women had distant recurrences, and 9.4% of the women had local or nodal recurrences [14]. Similar findings were observed in another retrospective analysis of women with early breast cancer (at a median follow-up of 44 months post surgery), where distant metastases accounted for 58.3% of recurrence events compared with local events (26.1%) or contralateral events (15.6%) [4].

While the presence of positive nodes confers more recurrence risk, even women with negative nodes may experience recurrence with distant metastases. In a study quantifying the risk of delaying primary surgery, 21% of node-negative patients with small (approximately 2 cm) tumors developed distant metastases [15]. When more than one half (51%) of distant metastases occurred with 18 months of follow-up from surgery, 14% of these were in node-negative patients [16].

Addressing the occurrence of distant metastases has importance for patients, because distant metastases are associated with poor survival. One study reported that the 5-year overall survival (OS) probabilities for patients with distant, locoregional, and contralateral recurrences and no relapse events were 41.3%, 59.3%, 83.4%, and 91.7%, respectively [4]. Data from adjuvant chemotherapy and endocrine trials indicate that improvements in distant DFS can signal subsequent improvements in OS [17], suggesting that the risk of metastases may be a better measure of the survival benefit of various therapies.

3. Currently available endocrine therapies for postmenopausal patients: Tamoxifen and aromatase inhibitors

The available adjuvant endocrine therapies for the treatment of postmenopausal women with hormone-sensitive breast cancer include tamoxifen and the third-generation AIs anastrozole, letrozole, and exemestane. Tamoxifen had been the standard adjuvant therapy until recently, but the AIs have shown superiority over tamoxifen in reducing recurrence risk and are currently recommended [18,19].

The Early Breast Cancer Trialists' Collaborative Group has, since 1984, collected data on more than 300,000 women treated for early breast cancer. Long-term follow-up shows that 5 years of adjuvant tamoxifen in postmenopausal women can almost halve the recurrence rate and reduces mortality by one-third [6,20]. Of concern, however, is the percentage of women who relapse long after tamoxifen therapy is complete. The British breast cancer database study ($N = 4159$) reported, at a median follow-up of 7.4 years, that relapse rates were 7.4%, 14.5%, and 25.9% at 2.5, 5, and 10 years, respectively, following initial diagnosis [21]. Another concern is the side-effect profile of tamoxifen. Significant adverse events associated with tamoxifen use include venous thromboembolic events, pulmonary embolism, vaginal bleeding, vaginal discharge, ischemic cerebrovascular events, and endometrial cancer [7,22–24]. An excess of serious, life-threatening adverse events