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Review Article

Current advances in endocrine therapy options for premenopausal women with hormone receptor positive breast cancer

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HIGHLIGHTS

- Consider exemestane plus ovarian function suppression for premenopausal HR+ women
- Premenopausal HR+ breast cancer patients should be treated with tamoxifen (10 yrs).
- Premenopausal HR+ breast cancer pts may benefit from endocrine therapy and ovarian function suppression.

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1. Introduction

The American Cancer Society estimates 252,710 women will be diagnosed with breast cancer in the United States in 2017 [1]. Breast cancer accounts for 30% of all new cancers in women. The median age of

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diagnosis is 61 years. Although breast cancer mostly occurs among older women, in rare cases it can occur in women younger than 45 years of age. About 11% of all new breast cancers in the United States are diagnosed in women younger than 45 years of age who are still premenopausal [2].

About 70% of invasive breast cancers are hormone receptor (HR) positive. The mainstay of treatment for all women with HR positive breast cancer is endocrine therapy either after chemotherapy or as endocrine therapy alone. The decision to recommend chemotherapy in HR positive breast cancer is multifactorial. Factors such as presence of HER2/neu overexpression, lymph node involvement, and genomic tests such as Oncotype DX (Genomic Health, Redwood City, CA) play a role in decisions to recommend chemotherapy in HR positive breast cancer. Whether or not chemotherapy is recommended, all patients with HR positive breast cancer are recommended to have adjuvant endocrine therapy.

Different options for endocrine therapy have recently been reported for premenopausal women with HR positive breast cancer and include ovarian function suppression (OFS).

In this review, we focus on the different strategies related to adjuvant endocrine therapy, including length of time of treatment, type of endocrine treatment, use of ovarian suppression, and adverse effects of different types of endocrine therapy.

2. Adjuvant endocrine therapy

Adjuvant endocrine therapy is recommended for all patients with HR positive breast cancer (including estrogen receptor [ER] positive, and/or progesterone receptor [PR] positive).

Recent studies have extended the recommendation of length of time for endocrine therapy to 10 years. Additionally, the International Breast Cancer Study Group (IBCSG) randomized phase 3 trials, the Suppression of Ovarian Function Trial (SOFT), and the Tamoxifen and Exemestane Trial (TEXT) have reported on the impact of OFS in premenopausal women with HR positive breast cancer who are recommended to receive endocrine therapy [3,4].

Current options for endocrine therapy now include tamoxifen alone, and ovarian suppression with tamoxifen or an aromatase inhibitor (AI). The decision to proceed with one particular therapy should not only factor into the risk of relapse and effectiveness of therapy, but also include presence of co-morbidities, side effects, and patient preference. Issues specific for younger patients, such as desire for future pregnancy, side effects, and quality of life, should also factor into treatment decisions regarding adjuvant endocrine therapy.

3. Duration of use of endocrine therapy

Tamoxifen use is the standard of care for premenopausal women with HR positive breast cancer, as 5 years of therapy has been demonstrated to reduce the annual breast cancer death rate by 31% [5]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2011 meta-analysis demonstrated that 5 years of tamoxifen compared to none was associated with a 15-year risk reduction for breast cancer-specific recurrence and a mortality reduction of 39% [6].

Additionally, data from the ATLAS (*Adjuvant Tamoxifen: Longer Against Shorter*) and aTTom (*The United Kingdom adjuvant Tamoxifen—To offer more*) studies demonstrate a reduction in recurrence and mortality after 10 years of tamoxifen therapy [7,8].

The ATLAS randomized trial included 12,894 women with early breast cancer who had completed 5 years of treatment with tamoxifen. They were randomly allocated to continue tamoxifen to 10 years or stop at 5 years. The ATLAS trial's analysis of 6846 women with ER positive disease demonstrated that allocation to continue tamoxifen reduced the risk of breast cancer recurrence (recurrence rate ratio [RR] 0.84, 95% confidence interval [CI] 0.76–0.94), reduced breast cancer mortality ($p = 0.01$), and reduced overall mortality ($p = 0.01$).

With regard to toxicity, there was a noted increased risk of endometrial cancer (RR 1.74, 95% CI 1.3–2.34) and pulmonary embolus (RR 1.87, 95% CI 1.13–3.07) after 10 years of use. It was noted that the cumulative risk of endometrial cancer during years 5–14 was 3.1% (mortality 0.4%) for women allocated to continue versus 1.6% (mortality 0.2%) for controls (absolute mortality increase 0.2%). The authors concluded that the small increase in endometrial cancer risk for women who were allocated to continue tamoxifen for 10 years was outweighed by the decrease in breast cancer mortality noted.

A similar trial, the aTTom trial, randomized 6953 women, of whom 2755 were ER positive and 4198 were untested, to 5 years or tamoxifen or extended tamoxifen (10 years) at 176 United Kingdom centers. Although 4198 tumors were untested for ER receptors, the investigators estimated that 80% of those untested would be ER positive if their statuses were known. This is consistent with the fact that the majority of breast cancers are HR positive, and, in many studies, testing for HR receptor status is not uniformly performed.

Similar to the ATLAS trial, aTTom noted allocation to continue tamoxifen for 10 years significantly reduced breast cancer recurrence (580/3468 vs 672/3485, $p = 0.003$). This reduction was time dependent, with the extended longer treatment demonstrating a reduction in both breast cancer mortality (rate ratio [RR] 0.86, 95% CI 0.75–0.97) and overall mortality. An increase in endometrial cancer was also noted (RR 2.20, 95% CI 1.31–2.34, $p < 0.0001$). In analyzing the patient population, the ATLAS trial included premenopausal women, as 19% of patients were under 45 years of age (median age 45 years) in each of the study arms and 32% of the women were between 45 and 54 years of age (median age 49 years) in each study arm.

Thus, extended duration of therapy benefits seen in premenopausal women mirrors what is noted in postmenopausal women with 10 years of endocrine therapy. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA-17 study randomized postmenopausal patients who had completed 5 years of tamoxifen to 5 years of letrozole or no further treatment. At a median follow-up of 30 months, letrozole significantly improved disease-free survival (DFS) ($p < 0.001$), the primary end point, compared with placebo (hazard ratio for recurrence or contralateral breast cancer 0.58; 95% CI 0.45–0.76, $p < 0.001$) [9]. Although it is likely that the extended therapy may have greatly contributed to the benefit, the addition of an AI to tamoxifen therapy may also have played a role.

In 2014 the American Society of Clinical Oncology (ASCO) updated its clinical guidelines to recommend women with stages I–III HR positive breast cancer who are premenopausal/perimenopausal after 5 years of tamoxifen therapy continue therapy for a total duration of 10 years [10].

4. Aromatase inhibitors (AIs)

The ATAC (*Arimidex, Tamoxifen, Alone or in Combination*) and BIG (*Breast International Group*) 1–98 trials found that adjuvant therapy with an AI is better than tamoxifen in HR positive postmenopausal breast cancer [11,12]. Data from these large studies highlighting the superiority of AIs over tamoxifen contributed to the interest in adding OFS to premenopausal women with the goal of achieving a postmenopausal state that would allow use of an AI. Premenopausal women are not candidates for AIs without OFS because AIs alone can result in incomplete hormonal blockade of endogenous estrogens.

Ovarian function suppression added to endocrine therapy

Ovarian ablation by surgical resection (oophorectomy) or radiation therapy as an adjuvant to breast cancer treatment was tested as early as the 1970s. Ovarian ablation was found to be an effective adjuvant therapy in the absence of chemotherapy for patients with early breast cancer.

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