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Original article

Adjuvant endocrine therapy for premenopausal women with hormone-responsive breast cancer

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A B S T R A C T

Multiple strategies for endocrine treatment of premenopausal women with hormone-responsive breast cancer have been assessed and results have been presented over the last two years. These include tamoxifen for 5–10 years (ATLAS and aTTom), tamoxifen for 5 years followed by aromatase inhibitor (AI) for 5 years for women who have become postmenopausal (MA-17); ovarian ablation (OA) by surgery (EBCTCG overview); ovarian function suppression (OFS) by LHRH agonist (LHRH agonist meta-analysis); or combinations of approaches including OFS plus tamoxifen or AI (SOFT, TEXT, ABCSG 12 and E3193). Many of these trials have taken place in the backdrop of (neo)adjuvant chemotherapy which can confound interpretation because such therapy can suppress ovarian function either transiently or permanently. Nonetheless these trials suggest in aggregate that 10 years of tamoxifen are better than 5 years and that a program of extended adjuvant therapy of tamoxifen for 5 years followed by aromatase inhibitor for 5 years is effective for suitable candidates. The SOFT and E3193 trials do not show a major advantage for use of OFS + tamoxifen compared to tamoxifen alone. The joint SOFT/TEXT analysis and ABCGS12 trials both suggest that outcomes can be excellent with the use of combined endocrine therapy alone in properly selected patients but give conflicting results with regard to potential benefits for OFS + AI compared with OFS + tamoxifen. Further work will be needed to ascertain long-term outcomes, identify factors that predict who will benefit from extended adjuvant endocrine therapy, and assess role of OFS by medical or surgical means. It is clear, however, that endocrine therapy is a critical part of the adjuvant regimen for most premenopausal women with hormone-responsive breast cancer, and a subset of these women with luminal A-type tumors can be safely treated with endocrine therapy alone.

Introduction

The past two decades have witnessed tremendous advances in the treatment of breast cancer with significant strides made in improving outcomes in women with early breast cancer [1]. Adjuvant endocrine treatment in hormone responsive breast cancer has significantly contributed to this positive trend [2]. Three major adjuvant endocrine treatment options exist - tamoxifen, aromatase inhibitors (AI) and ovarian function suppression (OFS) either by ovarian ablation (surgical bilateral oophorectomy or ovarian irradiation) or using medications such as Gonadotropin-Releasing Hormone (GnRH) agonists (also known as Luteinizing Hormone-Releasing Hormone [LHRH] agonists). Various meta-analyses of randomized clinical trials have helped define the use of these three approaches either alone or in combination or in sequence in the adjuvant setting [3–5]. However, recent publications of trials investigating extended endocrine therapy and refining our knowledge about the role of OFS have illuminated this field further [6–11]. This article aims to review the recent updates in the field of adjuvant endocrine treatment of breast cancer in premenopausal women, especially with regards to the type and duration of treatment.

Data about extended adjuvant endocrine treatment

Tamoxifen

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual patient data meta-analysis continues to show a

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significant reduction of breast cancer deaths in patients with hormone receptor-positive breast cancer who received five years of tamoxifen, including women who were likely premenopausal by virtue of age at time of diagnosis, even after 15 years from study entry [3]. This comprehensive meta-analysis proved several principles of tamoxifen therapy. First, tamoxifen was found to be useful in decreasing breast cancer death and recurrence in hormone responsive breast cancer, even in weakly hormone receptor-positive tumors; but it did not improve breast cancer outcomes in hormone receptor-negative disease. Second, the benefit of at least 5 years of tamoxifen carries over for at least 10 more years (carry-over effect). Third, an improvement in breast cancer mortality was seen across all age groups, irrespective of menopausal status; although the risk of uterine cancer was higher in older women (Relative Risk [RR] of 2.96 in ages 55–69, 1.75 in ages 45–54 and 1.04 in women less than 45 years old). Finally, it also confirmed that longer tamoxifen use (5 years) was more efficacious than shorter duration (1–2 years).

Based on small trials 5 years of adjuvant tamoxifen use has been the prevailing standard of care for more than a decade, though it was hypothesized that extended tamoxifen treatment could result in further improvement in outcomes. The joint analysis of E4181 and 5181 trials supported a longer time to relapse with a strategy of indefinite tamoxifen use compared to only 5 years in the subgroup of hormone receptor-positive disease ($p = 0.014$), whereas the National Surgical Adjuvant Breast and Bowel Project (NSABP) B14 and the Scottish Adjuvant Tamoxifen trial found no beneficial effect with extended tamoxifen use [12–14]. More recently, two large randomized trials with a similar study design - Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial and the adjuvant Tamoxifen—To offer more (aTTom) trial - provide further guidance to answer the important question of extended tamoxifen use in hormone responsive breast cancer [6,7].

Although the ATLAS trial randomized 12,894 women with early breast cancer, the primary analysis was restricted to patients with hormone receptor-positive disease ($n = 6846$) [6]. The study found a 2.8% absolute breast cancer mortality reduction for patients on extended tamoxifen use versus tamoxifen for 5 years after 10 years from randomization or 15 years from diagnosis of early-stage breast cancer (12.2% vs. 15.0%). The relative risk reduction was most notable after the end of the 10-year tamoxifen use (breast cancer mortality recurrence rate ratio in years 10–14 = 0.71 [95% confidence interval (CI) 0.58–0.88]). Both the recurrence rate ratio and breast cancer mortality rate ratio were non-significant between the two cohorts in the years 5–9. Similar effects were seen across all subgroups of clinical importance, such as age, nodal status, tumor size, and menopausal status at study entry although only about 11% of women were premenopausal.

The UK counterpart of the ATLAS trial – aTTom – randomized 6953 women who completed 5 years of adjuvant tamoxifen treatment to 5 more years of tamoxifen or none. Sadly estrogen receptor [ER] status was untested in many of these women [7]. The results of the aTTom trial were quite similar to the ATLAS. Patients on extended tamoxifen had significant reduction in breast cancer recurrence, breast cancer mortality and death during 10–14 years. The full publication of the aTTom trial is eagerly awaited. Taken together, ATLAS and aTTom trials provided strong evidence favoring extended tamoxifen for total treatment duration of 10 years rather than 5 years for selected patients [3,6,7]. The benefit appears to be enjoyed by premenopausal women though the numbers of such women in these studies are small.

Aromatase inhibitors

Aromatase inhibitors (AI) are a mainstay for management of breast cancer in postmenopausal women but are contraindicated as monotherapy for premenopausal patients. One proven strategy for extended adjuvant endocrine therapy in postmenopausal women involves completion of 5 years of tamoxifen followed by 5 years of adjuvant letrozole based on the results of the MA17 trial [15]. The MA17 trial found a 6% absolute improvement in 4-year disease-survival rate (87% vs. 93%) favoring letrozole compared with placebo. Importantly the same benefit was seen for women who were premenopausal at the time of tamoxifen initiation but became postmenopausal during tamoxifen administration [16]. Similar results were observed with the use of exemestane, a steroidal aromatase inhibitor (NSABP B33 trial) [17]. The results of the MA17 and NSABP B33 trials provide an alternative approach for extended adjuvant therapy for patients who are pre- or perimenopausal at the start of adjuvant tamoxifen treatment and then become postmenopausal while on treatment. This strategy might mitigate risk for endometrial cancer when compared with the use of 10 years of tamoxifen, making it an attractive strategy so long as it is clear that the patient has truly become menopausal before AI is started.

Adverse effects of extended endocrine treatment

The benefit of extended tamoxifen treatment comes with relatively low cost and toxicity, especially for premenopausal women. The ATLAS trial showed increased relative risk for incidence of pulmonary embolism (RR 1.87, 95% CI 1.13–3.07) and endometrial cancer (RR 1.74, 95% CI 1.30–2.34). No difference in risk for stroke was noted [6], and extended tamoxifen use was found to have a protective effect on the risk for ischemic heart disease. Unfortunately, the ATLAS trial does not report on quality of life outcomes such as sexual dysfunction or menopausal symptoms.

The major concern with extended tamoxifen was the report of a 0.2% absolute mortality increase due to endometrial cancer (0.4% vs. 0.2%) in this study in which about 90% of study participants were postmenopausal at study entry. Similarly, the aTTom trial also reported an increase in mortality with an absolute risk of 0.5% (1.1% vs. 0.6%; $p = 0.02$) [7]. It seems likely that the elevated risk of endometrial cancer is largely a function of the predominance of postmenopausal women in these trials, and this could support a strategy to switch from tamoxifen to an AI if the patient becomes postmenopausal.

This approach is not devoid of side effects however. The MA17 trial reports increased incidence of hot flashes, arthritis, arthralgia and myalgia and slightly higher incidence of osteoporosis in patients on extended letrozole compared to placebo (5.8% vs. 4.5%; $p = 0.07$), although there was no difference in fracture rates [15]. The NSABP B33 trial noted a higher incidence of grade 3 or 4 arthralgia (1.0% in exemestane group vs. 0.5% in placebo) and fatigue [17]. No difference in fracture rates was seen.

Overall, the strategy of extended tamoxifen use appears to be safe in premenopausal women. The efficacy and safety data from the extended aromatase inhibitor trials also support a switch strategy from tamoxifen to an AI upon attaining menopause, for up to 5 years (total 10 years of endocrine treatment).

American Society of Clinical Oncology guideline

After reviewing the above mentioned trials, the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline committee on adjuvant endocrine therapy for women with hormone responsive breast cancer recommended tamoxifen for 10 years, or tamoxifen for 5 years followed by either an aromatase inhibitor for 5 years (if patient is postmenopausal at the end of year 5) or tamoxifen for 5 more years (if patient is pre- or postmenopausal at the end of year 5) [18]. In aggregate then, the ASCO guideline endorsed extended adjuvant endocrine treatment for 10 years in