

Adjuvant hormonal therapy in premenopausal women with breast cancer

INTRODUCTION

Breast cancer remains the second most common cause of cancer worldwide.^[1] The American Cancer Society estimated in 2014 that women under 45 years of age would account for ~11% of new invasive breast cancer cases and ~6% of deaths from the disease.^[2] The incidence, particularly in younger women, has increased in the last decade. Approximately 60% of women under 50 years age have the estrogen receptor-positive (ER+) disease.^[3] Endocrine therapy is integral to the management of hormone-dependent breast cancers and the expression of the ER α and/or the progesterone receptor by the tumor is a well-established predictor of response to endocrine therapy.^[4,5] Estrogen production in the premenopausal woman is predominantly from the ovary, in contrast to the postmenopausal woman, whose primary source of estrogen is from peripheral aromatization (aromatase-mediated conversion of androstenedione and testosterone to estrone and estradiol in extragonadal tissues). As a result, strategies that prevent/impede ovarian estrogen production or that antagonize/modulate its effects at the receptor have been the mainstay of adjuvant endocrine therapy in premenopausal women. Recent data have now also defined a role for aromatase inhibitors (AIs) with ovarian suppression in this patient population but determining when and how to offer more than 5 years of tamoxifen for an individual remains a challenge in the clinic.

TAMOXIFEN

Tamoxifen is a first-generation selective ER modulator. Endoxifen, its active hydroxylated metabolite, produces its antagonistic effect on breast cancer cells by inhibiting translocation and nuclear binding of the ER.^[6] Tamoxifen has been the traditional standard of care recommendation for women with early stage ER+ breast cancer. From 1995, it was recognized as useful regardless of menopausal status.^[7] In 2011, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) ($n = 10,645$) reported that independent of age, nodal status, or use of chemotherapy, 5 years of tamoxifen considerably reduced recurrence rates (by 39% relative risk [RR] for recurrence 0.61, 95%) throughout the first 10 years, translating into

a 13% absolute reduction in the risk of recurrence at 15 years (33% vs. 46%).^[8] Tamoxifen also reduced breast cancer mortality risk by 30% (RR for death 0.70, 95% confidence interval [CI], 0.64-0.75) with a 9% absolute reduction in breast cancer-related death observed at 15 years (24% vs. 33%).^[8]

Duration of tamoxifen

Tamoxifen use was truncated at 5 years based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) B14 study. While this trial initially showed that 5 years of treatment was effective as compared to no-tamoxifen for hormone receptor positive, node negative breast cancer (mostly postmenopausal), a re-randomization of the treated cohort suggested that 10 years of therapy could be inferior to five.^[9,10] This observation guided practice globally.

Subsequently, Adjuvant Tamoxifen Longer Against Shorter (ATLAS) and Adjuvant Tamoxifen; to Offer more? (aTTom) were conducted and their results suggest a survival benefit for longer durations of tamoxifen.

The ATLAS trial reported outcomes in 6846 women allocated to continue tamoxifen to 10 years or stop at 5 years (open control).^[11] Women who continued tamoxifen had a reduced risk of breast cancer recurrence (617 recurrences in 3428 women allocated to continue vs. 711 in 3418 controls, $P = 0.002$), reduced breast cancer mortality by 2.8% (331 deaths vs. 397 deaths, $P = 0.01$), reduced risk of contralateral breast cancer and reduced overall mortality (639 deaths vs. 722 deaths, $P = 0.01$).^[11] The observed risk reductions were more significant after year 10.^[11] Nonbreast cancer mortality was little affected (691 deaths without recurrence in 6454 women allocated to continue vs. 679 deaths in 6440 controls; RR 0.99 [0.89-1.10]; $P = 0.84$).^[11] Continued tamoxifen was associated with an increased risk for pulmonary embolism (RR 1.87, 95% CI, 1.13-3.07, $P = 0.01$), but no increase in

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the incidence of stroke (RR 1.06, 95% CI, 0.83-1.36), and a decrease in the incidence of ischemic heart disease (RR 0.76, 95% CI, 0.60-0.95, $P = 0.02$). Endometrial cancer was significantly more common, with a cumulative risk during years 5-14 of 3.1% (mortality 0.4%) for women allocated to continue versus 1.6% (mortality 0.2%) for controls (absolute mortality increase 0.2%).^[11] Notably this risk was lower in premenopausal women. In the 10% of patients who were premenopausal at the time of randomization (post 5 years of tamoxifen), continued tamoxifen resulted in a reduced recurrence rate (19.6% vs. 24.0% of the women randomized to discontinue tamoxifen). This effect seemed more prominent in premenopausal patients (4.4% reduction vs. 2.7% in the postmenopausal population), but the menopausal status at study entry was not a statistically significant factor.^[11,12]

The UK adjuvant aTTom trial ($n = 7000$) confirmed that continuing tamoxifen to year 10 rather than just to year 5 produces further reductions in recurrence and breast cancer deaths.^[13] These benefits emerged only after 7 years from the start of treatment for recurrence and 10 years for mortality.^[13] Similarly, the reported incidence of endometrial cancer was also more common in women who received extended therapy with tamoxifen (2.9% vs. 1.3% in those who did not), but with a minimal increase in accompanying mortality related to those cancers (37 [1.1%] vs. 20 [0.6%] deaths [absolute hazard 0.5%, $P = 0.02$]).

The 2014 American Society of Clinical Oncology clinical practice guideline on adjuvant endocrine therapy now recommends additional adjuvant hormonal therapy for premenopausal women, based on menopausal status at the time of completion of 5 years of initial tamoxifen therapy.^[14] If a woman remains premenopausal, continued tamoxifen for a total duration of 10 years should be offered and if a woman becomes definitively postmenopausal, continued tamoxifen for a total duration of 10 years or switching to up to 5 years of an AI, for a total duration of up to 10 years of adjuvant endocrine therapy should be offered.^[14] Individual treatment recommendations will require balancing of the benefit and risk and potential adverse effects for that patient on the basis of age, comorbidities, tumor stage and biology. The magnitude of benefit of extended adjuvant therapy is lower for patients with stage I cancers than for those with higher stage tumors given their lower risk for recurrence after 5 years of adjuvant endocrine therapy.^[11,15-18] Indeed, the greatest impact of extended tamoxifen may be for the younger premenopausal woman at a higher risk for recurrence, whose options now include extended tamoxifen or ovarian function suppression (OFS) with an AI. Updated results from the aTTom trial are awaited along with a meta-analysis of trials of extended adjuvant tamoxifen therapy by the EBCTCG.

Ovarian ablation and suppression

The very first effective systemic therapy for breast cancer, and perhaps any solid tumor, was oophorectomy as reported for locally advanced breast cancer by Beatson.^[19] The very first randomized adjuvant trial tested oophorectomy^[20,21] and the removal of endogenous estrogen through ovarian ablation (OA) by surgical oophorectomy or radiation therapy, was shown as a single intervention by the EBCTCG in 1995 to reduce breast cancer recurrence and increase survival in women under 50 years of age.^[22] Suppression of ovarian estrogen production that is, OFS can also be achieved by the administration of luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide, goserelin, and deslorelin. However, a role in patients receiving chemotherapy was unclear, and the overall use of ovarian suppression/ablation was not clearly resolved in most parts of the world.

The 2005 EBCTCG overview showed that OA and OFS both reduced recurrence by 31% ($P < 0.00001$) and breast cancer mortality by 31% ($P = 0.004$) with a 28% reduction in mortality, but only in the absence of other systemic treatments. This meta-analysis of 194 randomized trials contained data on 7601 women aged 50 years of age or less with either ER+ or ER- unknown disease, randomized into trials of OA (4317 women, 63% ER unknown) and OFS (3408 women, 26% ER-unknown) compared with no adjuvant therapy.^[23] There was no difference in the effects of OA versus those of OS or in the risk reductions for women younger than 40 years of age at entry versus those aged between 40 and 49 years. However, because of the large number of patients (26%) overall with unknown receptor status, the true contribution of OA/OS may have been diluted.^[12,23] Notably, the outcome did not improve with OA/OS in the trials where adjuvant chemotherapy was also received, potentially as a result of chemotherapy-induced amenorrhea (CIA) attenuating any additional benefit from OA/OFS.^[24,25]

Individual prospective clinical trials did not provide clarity either. The ECOG-led Intergroup trial looked at the addition of OFS to adjuvant chemotherapy in 1503 premenopausal women with ER+ node positive breast cancer randomized to six cycles of cyclophosphamide, doxorubicin, and fluorouracil (CAF), CAF + OFS or CAF + OFS + tamoxifen. The disease-free survival (DFS) was improved with the addition of OFS and tamoxifen to chemotherapy; however, this benefit was not seen without tamoxifen.^[26] A subset analysis of the women aged 40 years or younger did show a benefit for OFS added to chemotherapy, as well as a benefit with the addition of tamoxifen to the combination.^[26] This trial was limited by the lack of a CAF + tamoxifen alone arm, as at the time of trial entry, tamoxifen was not the standard of care for premenopausal women and these authors concluded

that ovarian suppression could not be recommended as standard practice. Similarly, the International Breast Cancer Study Group (IBCSG) randomized trial VIII showed a small nonsignificant improvement in 5 years DFS from the addition of OFS to adjuvant CMF (hazard ratio [HR] 0.80; 95% CI, 0.57-1.11), however, women aged 40 years or younger derived a significant benefit (HR 0.34; 95% CI, 0.14-0.87).^[27]

In 2007 the LHRH-agonists in Early Breast Cancer overview group analyzed data from 16 randomized trials focusing on the 9022 hormone receptor-positive patients with almost 7 years of follow-up, to evaluate the role of LHRH agonists as adjuvant treatment in premenopausal women with ER+ breast cancer.^[28] Consistent with results from the 2005 EBCTCG overview, LHRH agonists when used as the only systemic adjuvant treatment, showed a 28% ($P = 0.08$) reduction in the risk of recurrence and 18% ($P = 0.49$) reduction in the risk of death.^[28] However, these results did not reach statistical significance, possibly due to small patient numbers ($n = 338$).^[29] Furthermore, adding OFS to tamoxifen did not significantly decrease recurrence (HR 0.85) or death after recurrence (HR 0.84). Nonetheless, the addition of LHRH agonists to chemotherapy with or without tamoxifen was shown to reduce significantly recurrence by 12.7% (2.4-21.9, $P = 0.02$); and death after recurrence by 15.1% (1.8-26.7, $P = 0.03$).^[28] However, a subanalysis according to age-restricted these benefits to women aged 40 years or younger (significantly reduced rates for recurrence by 25.2% [7.7-39.4, $P = 0.01$], death after recurrence by 28.3% [6.8-44.9, $P = 0.01$], and all deaths by 27.4% [6.5-43.6, $P = 0.01$]), with the greatest benefit seen in women aged 35 years or younger (HR 0.66).^[28] Again, suggesting the benefit of OFS in a younger population, less likely to be rendered amenorrheic following chemotherapy and most likely to have the spontaneous return of ovarian function.^[25,29] LHRH agonists were also shown to be as efficacious as older (nonanthracycline/taxane-based) chemotherapy regimens, however the trials assessed did not have tamoxifen in both arms and indeed in the trials of LHRH agonists plus tamoxifen versus chemotherapy, the endocrine combination did not significantly decrease rate of recurrence or death, despite a favorable trend to do so.^[25,28]

Chemotherapy induced amenorrhea

The indirect endocrine effect of CIA in premenopausal women with ER-positive tumors has been associated with the improved treatment outcome on retrospective analysis.^[30-33] Rates of CIA are dependent on a number of factors, including patient age, duration of adjuvant chemotherapy and the specific regimen received.^[33]

The IBCSG trial 13-93 randomized 1246 premenopausal women with node positive disease to adjuvant chemotherapy

with or without tamoxifen and showed that patients with ER-positive tumors who achieved CIA had a significantly improved DFS (HR for amenorrhea vs. no amenorrhea = 0.61; 95% CI, 0.44-0.86; $P = 0.004$), whether or not they received tamoxifen.^[32]

The NSABP B-30 randomized phase 3 trial of node-positive, early-stage breast cancer patients treated with both adjuvant anthracycline- and taxane-containing regimens, showed an improvement in both overall survival (RR, 0.76; $P = 0.04$) and DFS (HR for disease recurrence, a second malignant condition, or death, 0.70; $P < 0.001$) in premenopausal patients ($n = 2343$) with amenorrhea for 6 months or more after completion of chemotherapy.^[34]

Aromatase inhibitors

Aromatase inhibitors have been established as the preferred hormonal treatment for postmenopausal women in the adjuvant setting due to small but significant benefits compared with tamoxifen in terms of reduced risk of recurrent disease, distant metastases and contralateral breast cancers, and prolonged DFS and time to recurrence.^[35,36] In premenopausal women, AI's as monotherapy are ineffective due to ongoing ovarian estrogen production and are contraindicated due to the suppression of peripheral aromatase that results in negative feedback to the hypothalamus which increases the secretion of LHRH and consequently stimulates ovarian function.^[37]

The MA17 trial of extended adjuvant therapy with letrozole after 5 years of tamoxifen published an exploratory subgroup analysis of the 877 women who were premenopausal at diagnosis. This analysis suggested that these women gain a greater DFS benefit than those who were postmenopausal at diagnosis (interaction $P = 0.03$) and the authors concluded that women who were premenopausal at diagnosis should be considered for extended adjuvant therapy with an AI if menopausal after completing tamoxifen.^[38]

Aromatase inhibition combined with ovarian function suppression in premenopausal women

Given the demonstrated benefit of AI's over tamoxifen in the postmenopausal population,^[35,36] the next step was to examine if premenopausal women, rendered postmenopausal through OFS could garner a similar superior benefit from AI's compared with tamoxifen. Large randomized phase III trials sought to answer this question.

In the ABCSG-12 trial, 1803 premenopausal women with early stage breast cancer were randomized after surgery to OFS combined with tamoxifen or anastrozole. Notably this was a moderate risk population with 76% T1 tumors, 20% grade 3 tumors and 30% of patients having node-positive disease, and 23% were aged less than 40 years. At almost 8 years of median follow-up, 95% women were alive,

however worse overall survival was seen with anastrozole (53 of 134 vs. 33 of 117; HR = 2.0, 95% CI, 1.28-3.13; Cox $P = 0.002$), raising the question of inadequate OFS in these patients who did not receive chemotherapy.^[39,40] High body mass index (BMI) has also been suggested as a cause for the worse outcome observed with anastrozole in this study, with a 50% increased risk of disease recurrence (HR, 1.49; 95% CI, 0.93-2.38; $P = 0.08$) and three-fold increased risk of death seen (HR, 3.03; 95% CI, 1.35-6.82; $P = 0.004$) in patients with a high BMI treated with anastrozole compared with those treated with tamoxifen.^[41] This observation may be due to the influence of BMI on aromatase availability. The clinical relevance of BMI may be significant, given a third of premenopausal patients with breast cancer are overweight.^[41]

In the tamoxifen and exemestane trial (TEXT), 2672 premenopausal women were randomized to OFS plus tamoxifen or exemestane for 5 years. It is of interest that the 40% of women who had not received chemotherapy prior to randomization were a slightly higher risk group than the equivalent group in the suppression of ovarian function trial (SOFT), with more patients with node-positive (21% vs. 9% in SOFT) and grade 3 (12% vs. 7% in SOFT) disease. The SOFT trial randomized 2033 premenopausal women to tamoxifen or OFS combined with tamoxifen or exemestane for 5 years. The 53% of patients who received chemotherapy were generally younger with larger and higher grade tumors with more human epidermal receptor 2-positive and node positive disease. About 90% of the women aged <35 years received chemotherapy. In the SOFT trial, as distinct from previous studies, only patients clearly established as being hormone receptor positive and premenopausal were included.

After a median follow-up of 5.7 years, the joint primary analysis of the OFS arms from these 2 trials ($n = 4690$), concluded that adjuvant treatment for 5 years with exemestane plus OFS (with the gonadotropin-releasing-hormone agonist triptorelin, oophorectomy, or ovarian irradiation) significantly reduced recurrence compared with tamoxifen plus OFS, with an absolute improvement at 5 years of 4% in breast cancer-free interval (BCFI) and 1.8% in distant recurrence-free interval (DRFI).^[42] It is notable that although the TEXT group of patients who did not receive chemotherapy were slightly higher risk than their SOFT counterparts, they still garnered an absolute benefit of 3% (HR 0.41) from exemestane plus OFS versus tamoxifen plus OFS. In addition, treatment effects did not differ significantly between subgroups or based on whether chemotherapy was received or not.

Subsequently, the primary analysis of the SOFT trial ($n = 2033$) at a median follow-up of 5.6 years showed no benefit in DFS or BCFI from the addition of OFS to

tamoxifen in the general population.^[43] However, in women free from recurrence at 5 years, an absolute benefit in DRFI of 1.2% (HR 0.87) and BCFI of 4.5% (HR 0.78) was seen in the higher-risk patients who remained premenopausal after chemotherapy. This absolute benefit in BCFI increased to 11.2% in women aged <35 years. The addition of OFS to exemestane compared with tamoxifen showed an approximate 4% absolute benefit in DFS (HR 0.68) and BCFI (HR 0.64), and in those women free from recurrence at 5 years the absolute improvement was 7.7% in BCFI and 4.2% in DRFI. Similarly, this absolute benefit in BCFI increased to 15.7% in women aged <35 years. Adding OFS to tamoxifen resulted in increased adverse events (7.6% increase in grade 3 or higher) - most notably, menopausal symptoms, depression, hypertension, diabetes, a 2.3% increase of Osteoporosis.^[43] When exemestane was combined with OFS, adverse sexual, musculoskeletal, and bone-density effects were more frequent than with tamoxifen plus OFS.^[42] Interestingly the patient reported outcomes showed no difference in the global quality of life with the addition of OFS. Overall, patients receiving tamoxifen + OFS experienced worse endocrine symptoms and sexual functioning than those receiving tamoxifen alone during the first 2 years of treatment; however, most differences between treatments were no longer apparent thereafter with endocrine symptoms being much less pronounced after 2 years.^[44]

CONCLUSIONS

Endocrine therapy is a mainstay of curative treatment for early stage breast cancer. Treatment decisions need to include estimates of efficacy, toxicity, and the individual patient's tolerance for each. Given these variables tamoxifen alone remains a reasonable option for low-risk premenopausal women that do not have sufficient risk to warrant adjuvant chemotherapy. The standard duration of adjuvant endocrine therapy is at least 5 years, but 10 years of either tamoxifen or 5 years of tamoxifen, followed by a switch to 5 years of an AI (if confirmed as postmenopausal after 5 years of tamoxifen) can be considered in higher risk cohorts and when such therapy is well tolerated.

For high-risk premenopausal patients, particularly those aged <35 years who are more likely to regain ovarian function following completion of chemotherapy; there is a meaningful additional disease-specific benefit to be gained from OFS. Given that the benefit appears greater when combined with exemestane compared with tamoxifen, the former combination should be offered to young patients deemed at particularly high risk by standard clinico-pathological features. Again, however, individual patients will have to assess their tolerance for toxicities that can include many signs and symptoms of premature menopause.

Overall however, the SOFT and TEXT data reassure us how well premenopausal women with breast cancer can do without this added intervention. The lack of overall survival data in an adjuvant trial, albeit with relatively short follow-up for ER+ disease, would not necessarily support to its routine use. That said, all patients will require an individualized discussion that reviews the current literature, bearing in mind that the toxicities for each of these interventions can be significant and affect not only quality of life of these women, but also their subsequent adherence to therapy.

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