Optimizing Endocrine Therapy for Premenopausal and Postmenopausal Women With Breast Cancer

By Mary Cianfrocca, DO [2] and Antonio C. Wolff, MD, FACP [3]

The majority of invasive breast cancer patients present with hormone receptor-positive disease, and modulation of estrogen receptor (ER) activation is an essential component of systemic adjuvant therapy for these women. While tamoxifen has traditionally been the primary adjuvant endocrine therapy for all ER-positive women, recent trials evaluating the use of aromatase inhibitors (AIs) have challenged this standard in postmenopausal women, and ongoing trials are examining the optimal use of endocrine therapy in younger women. Issues regarding the optimal approach to endocrine therapy in both pre- and postmenopausal women are examined in this review.

Approximately three-quarters of invasive breast cancer patients present with hormone receptor-positive disease. As the estrogen receptor (ER) pathway is key to the growth of these cancers, modulation of ER activation is an essential component of systemic adjuvant therapy for these women. While tamoxifen, a selective estrogen receptor modulator, has traditionally been the mainstay of adjuvant endocrine therapy in pre- and postmenopausal women, recent trials evaluating the use of aromatase inhibitors (AIs) have challenged this standard in postmenopausal women (Table 1), and ongoing trials are examining the optimal use of endocrine therapy in younger women (Table 2).

The most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis demonstrated that 5 years of adjuvant tamoxifen reduced the annual death rate by 31% among...
women with ER-positive disease regardless of age.[1] However, we now recognize that not all patients with ER-positive disease benefit equally from various endocrine therapies. Resistance to endocrine therapy in ER-positive tumors may be intrinsic, occurring at first exposure (de novo), or may develop over time following an initial response to endocrine therapy (acquired). Identification of the key mechanisms involved is essential to predict response or resistance to specific treatments, and to facilitate development of new pharmaceutical agents targeted at the various molecular components of endocrine-resistance pathways.

Individual tumor characteristics as well as host factors likely influence both response and toxicity in an individual patient.[2] Gene-expression profiles have been used to identify at least two subtypes of ER-positive breast cancer-luminal A and B.[3] Furthermore, a commercial assay using formalin-fixed paraffin-embedded tissue has been validated retrospectively to have strong prognostic and predictive value for patients with lymph node-negative, ER-positive breast cancer treated with tamoxifen with or without chemotherapy.[4,5]

**Adjuvant Endocrine Therapy in Postmenopausal Women**

**Aromatase Inhibitors Instead of Tamoxifen**

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared 5 years of therapy with anastrozole (Arimidex) alone, tamoxifen alone, and the combination of both agents in 9,000 postmenopausal women with hormone receptor-positive breast cancer. The primary endpoints were disease-free survival (DFS) and safety/tolerability. The initial analysis, presented at a median follow-up of 33 months, revealed superior DFS for the anastrozole arm compared to the tamoxifen arm (89.4% vs 87.4%, respectively; \( P = .013 \)).[6] Results from the combination arm were not significantly different from those for tamoxifen alone; this arm was therefore discontinued and not included in subsequent analyses. The incidence of contralateral breast cancer was also significantly lower with anastrozole compared to tamoxifen, with an odds ratio of 0.42 (\( P = .007 \)). Anastrozole was significantly better tolerated than tamoxifen with respect to cerebrovascular events, venous thromboembolic events, endometrial cancer, vaginal bleeding, and hot flashes, whereas tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures.

The ATAC trial was recently updated with 68 months of follow-up, and the benefit of anastrozole over tamoxifen was maintained.[7] With only 8% of patients remaining on trial, DFS was significantly longer for anastrozole compared to tamoxifen, with a hazard ratio of 0.74 (\( P = .0002 \)) and an absolute difference of 3.7% between the two arms. At present, there is no significant survival difference between tamoxifen and anastrozole therapy.

The Breast International Group (BIG) 1-98 trial randomized 8,028 postmenopausal women with hormone receptor-positive breast cancer to one of four arms: 5 years of tamoxifen, 5 years of letrozole (Femara), 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen.[8] The first analysis of this trial compared the two groups assigned
to initial tamoxifen (4,007 women) to the two groups assigned to initial letrozole (4,003 women). At a median follow-up of 25.8 months, letrozole significantly improved DFS compared to tamoxifen, with a hazard ratio of 0.81 ($P = .003$). Estimates of 5-year DFS were 84% for the letrozole group and 81.4% for the tamoxifen group, leading to an absolute difference of 2.6% between the two groups—a magnitude of benefit similar to that seen in the ATAC trial.

As compared with tamoxifen, letrozole was associated with more fractures (5.7% vs 4.0%, $P < .001$) but fewer thromboembolic events (1.5% vs 3.5%, $P < .001$), a lower rate of vaginal bleeding (3.3% vs 6.6%, $P < .001$), fewer endometrial biopsies (2.3% vs 9.1%, $P < .001$) and fewer invasive endometrial cancers (0.1% vs 0.3%, $P = .18$). At present, there is no significant difference in overall survival. Data from the sequential arms is not currently available.

**Aromatase Inhibitors After Tamoxifen**

An alternative treatment approach—tamoxifen followed by an AI—has also been evaluated in multiple randomized trials. Boccardo et al randomized 426 postmenopausal, hormone receptor-positive women who had completed 2 years of tamoxifen to either continue tamoxifen for a total of 5 years or to switch to anastrozole for the remaining 3 years of therapy, with both groups receiving a total of 5 years of adjuvant endocrine therapy. At a median follow-up of 64 months, switching to anastrozole had significantly improved the hazard rates (HR) for event-free and relapse-free survival compared to continued tamoxifen (HR for event-free survival = 0.57, $P = .005$; HR for relapse-free survival = 0.56, $P = .01$).[9,10] While there were fewer deaths in the anastrozole group (12 vs 21 patients), this difference did not reach statistical significance in this underpowered trial.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 trial and the Arimidex-Nolvadex (ARNO) trial also randomized a combined total of 3,224 postmenopausal, estrogen receptor-positive women who had already been taking tamoxifen for 2 years to either continue tamoxifen for a total of 5 years or to switch to anastrozole for the remaining 3 years of therapy.[11] At a median follow-up of 28 months, switching to anastrozole resulted in a 40% proportional improvement ($P = .0009$) and a 3.1% absolute improvement in event-free survival compared to continued tamoxifen use. A separate analysis of the ARNO trial was recently presented at a median follow-up of 30.1 months, demonstrating a survival benefit for switching to anastrozole (15 vs 28 deaths, $P = .045$).[12] The International Exemestane Study (IES) randomized 4,742 postmenopausal women with ER-positive disease who had already received 2 to 3 years of adjuvant tamoxifen to either complete 5 years of tamoxifen or switch to exemestane for the remaining 2 to 3 years of therapy.[13] At the second interim analysis after 358 events, the data and safety monitoring committee recommended that the efficacy data be released. After a median follow-up of 36 months, switching to exemestane resulted in a 32% proportional and 4.7% absolute reduction in the risk of recurrence ($P = .00005$). Thromboembolic events were more common in the tamoxifen group ($P = .007$), while there was a trend toward an increased incidence of fractures in the exemestane group. Subsequent analysis of this trial with a 3 years of follow-up showed that the disease-free survival benefit was maintained (HR = 0.76, $P = .0001$), and a statistically significant survival benefit was seen in the subgroup of ER-positive/ER-unknown patients who switched to exemestane (HR = 0.83, $P = .05$).[14] The MA.17 trial randomized 5,187 women to 5 years of letrozole vs placebo after they had completed 5 years of tamoxifen therapy. After a median follow-up of 2.4 years, patients treated with letrozole had a 43% proportional reduction in the risk of recurrence compared to the placebo group ($P = .00008$). Estimated 4-year disease-free survival rates for the letrozole and placebo groups were 93% and 87%, respectively. Patients with both node-negative and node-positive disease had improved disease-free survival with letrozole. Distant disease-free survival was significantly improved by letrozole in the overall population ($P = .002$) and in the subgroup of node-positive patients ($P = .001$), and overall survival was significantly improved in node-positive patients ($P = .04$).[15-17]

Upon unblinding of the data in October 2003, all patients in the placebo arm were offered open-label letrozole. An analysis of the postunblinding data was recently presented.[18] Among the 2,594 women initially randomized to placebo, 1,655 women chose to receive open-label letrozole, and these patients were younger, had more advanced disease, and were more likely to have received adjuvant chemotherapy than those who declined to be crossed over. At 54 months of follow-up, a statistically significant benefit in disease-free survival favored the crossover patients (HR = 0.31, $P < .0001$), suggesting that women with ER-positive breast cancer could benefit from delayed letrozole therapy even after a prolonged period off tamoxifen. The switch to letrozole was well tolerated with no apparent significant difference in bone fractures or cardiovascular events.

All of the adjuvant AI trials have demonstrated a detrimental effect of AIs on bone density. A
subprotocol of the ATAC trial included 308 women from the study and a control group consisting of 46 nonrandomized postmenopausal patients with invasive early-stage breast cancer who were not receiving endocrine therapy.[19] After 1 year of therapy, anastrozole use was associated with a decrease in bone mineral density (BMD) in the spine and hip, whereas tamoxifen was associated with an increase in BMD. After 2 years of therapy, anastrozole continued to be associated with a decrease in BMD and tamoxifen with an increase in BMD. The rate of bone loss associated with anastrozole therapy appeared to be constant over years 1 and 2.

The 5-year BMD results of patients on the monotherapy arms of this bone subprotocol (tamoxifen, n = 86; anastrozole, n = 81) were recently reported.[19] Among patients with BMD measurements at baseline, 2, and 5 years, the rate of BMD loss in the lumbar spine was significantly less from 2 to 5 years, compared to baseline to 2 years (P = .0002), but this slowdown was not seen in the loss of total hip BMD. Of interest, no patient with a normal baseline BMD became osteoporotic at 5 years. Four patients on anastrozole and one patient on tamoxifen with osteopenic BMDs at baseline developed osteoporosis on treatment.

The American Society of Clinical Oncology convened a Technology Assessment Panel in 2002, 2003, and 2004 to review the available data and make recommendations regarding the optimal use of AIs in the adjuvant setting. This panel concluded in 2004 that optimal adjuvant endocrine therapy for a postmenopausal woman with hormone receptor-positive breast cancer should include an AI either as initial therapy or after a period of treatment with tamoxifen.[20] The panel left open the questions of which AI and which treatment algorithm is optimal. Several theoretical models examining the optimal therapy sequence (AI upfront vs tamoxifen followed by an AI) have been explored, but their utility in clinical practice remains uncertain.[21,22]

Many issues regarding the adjuvant use of AIs remain unsettled, including the optimal duration of treatment, the optimal sequencing with tamoxifen, and the optimal AI. The incidence of long-term side effects in a patient population expected to live for many years also remains to be determined. AIs are contraindicated in premenopausal women and should be used with extreme caution in women with chemotherapy-induced amenorrhea.[23] Ongoing clinical trials (eg, the Suppression of Ovarian Function Trial) are examining the role of AIs and ovarian suppression/ablation (OS/OA) in premenopausal women.

**Adjuvant Endocrine Therapy in Premenopausal Women**

A common misconception that endocrine therapy is ineffective in premenopausal women has been perpetuated by trial results confounded by the inclusion of patients with ER-negative disease, the belief that tamoxifen is ineffective in young women, and the indirect endocrine effects of chemotherapy. The EBCTCG overview analysis has since confirmed that adjuvant tamoxifen confers a survival benefit for ER-positive patients regardless of age.[24] Rather than being an independent prognostic and predictive factor, age is more likely an incomplete surrogate for the interaction of host and tumor biologic features (eg, expression of hormone receptors, tumor grade, mitotic rate, and lymphatic vascular invasion).

Similar confounding factors may also help explain the ongoing controversy regarding the role of OS/OA in premenopausal women. Accumulated clinical trial data as well as the EBCTCG overview analyses have confirmed that ablation of functioning ovaries significantly improves survival in breast cancer patients younger than age 50, at least in the absence of chemotherapy.[25]

**Ovarian Suppression as a Substitute for Chemotherapy**

Multiple trials have addressed the role of OS/OA as a substitute for cytotoxic chemotherapy. Interpretation of most of these trials is limited by multiple factors including mixed populations of estrogen receptor-positive and -negative patients, lack of tamoxifen in the chemotherapy arms, and in the majority of trials, lack of an anthracycline. Taxanes were also not included in these trials. Several studies evaluating OS/OA without tamoxifen compared to CMF (cyclophosphamide, methotrexate, and fluorouracil [5-FU]) chemotherapy, such as the Zoladex Early Breast Cancer Research Association (ZEBRA).[26] Takeda Adjuvant Breast Cancer Study with Leuprolide Acetate (TABLE),[27] International Breast Cancer Study Group (IBCSG) VIII (goserelin or leuprolide),[28] Scottish-Guys (oophorectomy),[29] and Danish Breast Cancer 89B (irradiation)[30] trials have demonstrated that OS/OA offers similar outcomes to chemotherapy for patients with hormone receptor-positive disease but is inferior to CMF in patients with hormone receptor-negative tumors. Furthermore, studies of OS/OA plus tamoxifen vs CMF (eg, the ABCSG-5 trial[31] and the Gruppo di Ricerca in Oncologia Clinica e Terapie Associate [GROCTA] trial[32]) or an anthra-cycline-regimen (eg, the French Adjuvant Study Group [FASG] trial 06[33]) have demonstrated that combined endocrine therapy with OS/OA and tamoxifen offers similar or improved outcome compared to chemotherapy.
Ovarian Suppression After Chemotherapy

Very young women are less likely to develop permanent amenorrhea following adjuvant chemotherapy.[34] Data suggest that very young women (below age 35) with hormone receptor-positive tumors primarily treated with chemotherapy have a statistically significantly higher risk of relapse than older premenopausal patients,[35] while younger and older premenopausal patients with hormone receptor-negative tumors have similar outcomes. These observations suggest that young premenopausal women with hormone receptor-positive disease who fail to develop complete ovarian failure after chemotherapy may potentially benefit from OS/OA.

The IBCSG VIII trial randomized 1,063 pre- and perimenopausal women with node-negative disease to goserelin every 28 days for 24 months vs six cycles of CMF vs six cycles of CMF followed by goserelin every 28 days for 18 months.[36] CMF was superior to goserelin in the patients with ER-negative disease but equivalent to CMF in the ER-positive patients. Among patients with ER-positive disease, there was a trend toward fewer recurrences among women younger than age 40 who were treated with CMF followed by goserelin.

Led by the Eastern Cooperative Oncology Group (ECOG), the Intergroup trial 0101/ECOG 5188 randomized 1,504 premenopausal, node-positive women to receive CAF (cyclophosphamide, doxorubicin, 5-FU) alone, CAF plus 5 years of monthly goserelin, or CAF plus 5 years of tamoxifen and monthly goserelin. Unfortunately, the study did not include an arm of CAF plus tamoxifen without goserelin. After a median follow-up of 5 years, a significant benefit was seen for the addition of tamoxifen to CAF plus goserelin but not for the addition of goserelin alone to CAF. An exploratory subset analysis in the CAF-followed-by-goserelin arm showed that any clinical benefit appeared to be limited to women younger than age 40.[37]

The Zoladex in Premenopausal Patients (ZIPP) four-arm trial, with a 2×2 factorial design, compared 2 years of therapy with tamoxifen and/or goserelin vs placebo, and showed a survival benefit in the goserelin arm that was less pronounced in patients treated with tamoxifen or chemotherapy.[38] A French trial with a mixed hormone receptor population did not show a benefit from adding OS/OA after various kinds of chemotherapy.[39]

OS/OA is not devoid of potential toxicities including weight gain, sexual dysfunction, and hot flashes, and at present, OS/OA should not be routinely used to replace or complement adjuvant chemotherapy. Several ongoing trials described in Table 2 are expected to definitively address the various roles of combining chemotherapy, OS/OA, tamoxifen, and AIs in premenopausal patients with early-stage, hormone receptor-positive breast cancer.

Conclusions

Endocrine therapy is an essential component in the adjuvant treatment of patients with hormone receptor-positive breast cancer, regardless of age. Many issues remain unclear, however, including the role of OS/OA in premenopausal women as well as the optimal schedule (instead of or used sequentially with tamoxifen) and duration (2 or 3 to 5 years or longer) of AIs in postmenopausal women. Endocrine therapy alone is insufficient for many patients. Not all patients derive the same benefit from endocrine therapy, and gene-expression profiling studies have identified subsets of patient with lymph node-negative disease who have a low, intermediate, or high risk of recurrence following therapy with tamoxifen alone.[40]

Meanwhile, it appears that some patients with ER-positive disease and limited nodal involvement may gain little or no benefit from the addition of chemotherapy to tamoxifen.[41] New molecular assays as well as advancements in risk stratification and predictive models will help further discriminate those with endocrine-responsive vs nonresponsive disease within the larger group of patients with hormone receptor-positive breast cancer. Furthermore, substantial progress has been made in recent years to better understand some of the molecular mechanisms involved in both de novo and acquired endocrine resistance. Our ability to optimize endocrine therapy for individual patients will undoubtedly continue to improve in the future.

References:


Source URL: http://www.physicianspractice.com/oncology-journal/optimizing-endocrine-therapy-premenopausal-and-postmenopausal-women-breast-cancer

Links: