Adjuvant Endocrine Therapy for Breast Cancer

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In this article, we review the current guidelines for adjuvant endocrine therapy in both premenopausal and postmenopausal women, and we discuss the clinical trials that were used to develop these guidelines.

Introduction

Adjuvant endocrine therapy is a standard treatment for hormone receptor (HR)-positive, early-stage breast cancer. Tamoxifen, a selective estrogen receptor modulator (SERM), has been used for several decades in this setting. The benefits of adjuvant tamoxifen were shown in the first Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[1] and have been confirmed in subsequent meta-analyses. Recently, aromatase inhibitors (AIs) have become the standard of care for postmenopausal women. In this article, we review the current guidelines for adjuvant endocrine therapy in both premenopausal and postmenopausal women, and we discuss the clinical trials that were used to develop these guidelines.

Guidelines for Premenopausal Women

The 2010 American Society of Clinical Oncology (ASCO) guidelines recommend tamoxifen for premenopausal women, since AIs are contraindicated in women with residual ovarian function.[2] These guidelines state that, currently, the benefit of ovarian suppression in this population is not known, and that the results of the Suppression of Ovarian Function (SOFT) trial are awaited to further define its role. The National Comprehensive Cancer Network (NCCN) guidelines recommend tamoxifen for 5 years (category 1 evidence) with or without ovarian suppression or ablation (category 2B evidence) if a woman is premenopausal at diagnosis.[3] At the end of the 5 years, if the patient is postmenopausal, another 5 years of treatment with an AI should be considered. The St. Gallen Expert Panel (2011) recommended tamoxifen alone, but stated that ovarian suppression plus tamoxifen was an acceptable alternative for premenopausal women.[4] For patients with a contraindication to tamoxifen, the St. Gallen Panel recommended ovarian function suppression plus an AI. The most recently published meta-analysis from the EBCTCG confirmed the benefits of tamoxifen in women younger than 45 years for reducing the risk of recurrence (hazard ratio [HR], 0.63; 2 \( P = .001 \)) and breast cancer mortality (HR, 0.71; 2 \( P = .00002 \)).[5]

Guidelines for Postmenopausal Women

The 2010 ASCO guidelines recommend that postmenopausal women with HR-positive breast cancer consider the use of an AI during adjuvant treatment, either as primary (initial) therapy, as sequential therapy (after 2 to 3 years of tamoxifen), or in the extended adjuvant setting (after 5 years of tamoxifen).[2] These guidelines state that the “optimal timing and duration of endocrine treatment remain unresolved,” although they recommend 5 years of an AI in the primary and extended adjuvant settings, and 5 years total endocrine therapy in the sequential setting. In absolute terms, the reduction in the risk of recurrence from AI-based therapy compared with tamoxifen is modest, less than 5%, through multiple years of follow-up, and the overall survival (OS) is equivalent in the primary and extended adjuvant trials. In two of the six sequential trials, there was a significant improvement in OS, although the absolute difference was small. Available data have not yet defined the optimal time for switching from tamoxifen to an AI. The guidelines recommend switching after 2 to 3 years of tamoxifen instead of after 5 years, although they do state that switching at 5 years is also supported by the available data.

The benefits of AI therapy appear to be a “class effect,” and if a patient is intolerant of one AI, she can switch to another. Randomized trials have not identified specific markers that predict maximum benefit from a certain adjuvant hormonal therapy—either tamoxifen or AI monotherapy, or
sequential therapy. The NCCN guidelines are in agreement with American Society of Clinical Oncology (ASCO) recommendations.[3] If a woman is postmenopausal at diagnosis, options include an AI for 5 years, tamoxifen for 2 to 3 years followed by an AI to complete 5 years or for a total of 5 years of AI therapy, or an AI for 2 to 3 years followed by tamoxifen to complete 5 years. Yet another option is tamoxifen for 4.5 to 6 years, followed by an AI for 5 years (category 1 evidence). If a patient has a contraindication to an AI, cannot tolerate AIs, or refuses to take an AI, tamoxifen for 5 years should be considered. Members of the St. Gallen Expert Panel (2011) were evenly divided on the question of whether all postmenopausal patients should receive an AI; however, more were supportive of an AI for node-positive patients.[4] The Panel felt that 5 years was a sufficient duration and opposed further prolongation of therapy, even if the patients were node-positive or in the younger postmenopausal range (< 55 years).

**Tamoxifen**

Tamoxifen has been the gold standard for breast cancer hormonal therapy for over 30 years. The most recent EBCTCG meta-analysis included updated data from 20 trials (N = 21,457) of adjuvant tamoxifen for approximately 5 years vs no adjuvant tamoxifen.[5] For patients with estrogen receptor (ER)-positive disease (n = 10,645), tamoxifen reduced the rate of recurrence by 39% (relative risk [RR], 0.61; 2 P < .00001). Specifically, tamoxifen halved the risk of recurrence during years 0 through 4 (RR, 0.53) and reduced it by a third during years 5 through 9 (RR, 0.68; both, 2 P < .00001). After year 10, recurrence rates were similar (RR, 0.97) in the two groups, indicating no loss of the gains during years 0 through 9. The benefits of tamoxifen were independent of progesterone receptor (PR) status/level, age, nodal status, tumor grade, tumor diameter, or the use of chemotherapy. Tamoxifen showed a substantial benefit even in patients with low levels of ER positivity. Tamoxifen reduced breast cancer mortality by about a third (RR, 0.70; P < .000001) throughout the first 15 years. Tamoxifen also reduced the risks of local recurrence (RR, 0.54; 2P < .00001), contralateral breast cancer (RR, 0.62; 2 P < .00001), and distant recurrence (RR, 0.63; 2P < .00001).

The established duration of tamoxifen therapy is 5 years. In the National Surgical Adjuvant Breast and Bowl Project (NSABP) B-14 trial, 2,892 women with ER-positive, node-negative breast cancer were randomly assigned to receive either tamoxifen or placebo for 5 years.[6] Long-term follow-up results of this trial show that women benefited from 5 years of tamoxifen through 15 years, in both recurrence-free survival (RFS) (HR, 0.58; 95% confidence interval [CI], 0.50–0.67; P < .0001) and OS (HR, 0.80; 95% CI, 0.71–0.91; P = .0008). This benefit was seen irrespective of age, menopausal status, and ER concentration.

Tamoxifen for 5 years has been shown to have a greater benefit than tamoxifen treatment for 1 to 2 years.[7] Continuation of tamoxifen for more than 5 years has not been shown to be more beneficial. In the NSABP B-14 trial, 1,172 women who remained disease-free after 5 years of tamoxifen were randomly assigned to receive either placebo or an additional 5 years of tamoxifen.[8] With a follow-up of 7 years after randomization, there was a slight advantage noted in disease-free survival (DFS) (82% vs 78%; P = .03), RFS (94% vs 92%; P = .13), and OS (94% vs 91%; P = .07) for the women who discontinued tamoxifen. The Scottish trial also showed no advantage to tamoxifen continuation beyond 5 years, with a nonsignificant trend toward a worse outcome for longer use (HR, 1.27; 95% CI, 0.87–1.85).[9] In contrast, different results were seen in two more recent trials, the Adjuvant Tamoxifen Long Against Short (ATLAS) trial[10] and the Adjuvant Tamoxifen—to Offer More? (aTTom) study,[11] which have been presented but not yet published. The ATLAS trial randomly assigned 11,500 women (59% ER-positive, 41% ER-untested) who were disease-free after 5 years of tamoxifen to either continue tamoxifen for another 5 years or stop. With a 5-year follow-up, the longer duration was associated with a 12% relative risk reduction in breast cancer recurrence (HR, 0.88; P = .05). The aTTom trial randomly assigned 6,934 women (39% ER-positive, 61% ER-untested) at the completion of 4 or more years of tamoxifen therapy to either 5 additional years of tamoxifen or cessation of tamoxifen therapy. With a median follow-up of 4.2 years, there was a slight, nonsignificant advantage for the 10-year arm (RR, 0.94; 95% CI, 0.81–1.09; P = .4).

Thus, the optimal duration of therapy is not known, but it is at least 5 years.

**Ovarian Suppression/Ovarian Ablation**

Ovarian suppression (OvS)/ovarian ablation (OA) can be used in the adjuvant treatment of premenopausal breast cancer. OA can be accomplished via surgery (oophorectomy) or radiation; OvS is achieved via medications (luteinizing hormone–releasing hormone [LHRH] agonists). The
EBCTCG meta-analysis included nearly 8000 women younger than 50 years of age with ER-positive or ER-unknown disease.[12] For women who received OvS/OA, there was a significant decrease in both the 15-year probability of breast cancer recurrence ($2P < .00001$) and mortality ($2P = .004$) compared with those who received no ovarian treatment. Ovarian treatment had a smaller effect in the trials in which both groups received chemotherapy. There was no indication that the effects of OA differed from those of OvS.

A meta-analysis was performed of 11,906 premenopausal women (9022 HR-positive) from 16 clinical trials involving LHRH agonists, with a median follow-up of 6.8 years. When LHRH agonists were used alone and compared to no systemic therapy, there was no significant decrease in the risk of breast cancer recurrence, although the sample size was small ($n = 338$).[13] In 407 patients, OvS plus tamoxifen did significantly reduce recurrence and death after recurrence compared to no treatment, but the effects may have been due to tamoxifen. In 1013 patients, the addition of LHRH agonists to tamoxifen did not significantly decrease the risk of recurrence (HR, 0.85; $P = .20$) or death after recurrence (HR, 0.84; $P = .33$). In 3754 patients, the addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced recurrence (HR, 0.88; $P = .02$) and death after recurrence (HR, 0.85; $P = .08$). When LHRH agonists were compared to chemotherapy ($n = 3184$), there were similar reductions in recurrence and death after recurrence. In addition, the comparison of LHRH agonists plus tamoxifen to chemotherapy without tamoxifen showed no significant differences ($n = 1577$). There was a benefit from LHRH agonists after chemotherapy in women younger than 40 years, in whom chemotherapy was less likely to cause permanent amenorrhea. In this meta-analysis, importantly, there were no trials that compared an LHRH agonist to chemotherapy with tamoxifen in both arms.

Data from studies combining OvS/OA with tamoxifen are still emerging, and results are unclear. Individual trials have failed to show any benefit for the addition of OvS/OA to tamoxifen compared to each therapy individually.[14-16]

Cancer Care Ontario (CCO) published guidelines on adjuvant ovarian ablation in the treatment of premenopausal women with early-stage invasive breast cancer, which were reviewed and endorsed by ASCO.[17] These guidelines state that OvS/OA is not recommended as an addition to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy. They also stipulate that OvS/OA alone is not recommended as an alternative to any other form of systemic therapy and should be considered only for women who will not receive systemic treatment (eg, those patients who cannot tolerate or who refuse systemic therapy). When OvS with LHRH agonists is being considered, monthly injection is suggested. The ASCO ad hoc ovarian ablation guideline review panel suggested that treatment every 3 months might also be efficacious, based on emerging data. ASCO panel members also put forward two additional points. First, in patients who do embark on OvS using LHRH agonists, complete ovarian suppression is not always achieved. OvS cannot be confirmed by cessation of menses alone, and estradiol assays are likely to be of variable quality. Second, many studies addressing the role of OA in premenopausal women with breast cancer included women with HR-negative disease or unknown HR status, and there is no evidence of OA benefit in these patients.

**AIs**

AIs should be considered as part of adjuvant endocrine therapy for postmenopausal women with HR-positive, early-stage breast cancer. Adjuvant studies of AIs can be separated into three categories: (1) initial therapy: head-to-head comparison of an AI vs tamoxifen for 5 years; (2) sequential: comparison of tamoxifen for 2 to 3 years followed by an AI to complete 5 years vs tamoxifen for 5 years or vs an AI for 5 years; and (3) extended adjuvant: evaluation of the benefit of adding an AI after 5 years of tamoxifen.

**TABLE 1**

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Results From the EBCTCG Meta-Analysis
The EBCTCG conducted a meta-analysis of randomized trials of AIs compared to tamoxifen (Table 1). In two randomized, prospective trials consisting of 9856 patients, AIs were compared to tamoxifen monotherapy. With a mean 5.8 years of follow-up, there was a significant reduction in recurrence but not in breast cancer mortality. In four trials (German Adjuvant Breast Cancer Group/Arimidex-Nolvadex [ARNO 95], Intergroup Exemestane Study/Breast International Group [BIG] 02-97, Italian Tamoxifen Anastrozole [ITA], and Austrian Breast and Colorectal Cancer Study Group [ABCSG] 8), a total of 9015 patients were randomly assigned after 2 to 3 years of tamoxifen to either continue tamoxifen or switch to an AI, both for a total of 5 years of endocrine therapy. With a mean follow-up of 3.9 years, switching to an AI demonstrated a reduction in the risk of recurrence and mortality. There was no difference in benefit associated with age, nodal status, tumor grade, or PR status.

TABLE 2

Josefsson et al Meta-Analysis

Another independent meta-analysis of studies comparing AIs to tamoxifen examined nine randomized controlled trials, which included 28,632 women and looked at three treatment strategies: monotherapy, sequential therapy (switching), and extended therapy (after tamoxifen) (Table 2). DFS was significantly better for AIs as monotherapy and sequential therapy. There was no difference in OS between monotherapy and extended therapy, but OS was prolonged for patients who switched from tamoxifen to AI therapy. The conclusion of the authors was that sequential therapy appears to be the preferred treatment.

AIs are not indicated for the adjuvant treatment of premenopausal women. The use of AIs with LHRH agonists is being studied, but data available to date do not suggest an advantage over tamoxifen and OvS/OA. ABCSG 12 randomly assigned 1803 premenopausal women with ER-positive, stage I/II breast cancer to receive either goserelin (Zoladex) and tamoxifen or goserelin and anastrozole (Arimidex). At a median follow-up of 62 months, there was no difference in DFS (HR, 1.08; 95% CI, 0.81–1.44; \( P = .591 \)), but OS was shorter with anastrozole than with tamoxifen (HR, 1.75; 95% CI, 1.08–2.83; \( P = .02 \)). A subset analysis of this trial based on body-mass index (BMI) calculations showed that for overweight patients treated with anastrozole, there were significant increases in the risk of disease recurrence (HR, 1.49; 95% CI, 0.93–2.38; \( P = .08 \)) and death (HR, 3.03; 95% CI, 1.35–6.82; \( P = .004 \)) compared with patients treated with tamoxifen.[21]

AIs as initial therapy

TABLE 3

ATAC Favors Anastrozole Over Tamoxifen Monotherapy

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was the first to show a benefit for an AI (anastrozole) over tamoxifen.[22] In this double-blind, placebo-controlled trial, 9366 postmenopausal women were randomly assigned to receive anastrozole alone, tamoxifen alone, or the combination of both drugs for 5 years (Table 3). The combination arm was closed due to inferiority. With a median follow-up of 120 months, the primary endpoint of DFS was significantly longer with anastrozole. Anastrozole was also associated with a longer time to recurrence, longer time to distant recurrence, and decreased contralateral breast cancers. The greatest relative reductions in DFS, time to recurrence, and contralateral breast cancer were in the first 2 years of active therapy, but these differences were sustained throughout the entire follow-up period, and persisted after treatment completion. There was no significant difference in OS. TABLE 4
BIG 1-98 Favors Letrozole Over Tamoxifen Monotherapy

The BIG 1-98 trial showed that letrozole (Femara) was more beneficial than tamoxifen (Table 4).[23] In this phase III, double-blind trial, 8010 postmenopausal women with ER-positive and/or PR-positive breast cancer were randomly assigned to 5 years of hormonal therapy in one of four arms: tamoxifen, letrozole, tamoxifen for 2 years followed by letrozole for 3 years, or letrozole for 2 years followed by tamoxifen for 3 years. The primary endpoint was DFS. The monotherapy arms included 4922 women. With a median follow-up of 51 months, there was an advantage in DFS for letrozole compared to tamoxifen.[24] An analysis at 71 months of follow-up showed a nonsignificant difference in OS favoring letrozole.[25] When the initial results were announced in January 2005, 25.2% of the women randomized to tamoxifen monotherapy crossed over to letrozole. With a median of 76 months of follow-up, inverse probability of censored weighted (IPCW) modeling was used to gain better estimates of the relative treatment effects in the presence of the selective crossover.[26] The DFS benefit for letrozole monotherapy was confirmed, and there was a benefit in OS as well. Letrozole was favored in nearly all subgroups.

Sequential use of tamoxifen and AIs

TABLE 5

IES Favors Switching

Some trials have compared switching to an AI after 2 to 3 years of tamoxifen to tamoxifen alone, for a total of 5 years of therapy. In the International Exemestane Study (IES), 4724 postmenopausal women with ER-positive or ER-unknown tumors, who were disease-free after 2 to 3 years of tamoxifen therapy, were randomly assigned to continue tamoxifen or switch to exemestane (Aromasin) (Table 5).[27] At a median follow-up of 55.7 months, DFS was superior for those who switched.[28] The OS was not significantly improved for the entire group of patients who switched, but there was a significant improvement in OS when the 122 patients who had ER-negative tumors were excluded (HR, 0.83; 95% CI, 0.69–1.00; P = .05). In the most recent publication of data from the trial, at a median follow-up of 91 months, the benefit in those patients who switched was sustained.[29] There continued to be a benefit in breast cancer-free survival (BCFS) in the ER-positive and ER-unknown group, and an OS benefit was seen for the patients who switched to exemestane.

TABLE 6

Jonat et al Meta-Analysis[30] and Other Switching Trials Favor Switch to AIs
A meta-analysis was performed on three trials that compared switching to anastrozole after 2 to 3 years of tamoxifen with 5 years of tamoxifen (Table 6).[30] The studies included ABCSG 8, ARNO 95, and ITA. These trials enrolled a total of 4,006 postmenopausal women with hormone-sensitive, early-stage breast cancer. In ARNO 95 and ITA, only patients who were relapse-free after 2 to 3 years of tamoxifen were randomized. In contrast, the ABCSG 8 study randomized patients at diagnosis. In this meta-analysis, the switch to anastrozole demonstrated an advantage in DFS, as well as significant improvements in event-free survival, distant disease-free survival (DDFS), and OS. Switching to anastrozole was beneficial, irrespective of nodal status, PR status, previous chemotherapy, or tumor size. An update of the ABCSG 8 trial with a median follow-up of 60 months[31] showed a modest, statistically nonsignificant improvement in the primary endpoint of RFS, and a significant improvement in the defined exploratory endpoint of distant relapse-free survival (DRFS) (see Table 6).

The National Surgical Adjuvant Study Breast Cancer 03 (N-SAS BC03) trial involved 706 Japanese women randomly assigned after 1 to 4 years of tamoxifen to either continue tamoxifen or switch to anastrozole, for 5 years of total adjuvant endocrine therapy.[32] At a median follow-up of 42 months, the primary endpoint of DFS as well as a secondary endpoint of RFS favored a switch to anastrozole (see Table 6).

Some trials have compared a switching strategy to AI monotherapy (Table 7). In the BIG 1-98 trial, the two sequential arms (tamoxifen for 2 years followed by letrozole for 3 years; letrozole for 2 years followed by tamoxifen for 3 years) were compared to letrozole monotherapy. With a median follow-up of 71 months, there was no significant difference in DFS for either switching arm compared to monotherapy.[25]

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) phase III trial was initially designed to compare 5 years of exemestane monotherapy to 5 years of tamoxifen monotherapy.[33] Women were randomly assigned to receive one agent or the other at treatment initiation. However, based on favorable results from the IES trial, the study design was amended to compare tamoxifen for 2 to 3 years followed by exemestane until the completion of 5 years vs exemestane for 5 years. This trial randomized 9229 postmenopausal women, and at a median follow-up of 5.1 years, it showed no difference in the primary endpoint of DFS.

The designs of these switching trials must be taken into consideration. In the IES, ARNO 95, and ITA trials, patients were randomized only if they were disease-free at 2 to 3 years, thereby excluding patients with a poor prognosis whose disease would have recurred before the randomized switch. A true test of the switching strategy requires randomization at baseline, as in the ABCSG 8, BIG 1-98, and TEAM trials. Furthermore, this is the only study design that helps the practicing oncologist, who cannot anticipate whether a patient's disease is going to recur in the first 2 to 3 years of tamoxifen treatment.

Extended adjuvant use of AIs

TABLE 8
MA.17: Extended AI Trial Favors Using AIs After ~5 Years of Tamoxifen

One large trial evaluated the use of AIs in the extended adjuvant setting (Table 8). MA.17 was a phase III, randomized, double-blind, placebo-controlled trial in which 5187 postmenopausal women who had completed about 5 years of adjuvant tamoxifen were randomly assigned to receive another 5 years of therapy with letrozole or placebo.[34] At a median of 2.5 years, there were significant improvements in the primary endpoint of DFS as well as DDFS for the women who received letrozole.[35] There was no difference in OS between the two groups overall, but for the subset of lymph node–positive patients OS was statistically significantly improved for those who received letrozole. Because the initial interim analysis showed an improvement in DFS for the letrozole arm, the independent data and safety monitoring committee recommended unblinding the study. Patients in the placebo arm were offered letrozole, at a median of 2.8 years after the completion of tamoxifen.[36] Of the 2594 patients in the placebo arm, 66% (1579 patients) chose to start letrozole. When compared to the women in the placebo arm who chose no further therapy, these women had an improvement in DFS and DDFS.

In an intent-to-treat (ITT) analysis with a median follow-up of 64 months, there was still a significant difference in DFS, but no significant differences in DDFS or OS, between the groups created in the original randomization to letrozole or placebo. These results were difficult to interpret and likely underestimated the benefit of letrozole, given that nearly two-thirds of patients randomly assigned to placebo crossed over to active treatment.[37] In the most recent analysis, two approaches were used to adjust for the crossover from placebo to active treatment: IPCW modeling and a Cox model with a time-dependent treatment covariate (see Table 8).[38] Both approaches suggested that letrozole showed statistically significant improvements in DFS, DDFS, and OS that had not been significant in either the first interim analysis[35] or the post-blinding ITT analysis.[37] Two smaller studies also evaluated AIs in the extended adjuvant setting. NSABP B-33 was a randomized, double-blind, phase III trial in which patients with T1-3, N1, M0 breast cancers who were disease-free after 5 years of tamoxifen were randomly assigned to 5 years of exemestane or placebo.[39] The primary endpoint was DFS. Accrual was terminated early, patients were unblinded, and the patients receiving placebo were offered the opportunity to cross over to exemestane after October 2003, when the MA.17 trial data were released. At that time, of the 1598 patients on trial, 72% of those randomized to exemestane continued therapy, whereas 44% of those on placebo chose to start exemestane. In an ITT analysis, there was a borderline statistically significant improvement in 4-year DFS favoring the AI, 91% for exemestane vs 89% for placebo. In a second study, ABSCG 6a, 856 patients who were disease-free at the end of the ABCSG 6 trial (which compared 5 years of tamoxifen with or without aminoglutethimide [Cytadren] for the first 2 years) were randomly assigned to receive 3 years of anastrozole or no further therapy.[40] With a median follow-up of 62.3 months, there was a statistically significant reduction in the risk of recurrence for patients who received anastrozole.

Thus, on the basis of these three clinical trials, there is strong evidence for the value of extended adjuvant therapy with AIs following 5 years of tamoxifen.

**Comparison of different AIs**

The benefits of AI therapy appear to be a “class effect,” and the different AIs appear to have
equivalent efficacy. This was confirmed in the MA.27 trial, which compared anastrozole to
exemestane as initial adjuvant therapy for 5 years in 7576 postmenopausal women with HR-positive
primary breast cancer.[41] There was no difference between the two arms for the primary endpoint,
event-free survival (HR, 1.02; \( P = .85 \)), or for the secondary endpoints of OS, DDFS, or contralateral
breast cancer.

Biomarker analysis and benefit from AIs

An initial exploratory analysis from the ATAC trial suggested that the benefit of anastrozole
compared to tamoxifen was substantially greater in the PR-negative subgroup.[42] A subsequent
central analysis of ER, PR, and human epidermal growth factor receptor 2 (HER2) expression in 2006
of the 5880 specimens showed that quantitative expression of ER, PR, and HER2 did not identify
patients with differential relative benefits from anastrozole.[43] In the BIG 1-98 study, central review
of ER, PR, HER2, and Ki-67 expression was performed on 84% of tumors.[44] Much as in the ATAC
trial, in patients with at least some ER expression, PR levels were not predictive of a relative benefit
of letrozole over tamoxifen monotherapy. When analyzed for a differential treatment effect, each of
the four markers showed a trend favoring letrozole monotherapy at the “higher end” of its spectrum,
but none of the markers significantly predicted treatment selection. A composite measure of
prognostic risk that incorporated clinical, pathological, and biological markers was better able to
predict the relative benefits of the different regimens. For patients at the highest risk, the best
outcome was achieved with letrozole monotherapy. For patients at intermediate risk, any of the
three letrozole-containing regimens performed equally well. Patients at the lowest risk did equally
well with letrozole monotherapy, either sequence of letrozole and tamoxifen, or tamoxifen
monotherapy. A biomarker analysis of the TEAM trial showed that both ER and PR quantitative
expression were associated with DFS and that the relative risk of relapse increased proportionally
with decreased expression of either.[45] PR status did not predict an additional benefit of
exemestane over tamoxifen.

Side Effects of Adjuvant Endocrine Therapy

Tamoxifen

TABLE 9

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<tr>
<th>Adverse Effects of Tamoxifen From NSABP P-1</th>
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<td>Side effects of tamoxifen are well documented. In the NSABP P-1 trial, which compared tamoxifen to placebo in over 13,000 women with a high risk for developing breast cancer, women who received tamoxifen had increased hot flashes, vaginal discharge, and difficulties in some areas of sexual functioning.[46,47] There were no differences between the tamoxifen and placebo arms with regard to depression, overall physical or mental quality of life, and weight gain. The more serious side effects included pulmonary embolism, deep venous thrombosis, and endometrial cancer (Table 9). Tamoxifen reduced the risk of bone fractures (see Table 9). In the most recent EBCTCG overview analysis, there was a nonsignificant increase in stroke deaths (3 extra per 1000 during the first 15 years) balanced by a nonsignificant reduction in cardiac deaths (3 fewer per 1000 during the first 15 years), with a resulting minimal net effect of tamoxifen on overall cardiovascular mortality.[5]</td>
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AIs

TABLE 10

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<th>Adverse Effects of Tamoxifen vs AIs</th>
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<td>Compared to tamoxifen, AIs have a distinct toxicity profile (Table 10). This was demonstrated in a</td>
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A meta-analysis of seven randomized phase III trials that included 30,023 patients.[48] There was a decreased incidence of venous thromboembolism and endometrial cancer for patients taking AIs compared with tamoxifen; however, the risk of cardiovascular disease was increased in patients taking AIs. This comparison may be confounded by the fact that tamoxifen may reduce cardiovascular events. One factor that may affect the risk of cardiovascular events is treatment-related hypercholesterolemia. Hypercholesterolemia was only assessed in four trials, it was not graded consistently, and fasting levels were not obtained in all trials.[24,28,33,49] Despite these caveats, there was a higher incidence of hypercholesterolemia in patients taking AIs. This was most apparent in the trials with AIs as initial therapy, and there was a suggestion that a shorter duration of AI therapy might reduce the odds of hypercholesterolemia.

MA.17 was the only large trial in which an AI was compared to placebo.[36] When comparing the patients who remained on placebo after unblinding to those who chose to switch to letrozole, there was little difference in the rate of cardiovascular events (3.1% vs 4.2%, respectively; \(P = .17\)). The rate of bone fractures was increased in the patients who received letrozole (3.1% vs 5.2%; \(P = .02\)), as was the rate of newly diagnosed osteoporosis (1.6% vs 5.3%; \(P < .0001\)).

The most common side effects seen with AIs are myalgias and arthralgias. In the ATAC trial, 27.8% of women receiving anastrozole reported musculoskeletal disorders compared with 21.3% of those receiving tamoxifen.[50] In the BIG 1-98 trial, 20.3% of patients receiving letrozole vs 12.3% of those receiving tamoxifen reported arthralgias of any grade.[23] The incidence of musculoskeletal problems may actually be higher than the rates reported in the large trials. In a survey of 200 postmenopausal women receiving AIs for early-stage breast cancer, 47% reported joint pain and 44% reported joint stiffness.[51] A placebo-controlled trial would be required to substantiate these findings.

AIs accelerate bone loss in postmenopausal women. There were more fractures while on treatment in the ATAC trials in patients receiving anastrozole (odds ratio [OR], 1.33; 95% CI, 1.15–1.55; \(P < .0001\)).[22] After the completion of treatment, the incidence of fractures was similar (HR, 0.98; 95% CI, 0.74–1.30; \(P = .9\)). In the BIG 1-98 trial, a comparison of the monotherapy arms also showed an increase in bone fractures in women receiving letrozole, with a 60.3-month median follow-up (RR, 1.38; 95% CI, 1.13–1.69).[52]

Nonadherence to Therapy

While studies have found that adjuvant hormonal therapy for hormone-sensitive breast cancer dramatically reduces recurrence and mortality, adherence to medications is suboptimal. In a study of 8769 patients with stage I-III breast cancer diagnosed from 1996 to 2007, only 49% of the patients took adjuvant hormonal therapy for the full duration on an optimal schedule.[53] A recent study analyzing medical and pharmaceutical claims data from three national longitudinal databases found that adherence to adjuvant anastrozole therapy decreased from between 69% and 78% at year 1 to between 50% and 68% at year 3.[54] The success of AI treatment depends on adherence to the regimen. Thus, it is important for the oncologist to ask a patient about adherence. One nonjudgmental way of doing this is to ask how many pills the patient has missed in the last month, rather than asking if she has been taking her medication. Switching to another AI may be an alternative for women who are nonadherent because they are unable to tolerate the side effects of a particular AI.

Ongoing Clinical Trials

TABLE 11
Ongoing Clinical Trials

Ongoing clinical trials are listed in Table 11. These trials are designed to answer a number of questions, including how one AI performs compared to another (MA.27 and FACE [Femara Anastrozole Clinical Evaluation]), the role of extended adjuvant therapy (ANZ [Australian New Zealand] 0501, NSABP B-42), and the optimal duration of extended adjuvant therapy (MA.17R, SALSA [Secondary Adjuvant Long-term Study with Anastrozole], SOLE [Study of Letrozole Extension]). Data from the trials in premenopausal women of ovarian suppression with an AI compared to tamoxifen or ovarian suppression with tamoxifen (SOFT, TEXT [Tamoxifen and Exemestane Trial]) are eagerly awaited.

Conclusions

For many decades, tamoxifen has been the standard adjuvant endocrine treatment for HR-positive, early-stage breast cancer. For premenopausal women, it remains so. In premenopausal women, the role of ovarian suppression or ovarian ablation is not clear, and the results of studies examining these strategies in combination with tamoxifen or AIs—the SOFT and TEXT trials—are eagerly awaited.

In postmenopausal women, studies over the last decade have shown that AIs are more beneficial than tamoxifen in preventing disease recurrence. Trials have looked at tamoxifen directly compared to AIs upfront, at sequential therapy with tamoxifen and AIs, and at the extended use of AIs. It seems that the evidence from the sequenced therapy trials is strongest. However, in many of these trials, patients were randomized after having been disease-free for the first 2 to 3 years of tamoxifen therapy. The monotherapy trials have shown that the increased effectiveness of anastrozole and letrozole, compared to tamoxifen, seems to be greatest in the first 2 years. This benefit is not taken into account if the randomization occurs after that time. Among the questions still being studied are the optimal duration of extended adjuvant therapy with AIs, how one AI performs compared to another, and whether there is a benefit to intermittent extended adjuvant treatment.

Recommendations

Premenopausal women: Use tamoxifen for 5 years. If a patient becomes postmenopausal during treatment, consider extended adjuvant therapy with AI for 5 years.

Postmenopausal women:
  • If considering using monotherapy, AIs are superior to tamoxifen.
  • If considering a switch strategy (from AI to tamoxifen or from tamoxifen to AI, with a total duration of therapy of 5 years), randomized trials in which the randomization occurred at diagnosis showed no difference between switching and AI monotherapy.
  • Extended AI therapy after 5 years of tamoxifen is superior to 5 years of tamoxifen alone.

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