VOLUME 23 · NUMBER 8 · MARCH 10 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Advances in Adjuvant Hormonal Therapy for Postmenopausal Women

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J Clin Oncol 23:1751-1759. © 2005 by American Society of Clinical Oncology

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Submitted November 15, 2004; accepted December 7, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2308-1751/$20.00

DOI: 10.1200/JCO.2005.11.038

INTRODUCTION

Since George Beatson[1] and A. Schinzinger[2] produced remissions of advanced breast cancer by performing bilateral oophorectomy in premenopausal patients more than 100 years ago, the effect of antihormonal therapy on breast cancer has been known. Initial endocrine therapy included oophorectomy, hypophysectomy, and adrenalectomy. The latter two were abandoned when tamoxifen citrate was approved by the US Food and Drug Administration for use in advanced breast cancer in 1978. Selective estrogen receptor modulators (SERMs), such as tamoxifen, antagonize estrogen receptor (ER) function by binding competitively to it. Since 1978, more than 40,000 breast cancer patients, most of them postmenopausal, have been treated with tamoxifen, either in the context of clinical research studies or in clinical practice.

TAMOXIFEN AS THE STANDARD OF CARE

The available data on the use of tamoxifen in the adjuvant setting of ER-positive breast cancer have been extensively reviewed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[3-5] In their most recent meta-analysis including 37,000 women, adjuvant treatment with 5 years of tamoxifen resulted in a reduction of 47% in disease recurrence, and a mortality reduction of 26%.[5] The benefit of tamoxifen was restricted to the group of women with ER-positive tumors. In this meta-analysis, 5 years of tamoxifen therapy was better than 1 or 2 years of treatment, and the benefit from 5 years persisted through 10 years of follow-up. In the EBCTCG overview, the relative benefit from tamoxifen was independent of axillary lymph node involvement, age, tamoxifen dose, menopausal status, or use of chemotherapy. Based on these data, the 2000 US National Institutes of Health Consensus Development Conference recommended the use of adjuvant tamoxifen therapy for women "regardless of age, menopausal status, involvement of axillary nodes, or tumor size."[6] The 2001 St Gallen Consensus Panel came to a similar conclusion, suggesting the use of tamoxifen in most women with ER-positive breast cancer unless the patient has an absolute contraindication.[7] In both consensus statements, it was pointed out that for women with low-risk, hormone-responsive disease, no adjuvant medical treatment is an alternative choice to tamoxifen.

WHY NOT INDEFINITE TAMOXIFEN?

When 1,172 women who had completed 5 years of adjuvant tamoxifen within the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 adjuvant study were randomly assigned to a further 5 years of tamoxifen or placebo, no additional advantage was obtained from extending tamoxifen beyond 5 years.[8,9] In fact, prolonged tamoxifen conferred a worse prognosis than discontinuing therapy after 5 years. This might, in part, be explained by the fact that tamoxifen has partial agonist effects on the ER. In the preclinical setting, it was shown that tamoxifen resistance is acquired if MCF-7 cells are

cultured with tamoxifen for a prolonged period.[10,11] In the clinical setting, tamoxifen's agonistic action on the ER may even lead to growth stimulation of the tumor after 5 years. For example, it was shown in nude mice that long-term exposure to tamoxifen causes MCF-7 cells to grow in response to either tamoxifen or low doses of estrogen.[12-14] These demonstrable resistance/dependence mechanisms, together with the clinical observations, have lead to the current recommendation of restricting tamoxifen use to 5 years outside of clinical trials. The ongoing ATLAS (Adjuvant Tamoxifen—Longer Against Shorter) and aTTom (adjuvant Tamoxifen Treatment offer more?) studies, in which patients are randomized to 5 versus more than 5 years of adjuvant tamoxifen, will help to clarify the optimal duration of tamoxifen therapy.

In addition to acquired tamoxifen resistance, some tumors are primarily resistant to tamoxifen, for example, those expressing high levels of HER-2 or the receptor coactivator AIB1.[15] It has recently been shown that this is due to enhanced cross-talk between the ER and HER-2 pathways. In MCF-7 cells expressing high levels of ER and HER-2, both estrogen and tamoxifen induce activation of the ER, the epidermal growth factor receptor/HER-2 receptor, and the signaling molecules AKT, MAPK, and AIB1.[16]

AROMATASE INHIBITORS IN THE ADJUVANT SETTING

In contrast to SERMs, aromatase inhibitors (AIs) work by blocking the enzyme complex responsible for the final step in estrogen synthesis, aromatase, thus preventing the production of the substrate of the ER. Therefore, unlike tamoxifen, the AIs have no partial agonist activity. In postmenopausal women, all of the third generation AIs suppress circulating estrogen levels by approximately 98%.[17-19] In contrast to the second generation inhibitors (eg, formestane), they are highly specific with almost no effect on cortisol or aldosterone levels. In addition to the suppression of circulating estrogen levels, the AIs also have the potential to abrogate autocrine and paracrine estrogen production by peritumoral stromal cells in both primary and metastatic sites of the disease.[20] Evidence suggests that this local estrogen production plays an important role in tumor growth.[21-24]

AIs can be classified by their mechanism of action into steroidal (irreversible, type I) and nonsteroidal (reversible, type II) inhibitors.[25,26] The inhibitors in clinical use today include the third-generation nonsteroidal agents anastrozole and letrozole and the third-generation steroidal aromatase inactivator exemestane. Their pharmacokinetic profiles are similar, with anastrozole and letrozole having longer half-lives (48 hours) than exemestane (27 hours).[27-29] All of them are administered orally once daily. Pharmacologic interactions of tamoxifen have been demonstrated in combination with both letrozole and anastrozole,[30,31] and while suppression of circulating estrogen is unaffected, the therapeutic consequences of this interaction are unknown.

Efficacy of Aromatase Inhibitors

New therapeutic approaches to adjuvant therapy should address two issues. First, is there a strategy rendering 5 years of adjuvant treatment more effective by adding to, or substituting tamoxifen with, AIs? And second, can adjuvant treatment be improved by extending its duration, and administering AIs after tamoxifen? At least 10 adjuvant trials of AIs, with a total of over 40,000 women with primary breast cancer, are currently addressing these issues. Results of three trials are available to date and will be discussed in the following sections.

Improving Adjuvant Therapy Within the First 5 Years

Numerous large trials are evaluating the use of AIs instead of tamoxifen, or in combination or in sequence with tamoxifen, during the first 5 postoperative years (Fig 1). Results from the first and largest of these studies, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial ($N = 9{,}366$), were published in 2002 and updated in 2003.[32-34] When anastrozole was compared with tamoxifen for 5 years, the AI led to improved disease-free survival (hazard ratio [HR], 0.86; $P = .03$) and time to recurrence (HR, 0.83; $P = .015$) after a median follow-up of 47 months.[34] There was also a lower incidence of contralateral breast cancer with anastrozole (HR, 0.62; $P = .062$), reaching statistical significance in the ER-positive subgroup (HR, 0.56; $P = .042$). To date, there is no difference in the rates of death from any cause or of breast cancer–related deaths.

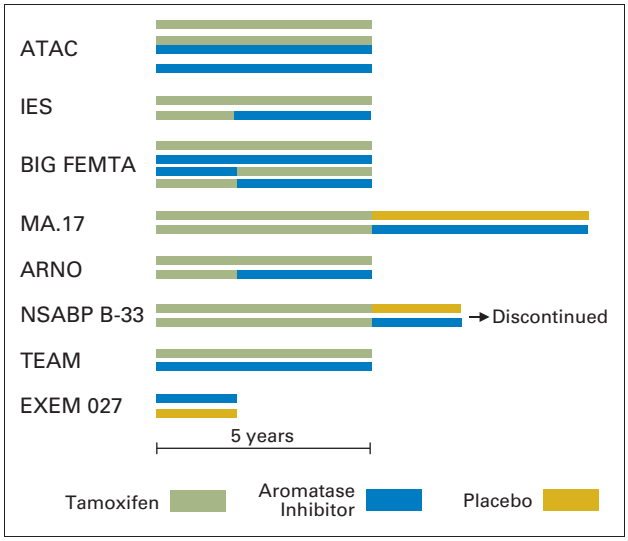

Fig 1. Ongoing and completed adjuvant breast cancer trials including aromatase inhibitors. ATAC, Arimidex, Tamoxifen, Alone or in Combination; IES, Intergroup Exemestane Study; ARNO, Arimidex versus Nolvadex; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Based on the published results from ATAC, the 2003 St Gallen consensus panel included the option of giving anastrozole to postmenopausal women in the adjuvant breast cancer setting "if tamoxifen is contraindicated" in their recommendations.[35] A similar recommendation was published by the American Society of Clinical Oncology Technology assessment.[36] In the updated position statement in 2005, the panel recommends that adjuvant hormonal therapy for postmenopausal women with hormone receptor–positive breast cancer should "include an AI as initial therapy or after treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by AIs for 2 to 3 years or 5 years.[37]

Data from a trial (Intergroup Exemestane Study [IES]) employing exemestane within the first 5 years after breast cancer diagnosis were published recently.[38] After 2 to 3 years of adjuvant tamoxifen, 4,742 women were assigned to either tamoxifen or exemestane for the remainder of the 5 years. After a median follow-up of 30.6 months, the HR for breast cancer recurrence in the exemestane group compared with tamoxifen was 0.68 ($P < .001$), reflecting an absolute benefit in disease-free survival of 4.7% after 3 years. Up to this point of follow-up, no difference in survival was noted, but as 90% of patients had completed their 5 years of therapy at the time of unblinding, assessing survival should be possible with longer follow-up. As yet, the results from this study have not influenced treatment recommendations in early-stage breast cancer, because long-term toxicity data are not yet available. However, for women finding adjuvant tamoxifen difficult to tolerate after 2 to 3 years, continuation of adjuvant treatment with exemestane might be an option.

Among the ongoing adjuvant AI studies in the adjuvant setting, the Arimidex versus Nolvadex trial is of similar design to the exemestane study presented above. After 2 years of adjuvant tamoxifen, patients are randomly assigned to either tamoxifen or anastrozole for the following 3 years. Furthermore, the large adjuvant letrozole study, BIGFEMTA, is still recruiting patients. It is a four-arm trial comparing letrozole with tamoxifen for 5 years, but also including two additional arms with a cross-over design from tamoxifen to letrozole and vice versa. Two other ongoing exemestane studies are the TEAM study, comparing exemestane to tamoxifen for 5 years, and the EXEM 027 trial, in which exemestane or placebo are administered for 2 years in very low-risk patients. Other studies, discussed below, are combining AIs with a cyclooxygenase-2 (COX-2) inhibitor. Figure 1 provides a summary of adjuvant single-agent AI studies.

A direct comparison of each of the three AIs for 5 years versus tamoxifen for 5 years will be available in a few years. For anastrozole, superiority to tamoxifen has already been demonstrated. Furthermore, the sequence of an AI after 2 to 3 years of tamoxifen has also been studied with all three agents. Data coming from the IES look promising. The inverse sequence, tamoxifen given after 2 to 3 years of an AI, will only be looked at in the BIGFEMTA trial with letrozole, making this study particularly important. To date, it can be said that AIs as monotherapy included in a 5-year adjuvant hormonal regimen seem to improve efficacy, and possibly, tolerability. However, as the optimal duration of adjuvant therapy is not known, other treatment regimens including AIs might still be superior.

Improving Adjuvant Therapy Beyond 5 Years

It is known that approximately half of all breast cancer recurrences in women with ER-positive tumors taking 5 years of adjuvant tamoxifen occur between 5 to 15 years after surgery, and that the risk of recurrence appears to continue indefinitely.[3-5] Based on this, there is a rationale for extending adjuvant endocrine therapy beyond 5 years of tamoxifen with an AI.

Results from the first large study employing an AI after 5 years of tamoxifen (MA.17) were published recently.[39] After having completed 4.5 to 6 years of prior adjuvant tamoxifen, a total of 5,187 women were randomly assigned to a further 5 years of letrozole 2.5 mg daily or placebo. After a median follow-up of 2.4 years, when the first interim analysis was conducted, the independent data and safety monitoring committee recommended termination of the trial and prompt communication of the results, because women on letrozole had a significantly superior disease-free survival (93% *v* 87%; $P < .001$), and in order to offer women taking placebo an opportunity to take letrozole. The HR for local or metastatic recurrence or new contralateral breast cancer in the letrozole group was 0.57 ($P = .00008$) compared with placebo. There was also a trend towards improved 4-year overall survival for women receiving letrozole (96% *v* 94%), but this was not statistically significant at the time of the first interim analysis.

The data from MA.17 show that extending adjuvant endocrine therapy beyond 5 years with an AI offers significant benefit in disease-free survival. The unique opportunity to re-randomize MA.17 patients who complete 5 years of letrozole to a further 5 years or placebo is now being undertaken. This will allow duration of efficacy and toxicity to be further evaluated. The second trial testing an AI after tamoxifen in the adjuvant setting was the NSABP B-33 study. This trial compared exemestane with placebo for 5 years after the standard 5 years of tamoxifen. Based on the results of MA.17, accrual to this trial was discontinued, the study medication unblinded, and all participants taking placebo were offered exemestane.

TOLERABILITY OF ENDOCRINE AGENTS IN THE ADJUVANT SETTING

The side effect profile of tamoxifen has been examined in adjuvant studies. In addition, important toxicity data

were gained from four large tamoxifen prevention trials in which tamoxifen was compared with placebo, and as a result, probably most accurately reflect its true toxicities.[40] The third-generation AIs are generally well tolerated. The available data from the first-line metastatic setting indicate at least equal short-term safety of the AIs compared with tamoxifen, including symptoms of menopause and quality of life.[41-45] However, for use of AIs in the adjuvant setting, short-term tolerability and long-term effects in a healthy population are relevant. The most relevant data on the toxicity profile of AIs are derived from adjuvant trials in which the agents are evaluated in disease-free women over a prolonged period.

Hot Flashes and General Tolerability

Tamoxifen significantly increases bothersome hot flashes and vaginal discharge, but this did not affect overall physical and emotional well-being in the NSABP P-1 chemoprevention trial, which included more than 13,000 women.[46] The reported effects of tamoxifen on cognition are variable and appear dependent on the parameters that are measured. Several ongoing studies are addressing this point.

In the two adjuvant AI studies in which tamoxifen is the standard arm (ATAC and IES), the short-term tolerability of the AI was at least as good as that of tamoxifen.[38,47] In ATAC, patients receiving anastrozole suffered from significantly fewer hot flashes, which were, however, not confirmed in a parallel quality-of-life study.[46] There was a significantly decreased rate of vaginal bleeding in patients receiving anastrozole (4.5% *v* 8.2%; $P < .0001$). This reflects the nonstimulatory effect of the AIs on the endometrium. In the IES trial, the frequency of hot flashes and vaginal bleeding was similar in both arms. In a study of letrozole in women completing tamoxifen, more rapid return to normal endometrial thickness was noted after tamoxifen in women receiving letrozole than those on no treatment.[48] Other short-term adverse effects such as nausea and vomiting, fatigue, mood disturbance, headaches, and dizziness were noted with equal frequency in both arms. The weakness of data coming from the ATAC and IES studies is that there was no placebo arm allowing for a true estimation of the toxicities of the AI. This is now possible with data from the adjuvant MA.17 study, comparing letrozole with placebo. In this trial, hot flashes occurred more often in the letrozole arm (47.2% *v* 40.5%). Symptoms were, in general, grade 1 to 2 out of 4 according to the National Cancer Institute Common Toxicity Criteria. Otherwise, the short-term tolerability of the study drug in MA.17 was excellent, with symptoms such as fatigue, sweating, constipation, headache, dizziness, and vaginal bleeding being equally distributed between letrozole and placebo. The percentage of women discontinuing treatment because of adverse events was not different between the two arms.

Lipid Metabolism

While in retrospective analyses of three randomized tamoxifen trials a reduction in coronary heart disease was observed, no such benefit was demonstrated in NSABP P-1.[49-52] In the EBCTCG overview of 1998, mortality rates for causes "not attributed to breast or endometrial cancer" were nearly identical in patients receiving tamoxifen or placebo in the adjuvant setting.[5] In view of the recently published data from the Women's Health Initiative study,[53] it is uncertain whether the favorable influence of tamoxifen on lipid metabolism translates into a true reduction in coronary heart disease.

In the ATAC trial, influences of either anastrozole or tamoxifen on the serum lipid profile have not been reported. In a small study, no influence of anastrozole on the lipid profile was seen when postmenopausal women were treated for less than 20 months.[54]

Studies on the effects of letrozole on lipid metabolism have yielded conflicting results. When letrozole was given to healthy women for 3 months, no influence was seen on their plasma lipid levels.[55] However, in another study including 20 women with breast cancer, letrozole significantly increased total and low-density lipoprotein (LDL) cholesterol levels, as well as the atherogenic risk ratios total/ high-density lipoprotein (HDL) and LDL/HDL cholesterol.[56] In the adjuvant MA.17 study, there was a (nonsignificant) trend towards a higher rate of cardiovascular events in the letrozole group compared with placebo (4.1% *v* 3.6%).[39] There were no reports of drug-related hypercholesterolemia. Publication of the results of the lipid substudy of MA.17 is pending and follow-up of the companion trial participants is ongoing.

Exemestane might have effects converse to the other AIs in terms of lipid metabolism. When exemestane was compared with tamoxifen in breast cancer patients, it had beneficial effects on triglycerides and a stabilizing effect on HDL and total cholesterol levels after 24 weeks.[57] Similarly, in animal experiments, exemestane improved the serum lipid profile in treated rats compared with either oophorectomy or letrozole.[58] In a small European Organisation for Research and Treatment of Cancer (EORTC) study of metastatic breast cancer patients, exemestane had no detrimental effect on cholesterol levels and atherogenic indices, and had a beneficial effect on triglyceride levels compared with tamoxifen.[59] It is therefore possible that being an androgenic steroid makes exemestane superior to the other inhibitors in terms of adverse effects caused by estrogen depletion of target tissues other than the breast. In the adjuvant IES study, the effect of exemestane on cholesterol levels was not systematically measured.[38] There was no significant increase in the rates of

myocardial infarction in the exemestane arm compared with tamoxifen.

Skeletal Effects

Tamoxifen has been shown to preserve bone mineral density in postmenopausal breast cancer patients.[60,61] NSABP P-1 is the only prospective trial that has evaluated the effect of tamoxifen on bone fractures versus placebo and it showed a reduction in the risk of long bone and symptomatic vertebral fractures of borderline statistical significance (risk ratio [RR] = 0.81; 95% CI, 0.63 to 1.05).[49] To date, tamoxifen has not been evaluated in a prospective trial in women with osteoporosis.

In the ATAC trial, women taking anastrozole were more likely to suffer from musculoskeletal disorders (30.3% versus 23.7%, $P < .001$), in particular fractures (7.1% versus 4.4%, $P < .001$).[34]

In the ATAC trial, women taking anastrozole were more likely to suffer from musculoskeletal disorders (30.3% *v* 23.7%; $P < .001$), in particular, fractures (7.1% *v* 4.4%; $P < .001$).[34] Similar to anastrozole, letrozole has, in several studies, been shown to significantly increase parameters of bone resorption.[55] In healthy postmenopausal women, letrozole given for 12 weeks increased bone resorption and reduced bone formation.[62] In the adjuvant MA.17 study, more women in the letrozole group compared with placebo suffered from new-onset osteoporosis and fractures (3.6% *v* 2.9%).[39] In addition, arthritis, arthralgia, and myalgia were reported more often by women in the experimental arm (5.6% *v* 3.5%, 21.3% *v* 16.6.%, and 11.8% *v* 9.5%, for letrozole and placebo, respectively).

The effect of exemestane on markers of bone metabolism was studied in a preclinical study of ovariectomized rats. In this model, exemestane protected against the negative effects of oophorectomy.[58] In healthy postmenopausal women, exemestane given for 12 weeks appeared to cause similar increases of bone resorption as the other inhibitors, but in addition, increased serum propeptide of type 1 collagen, a marker of bone formation, a feature not seen with the nonsteroidal inhibitors.[62] This supports the notion that exemestane may have a superior safety profile compared with other third-generation inhibitors with regard to bone metabolism. In the adjuvant IES study, there was a higher frequency of osteoporosis and arthralgia in the exemestane group compared with tamoxifen (7.4% *v* 5.7% and 5.4% *v* 3.6% for exemestane and tamoxifen, respectively).[38] There was no significant increase in fractures. When studying the effects of AIs on bone metabolism in comparison with tamoxifen, it should be noted that tamoxifen has a beneficial (estrogen-agonistic) effect on bone.[63] Therefore, the negative effects on bone caused by the AIs in the ATAC and IES studies might, in part, be the result of a protective effect of tamoxifen.

Thromboembolic Events and Endometrial Cancers

Participants in the tamoxifen breast cancer prevention trials had a 2.4 times greater risk of developing invasive endometrial cancer on tamoxifen than those receiving placebo ($P = .00005$),[40] and this effect was more pronounced in women over 50 years of age compared with younger women (RR = 4.01 *v* 1.21).[49] When the data from the adjuvant studies included in the 1998 EBCTCG analysis are taken together, this excess of endometrial cancer risk is confirmed (odds ratio [OR], 3.4; $P = .00002$).[5]

Tamoxifen also leads to an excess risk of thromboembolic events when compared with placebo. In the NSABP P-1 prevention study, pulmonary embolism was three times as common (RR = 3.01), and strokes were nearly twice as frequent among women > 50 years of age receiving tamoxifen compared with younger women taking the drug (RR = 1.75).[49] Venous thromboembolic events were also increased in all prevention trials, with a relative risk of 1.9 in the tamoxifen compared with the placebo arms ($P < .0001$).[40] Overall, the increase in vascular events with tamoxifen was comparable to that seen with hormone replacement therapy.

In all the trials comparing the third-generation AIs with tamoxifen, the adverse events caused by tamoxifen's estrogenic properties were significantly less common in the AI groups.[38,64,65] This is particularly important with respect to ischemic cerebrovascular and venous thromboembolic events (including deep venous thrombosis) and endometrial cancer. Compared with placebo, letrozole did not lead to increased rates of any of these serious adverse events in the MA.17 study and vaginal bleeding occurred more often in the placebo arm ($P = .01$).[39]

FUTURE DIRECTIONS

Comparison Between AIs

In a pharmacodynamic cross-over study, letrozole was associated with a more profound suppression of aromatase than anastrozole.[66] In a clinical trial in advanced disease after tamoxifen, time to progression, time to treatment failure, duration of response and of clinical benefit were similar between letrozole and anastrozole. In this study, letrozole was associated with a significantly better overall response rate (19.1% *v* 12.3%; $P = .014$), which was, however, not seen in the ER-positive subgroup.[67] There are no data directly comparing exemestane to any of the other inhibitors. A large first-line adjuvant trial is now underway, comparing anastrozole to exemestane as outlined below (MA.27).

AIs Used Sequentially

The results of several studies suggest that breast cancer might be sensitive to steroidal AIs even after failure of a nonsteroidal inhibitor. Exemestane led to clinical benefit

in 24.3% of 241 patients with advanced breast cancer after failure of tamoxifen and a nonsteroidal inhibitor.[68] A Spanish randomized cross-over study including 100 breast cancer patients is currently evaluating the use of exemestane after anastrozole versus the opposite in metastatic disease. Preliminary results of a small study in the metastatic setting comparing various sequences of AIs showed no difference between overall response and clinical benefit rates, implying that nonsteroidal inhibitors can be used after exemestane as well.[69] There are no ongoing adjuvant studies exploring the sequence of two AIs.

Combination of Agents

Tamoxifen plus AIs. The obvious combination of tamoxifen and an AI in postmenopausal women was evaluated in the adjuvant ATAC trial.[47] In the first interim analysis, the combination of the two endocrine agents was equivalent to tamoxifen alone, but significantly worse than anastrozole. A possible explanation of this finding might be that the estrogen agonistic properties of tamoxifen are more effective in an estrogen-depleted environment. Based on these findings, the combination arm of ATAC was suspended. It has been hypothesized, however, that use of a less agonistic SERM with an AI may achieve the intended total estrogen blockade. While toremifene appears equivalent to tamoxifen as a single agent in patients in vitro in a depleted estrogen environment, it is significantly less estrogen agonistic. Based on this finding, toremifene is being combined with an unregistered steroidal inhibitor, atamestane, in a trial comparing the combination to letrozole in women with locally advanced or metastatic breast cancer.

AIs plus COX-2 inhibitors. In recent years, several preclinical studies have implicated a role for COX-2, an enzyme generating prostaglandins, in the pathogenesis of breast cancer.[70] In an analysis of 1,576 human breast cancer samples, COX-2 expression was found in 37.4% and correlated with adverse prognostic features.[71] Preclinically, inhibition of COX-2 by celecoxib was effective in the treatment and prevention of ER-positive mammary tumors.[70] Importantly, celecoxib also inhibits the proliferation of ER-negative breast cancer cells.[72]

There is a close relationship between the COX-2 and aromatase pathways. Prostaglandin E_2–dependent expression of aromatase has been shown in several studies,[70,73,74] and a positive correlation between COX-2 and aromatase expression was demonstrated in human breast cancer specimens.[75,76]

Several trials are evaluating the potential of COX-2 inhibition in treating breast cancer. In a phase II study of 13 breast cancer patients with ER-positive or progesterone receptor–positive metastatic disease, the combination of exemestane and celecoxib produced a clinical benefit rate of 73%.[77] In the adjuvant setting, the National Cancer Institute of Canada–Clinical Trials Group (NCIC-CTG) MA.27 trial is evaluating the addition of celecoxib to exemestane or anastrozole (Fig 2). Enrollment to MA.27 exceeds 1,000 women to date. A neoadjuvant three-arm study (Celecoxib Anti-Aromatase Neoadjuvant) is comparing exemestane plus celecoxib to exemestane or to letrozole.

Other studies, including the recently launched, randomized NCIC-CTG MAP.3 study are prospectively evaluating the chemopreventive potential of celecoxib in combination with an AI (Fig 3). Very recently, at the time of this submission, concern arose regarding the potential cardiotoxicity of inhibitors of the COX-2 enzyme, including adverse events noted in an adenomatous polyposis coli trial. This has led to the suspension of the celecoxib/placebo randomization within the MA.27 trial and to elimination of the exemestane plus celecoxib arm from the MAP.3 trial. Review of other celecoxib-containing trials is also being undertaken.

Strategies to Overcome Endocrine Resistance in Postmenopausal Breast Cancer

It has been known since the early development of endocrine therapies that some patients with ER/PR -positive breast cancer do not benefit from endocrine therapy. In addition, even patients whose tumors initially respond to endocrine treatment will eventually experience disease progression. In recent years, substantial progress has been made in understanding specific mechanisms of endocrine resistance. One major mechanism for tumor insensitivity to hormonal agents seems to be cross-talk between the ER and other growth factor signaling pathways. The studies investigating this interaction have revealed at least three different levels of cross-talk between signal transduction pathways and steroid hormone receptors.[78-81] In breast cancer patients, overexpression or aberrant activation of epidermal growth factor receptor 2 (EGFR-2/ErbB2/HER-2) has been widely demonstrated in breast

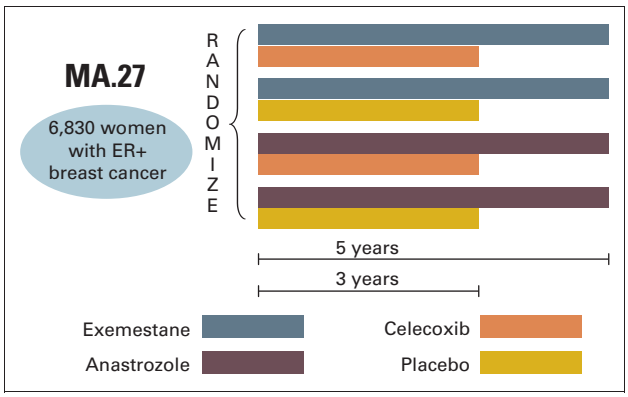

Fig 2. The National Cancer Institute of Canada Clinical Trials Group MA.27 adjuvant breast cancer trial. Exemestane versus anastrozole and celecoxib versus placebo; 2 × 2 factorial design. ER+, estrogen receptor–positive.

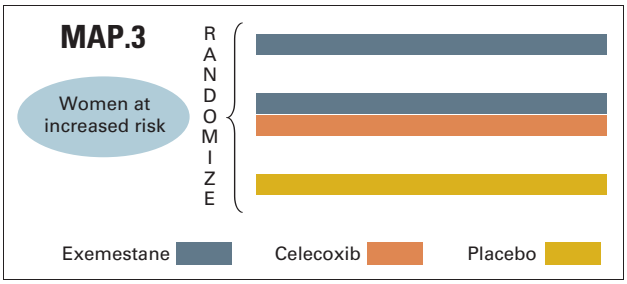

Fig 3. The National Cancer Institute of Canada Clinical Trials Group MAP.3 breast cancer prevention trial. Exemestane versus placebo +/− celecoxib; n = 3 × 1,700 = 5,100.

tumors and linked to an adverse prognosis and endocrine resistance. Consequently, combining endocrine therapies with signal transduction inhibitors might be a strategy to overcome the development of endocrine resistance.[82] In preclinical studies, signal transduction inhibitors such as the tyrosine kinase inhibitor of EGFR-1, ZD-1839, seem to be only marginally successful if used as monotherapy. However, in a recently published study in a breast cancer xenograft mouse model, significant synergism was shown between ZD-1839 and tamoxifen.[83] In this study, mice bearing ER-positive MCF-7 breast tumors were treated with tamoxifen, ZD-1839, or the combination of both. ZD-1839 improved the antitumor effect of tamoxifen, and markedly delayed the emergence of acquired resistance from 2 to 3 months to over 6 months. Importantly, in mice treated with estrogen deprivation, there was no demonstrable benefit from adding ZD-1839, indicating that activation of the EGFR pathway enhances the agonist effects of tamoxifen. Apart from ZD-1839, numerous other growth factor tyrosine kinase inhibitors are in different stages of preclinical and clinical development, including OSI-744, PKI-166, GW-572016, and CI-1033, which is an irreversible pan-erbB tyrosine kinase inhibitor. These compounds are being studied as monotherapy in numerous tumor types and clinical studies evaluating them in combination with endocrine agents are awaited with great interest.

Downstream of the growth factor receptor tyrosine kinases, the Ras proteins, for which aberrant function has been demonstrated in breast cancer, play a major role in intracellular signal transduction. The enzyme farnesyl transferase, which is needed for post-translational processing of Ras, can be inhibited with the newly developed farnesyl transferase inhibitors.[84] One of these compounds, R115777, is active in breast cancer models[85] and has already been studied in women with advanced hormone-resistant breast cancer.[86] Among 76 patients, 24% of patients derived clinical benefit from R115777. The farnesyl transferase inhibitors have, as yet, not been studied in combination with endocrine therapy.

Other signal transduction inhibitors in clinical development include the Raf kinase and MEK inhibitors, cell cycle inhibitors, and the mTOR inhibitors, of which CCI-779 (rapamycin) has entered clinical development in advanced breast cancer.[87] For CCI-779, improved efficacy has been demonstrated in combination with endocrine therapy, and a phase II trial combining the compound with AIs is being planned.[78]

CONCLUSION

Tamoxifen has played a major role in postmenopausal, hormone-sensitive, early-stage breast cancer. De novo and acquired resistance to tamoxifen have limited its efficacy, but identification of specific signal transduction pathways responsible for tamoxifen resistance promises to allow combinations of tamoxifen and inhibitors of these pathways to improve patient outcome. AIs are proving to be an important new class of endocrine therapy and whether to use them instead of, or in sequence with, tamoxifen is being determined. Understanding resistance mechanisms to AIs and finding tumor and host prognostic and predictive markers should allow selection of patients for treatment with the inhibitors. Long-term adverse effects of the AIs are being determined in the follow-up of several trials including the NCIC-CTG MA.17 and the re-randomization phase of this trial. Whether steroidal AIs are superior to nonsteroidals is being determined in the NCIC-CTG MA.27 trial now underway. The outlook of postmenopausal women with hormone-dependent breast cancer promises to improve as a result of these new therapeutic approaches.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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