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ABSTRACT

Third-generation aromatase inhibitors and inactivators have been successfully implemented in therapy of metastatic breast cancer, and three large phase III trials have revealed superiority compared with tamoxifen monotherapy in the adjuvant setting. Notably, each of these trials recorded a substantial reduction in contralateral breast cancer among patients exposed to the aromatase inhibitor/inactivator. A major concern in implementing use of these compounds in the preventive setting relates to potential detrimental effects of estrogen suppression on bone and lipid metabolism. Recent data from a placebo-controlled study now reveal 2 years of treatment with exemestane compared with placebo to have moderate effects on bone metabolism and plasma lipid profile, supporting further evaluation of exemestane as a potential preventive agent for breast cancer in postmenopausal women.

INTRODUCTION

Much evidence points to a role of endocrine-based prevention strategies for breast cancer. The first observations were made in relation to long-term adjuvant therapy with tamoxifen, which was found not only to improve relapse-free and overall survival in patients treated for breast cancer but also to significantly reduce the incidence of contralateral breast cancer (1). Although this could be due to inhibition of the growth of small, invasive, subclinical carcinomas, the National Surgical Adjuvant Breast Project protocol B-24 found that tamoxifen also reduced the relapse rate in patients surgically treated for ductal carcinoma in situ (2).

Four trials have evaluated tamoxifen versus placebo as a preventive agent for breast cancer in high-risk postmenopausal women (3–6). Although the results of these trials are at variance probably due to different inclusion criteria, combined data showed that tamoxifen suppressed the overall incidence of breast cancer by ~38%, with a mean reduction of 48% for hormone receptor–positive tumors (7). In addition, the Multiple Outcomes of Raloxifene Evaluation trial, designed to evaluate the effect of raloxifene on bone mineral density, revealed a substantial reduction in breast cancer incidence for women exposed to this compound compared with placebo (8). These two selective estrogen receptor modulators are currently being compared head-to-head in breast cancer prevention in the Study of Tamoxifen and Raloxifene trial.

There are several reasons to focus on aromatase inhibitors and inactivators as potential preventive agents in postmenopausal breast cancer. Considering therapeutic efficacy in established cancer, the third-generation nonsteroidal aromatase inhibitors anastrozole and letrozole as well as the third-generation inactivator exemestane have all revealed superiority compared with tamoxifen in metastatic breast cancer (9–11). Recently, three large phase III studies found superiority for anastrozole monotherapy compared with tamoxifen, tamoxifen followed by exemestane versus tamoxifen monotherapy, and letrozole versus placebo following 5 years of tamoxifen in the adjuvant setting (12–14). The fact that endocrine therapy in general may provide temporary tumor control but no cure in metastatic disease, whereas it has been shown to improve long-term survival and thereby curability in the adjuvant setting, suggests that early implementation of therapy may be beneficial. In addition, any potential difference detected in the advanced setting may be escalated into a larger therapeutic benefit in early disease. Further, the findings in numerous prospective studies that estrogen levels are associated with subsequent breast cancer risk in postmenopausal women provide a rationale for evaluating aromatase inhibitors in breast cancer prevention (15–23). Major concerns remain, however, about the potential detrimental effects of estrogen suppression on bone and lipid metabolism.

PHARMACOLOGY OF AROMATASE INHIBITORS AND INACTIVATORS

Whereas first- and second-generation aromatase inhibitors were found to inhibit estrogen synthesis by ~90% (24–28) and to have antitumor effects similar to conventional agents (see ref. 29 for references to original articles), the introduction of the third-generation aromatase inhibitors anastrozole and letrozole as well as the third-generation inactivator exemestane represented major breakthroughs. These compounds inhibit in vitro aromatization by ≥98% (30–32), which translated into a superior therapeutic efficacy for metastatic as well as early breast cancer (see ref. 29 for references).

A major issue relates to potential differences between the nonsteroidal inhibitors and the steroidal inactivators. Not only do the compounds differ with respect to chemical structure (Fig. 1), but also the nonsteroidal inhibitors bind in a reversible manner to the p450 part of the aromatase enzyme, whereas the inactivators bind irreversibly into the substrate binding pocket (33). Although the clinical importance of that difference is uncertain, steroidal inactivators in addition express intrinsic steroidal activity. Thus, the third-generation inactivator exemestane has been found to suppress sex hormone binding globulin in a dose-dependent manner, consistent with a slight androgenic effect on the liver (Fig. 2). Although clinical adverse effects related to androgenic action appeared during long-term treatment with doses in the range of 100 to 200 mg/d, the biochemically detectable influence on sex hormone binding globulin appears at


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the therapeutic dose of 25 mg/d (34). Notably, several studies have revealed a lack of cross-resistance between nonsteroidal and steroidal inhibitors, suggesting that patients becoming resistant to nonsteroidal compounds may subsequently benefit from treatment with a steroidal drug (35–39). Only one small study assessed the use of a nonsteroidal compound following a steroidal one, reporting stable disease in some patients on second-line treatment (37). Importantly, in one study, patients becoming resistant to anastrozole and letrozole subsequently benefited from treatment with the second-generation aromatase inactivator formestane (39). As this compound is a less potent aromatase inhibitor, this suggests that the lack of cross-resistance may not be due to more effective inhibition but related to other biochemical effects of the different compounds.

**RATIONALE FOR AROMATASE INHIBITORS AND INACTIVATORS IN PREVENTION**

The importance of estrogen exposure to breast cancer development is well known. Thus, women losing their ovarian function early in life will have a substantial reduction in breast cancer risk (40). In contrast, long duration of estrogen exposure (early menarche as well as late menopause) and hormone replacement therapy both increase the risk of breast cancer.

More surprising is the recent evidence from several different prospective studies, all revealing a substantial risk of breast cancer linked to postmenopausal estrogen levels (15–23), with risk ratios between the upper and the lower tertiles of plasma estradiol reaching up to 5 in one study (17). In addition, increased breast density and high bone mineral content, both indicators of durable estrogen exposure in postmenopausal women, are associated with increased risk of breast cancer (41, 42). Considering the substantial influence of variations in natural estrogen levels on subsequent breast cancer risk, it is reasonable to speculate that profound hormone suppression, achievable with the third-generation aromatase inhibitors/inactivators, could significantly suppress breast cancer risk.

**RESULTS FROM ADJUVANT STUDIES**

Notably, the three large studies evaluating aromatase inhibitors or inactivators in the adjuvant setting all revealed a profound reduction in contralateral breast cancer. Thus, in the first result from the Arimidex, Tamoxifen Alone or in Combination study comparing anastrozole monotherapy to tamoxifen (12), contralateral breast cancer was reduced by 58% in the anastrozole arm compared with tamoxifen. In the International Exemestane Study comparing exemestane to tamoxifen following exposure to tamoxifen for 2 to 3 years, the number of new primary tumors in the contralateral breast was 20 in the tamoxifen arm compared with 9 in the exemestane arm (14). Finally, the Ma.17 study comparing letrozole to placebo recorded 26 and 14 new primary tumors in the placebo versus letrozole arms, respectively (13).

**PREVENTION: DELAYING EMERGENCE OF CLINICAL CANCERS OR PREVENTING CARCINOGENESIS?**

Notably, as all these studies included short-term follow-up only, there is a need to interpret these results carefully. Thus, radiotherapy to the breast following breast conservative surgery significantly reduces the risk of a new primary tumor as well as relapse in the local area during the first decade following therapy; thereafter, the annual risk of a new primary seems to be similar in the two breasts and the risk for a local relapse seems independent of therapy (43, 44), with the curves running in parallel. Whether a similar effect may be achieved with hormone prevention, or the benefits may be further escalated or diminished, can only be addressed through long-term follow-up in these studies.

Based on the evidence discussed above, there is no doubt estrogens promote development of clinical breast cancers. There is also evidence suggesting certain estrogen metabolites created through hydroxylation at the 4 position may be carcinogenic (45, 46). Whereas the short-term effects observed with respect to development of contralateral breast cancer with use of aromatase inhibitors in the adjuvant trials most likely are due to effects on subclinical invasive carcinomas, the results from the National Surgical Adjuvant Breast Project protocol B-24 suggest effects on preinvasive tumors as well (2). Whether carcinogenesis occurs in postmenopausal life or earlier in life is another question. In case the carcinogenic effect may be of importance in

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**Fig. 1** Chemical structure of the two third-generation aromatase inhibitors (anastrozole and letrozole) and the third-generation inactivator exemestane together with the first/second-generation compounds amino-glutethimide and formestane.

**Fig. 2** Plasma sex hormone binding globulin levels during treatment with exemestane. Points, geometric mean; bars, 95% confidence interval. Reproduced with permission from Johannessen et al. (34).
postmenopausal women, aromatase inhibitors may have an advantage compared with tamoxifen. These agents inhibit production of estrogens and thereby their toxic metabolites, which does not happen with tamoxifen. The potential importance of the different effects in the clinical setting can only be addressed through long-term follow-up in clinical studies.

**PREVENTION: POTENTIAL ADVERSE EFFECTS OF ESTROGEN DEPRIVATION**

Of little concern in metastatic breast cancer, effects of estrogen depletion on bone metabolism and plasma lipids are a concern to adjuvant treatment and particularly to use of aromatase inhibitors/inactivators for breast cancer prevention. Although some small studies have assessed the effects of agents on these variables in patients with advanced breast cancer, such patients often suffer from skeletal metastases as well as disturbances in metabolic function, limiting interpretation of the results (47).

Although different adverse effects were carefully recorded in the three major adjuvant studies (13, 14, 48), there are limitations with respect to interpretation of the results. Thus, in two of these trials, the incidence of adverse effects associated with the aromatase inhibitor was compared with the incidence among patients treated with tamoxifen. Second, regarding subjective adverse effects, the same variables were not universally recorded. Thus, although all trials confirmed previous observations of an increased incidence of musculoskeletal pain during treatment with aromatase inhibitors, the finding that exemestane increased the incidence of diarrhea from ~2% (tamoxifen arm) to 4% (14) may not necessarily indicate a difference from the other aromatase inhibitors, inasmuch as this variable is not reported in the other publications. A major concern, however, relates to bone metabolism and fracture rate; thus, in the adjuvant studies, the incidence of fractures was increased by 22%, 36%, and 60% with letrozole, exemestane, and anastrozole treatment, respectively, although this increase was of statistical significance for anastrozole only. Needless to say, cross-study comparisons based on these data would be inappropriate. This relates in particular to the fact that exemestane and anastrozole both were compared with tamoxifen, known to have a beneficial effect on bone metabolism in postmenopausal women (3, 49) but also to potential “hangover effects” in patients exposed to tamoxifen prior to commencing treatment with the aromatase inhibitor (exemestane and letrozole). Ideally, the effects of an aromatase inhibitor on bone metabolism as well as other variables should be assessed in tamoxifen-naive patients in placebo-controlled, double-blind studies.

Using a rat model, Goss et al. (50) found exemestane to express anabolic effects on bone metabolism. In a recently reported study (Fig. 3), we evaluated the effect of exemestane versus placebo on bone mineral density as well as bone biomarkers, plasma lipids, coagulation factors, and plasma homocysteine in patients treated for early breast cancer (51–53). In contrast to the findings of Goss et al., we found 2 years of treatment with exemestane to increase bone loss from the hips (statistically significant) as well as the lumbar spine (nonsignificant) compared with placebo. The discrepancy could be related to species differences but also to drug dosing in the animal model. The drop in T-score in the exemestane and placebo-treated arms in our study was 0.30 and 0.21 with respect to the hips and 0.21 versus 0.11 regarding the lumbar spine, respectively. The change in T-score, however, corresponded to an increase in the hazard ratio for a hip fracture to ~1.15 (54). Considering the fact that a normal postmenopausal woman may have a lifetime risk of achieving a hip joint fracture in the range of ~20% (54), these figures suggest that the risk may increase to ~23%. However, the fact that none of our patients with a normal bone mineral density at baseline became osteoporotic during the 2-year period suggests that potential problems related to bone mineral density loss may occur in patients who are osteopenic and osteoporotic at baseline, a risk that may be reduced by regular bone mineral density assessment and interventions according to general guidelines for treating these problems.

Interestingly, looking at the bone biomarkers, we found that exemestane not only enhanced bone degradation but also increased markers of bone synthesis (52). In a poster presented at the 2004 Annual Meeting of the American Society of Clinical Oncology, Subar et al. (55) reported that exemestane, but none of the nonsteroidal aromatase inhibitors, increased markers of bone synthesis in healthy volunteers. Notably, the 17-hydrometabolite of exemestane expresses androgen-agonistic activity determined by suppression of sex hormone globulin when administered at therapeutic doses (34). Although androgens are known to influence bone synthesis but not resorption (56), we do not know yet whether there is a real difference between steroidal and nonsteroidal inhibitors regarding bone biomarkers and, if so, whether this may signal any androgen-agonistic interaction. Thus, more data are needed to define whether there may be a difference between steroidal and nonsteroidal aromatase inhibitors on bone metabolism.

Concerning plasma lipids, exemestane was found to cause a modest suppression of high-density cholesterol and apolipoprotein A1 (associated with the high-density cholesterol), but no significant effects on any of the other lipid variables were recorded (53). Although high-density cholesterol has been...
considered protective with respect to cardiovascular risk profile (57, 58), recent large studies assessing the role of hormone replacement therapy have revealed no effect of estrogen replacement on cardiovascular risk profile despite a 6% to 10% increase in plasma high-density cholesterol levels (59–63). Considering the International Exemestane Study trial, a nonsignificant increase in cardiovascular “events other than myocardial infarction” was recorded (14); however, the short follow-up time underlines the need for careful monitoring and long-term follow-up of events. Treatment with exemestane had no detrimental effect on any of the coagulation variables. A moderate increase in homocysteine levels of 11% was recorded. Although homocysteine has been considered as a risk factor for cardiovascular morbidity, recent evidence does not suggest this factor to be of such a magnitude as suggested previously (64).

ONGOING TRIALS ASSESSING EXEMESTANE IN THE PREVENTIVE SETTING

There are three ongoing studies assessing exemestane as a potential preventive agent in high-risk breast cancer patients (Fig. 4). In the multicenter Italian study (Aromasin Prevention Study), postmenopausal women carrying BRCA1/2 mutations who have not developed breast cancer are randomized to exemestane 25 mg/d versus placebo for a 3-year period. Primary end points are to assess the effects of exemestane on development of invasive breast cancer, microcalcifications, and proliferative breast disorders. Secondary end points include effects on body mass index, bone density, and bone biomarkers. The planned enrollment is 666 women.

In addition, there are two National Cancer Institute of Canada preventive trials under way. The first study, protocol National Cancer Institute of Canada Clinical Trials Group MAP.2, addresses the potential effects of exemestane versus placebo for 1 year on breast density in postmenopausal women with mammographic density of 4 to 6 occupying >25% of the breast. In addition to assessing the effect of 1 year on therapy, repeated assessment will be done 1 year after terminating treatment. In the second National Cancer Institute of Canada protocol, EXCEL (National Cancer Institute of Canada Clinical Trials Group MAP.3), 5,100 women are randomized to exemestane for 5 years with or without celecoxib for 3 years versus placebo for each drug (Fig. 4). Eligibility requirements are as follows: a Gail score exceeding 1.66, age >60 years, or a diagnosis of prior breast pathology (ductal or lobular hyperplasia, lobular carcinoma in situ, or ductal carcinoma in situ treated by a mastectomy). The primary end point is to assess subsequent risk of breast cancer; secondary end points include emergence of ductal carcinoma in situ as well as other disease events.

CONCLUSIONS

Exemestane has produced promising results in the adjuvant setting. Theoretical assumptions, as well as the findings of the adjuvant phase III studies with the three different aromatase inhibitors/inactivators, suggest a potential role of exemestane in breast cancer prevention. The findings of only moderate bone loss and little effect on plasma lipid levels indicate the relative safety of the compound.

Yet, there are several important issues to be addressed at this stage. If prevention works, it is mandatory to assess not only short-term but long-term effects, addressing whether we may see just a delay or a long-term reduction in breast cancer risk. An important question is whether long-term effects may be achieved by treatment over a limited time (as seen with 5 years of adjuvant therapy) or require continuous treatment. In that respect, long-term adverse effects will be of critical importance.

Another important issue is to define risk populations for treatment. Breast cancer incidence is much higher in countries with a “western” lifestyle. Although there has been continuous debate regarding which lifestyle factors are responsible for breast cancer risk, recent findings of a strong association between body mass index and plasma estrogen levels, probably the most important risk variable in postmenopausal women, emphasize the importance of individual lifestyle to breast cancer risk (65).

OPEN DISCUSSION

Dr. Aman Buzdar: You don’t think that the suppression of HDL levels is significant?

Dr. Per Lønning: No. The reason why I don’t think so is that when you look at all the hormone replacement studies, you see exactly the opposite effect on the high density cholesterol, yet you don’t see a change in the risk of cardiovascular diseases. This is speculation on my side. The thing is, we don’t see any change in the other lipids, and we don’t see changes in coagulation factors. So, when all of these factors are added together, it is likely that they will not have a major influence of cardiovascular risk.

Dr. Buzdar: When you look at the data of the exemestane study after 2 to 3 years of tamoxifen, cardiovascular events were number 1. Not significantly but numerically, there were more in the exemestane arm.

Dr. Lønning: I agree with you, but the problem we are facing there is the same as with the issue of bone fractures. That is, as long as tamoxifen influences all of these parameters, it is difficult to do that type of comparison. That is the main reason why we designed this placebo-controlled study, because we
wanted to assess what was the effect of an aromatase inhibitor compared to placebo, and not compared to tamoxifen.

**Dr. Richard Santen:** My endocrinology colleagues emphasize the concept that it is bone quality and not bone quantity that is important. On this basis, if one starts an estrogen, one gets a reduction in fracture risk within 6 months and before there is any major change in bone density. So, I would emphasize the need to obtain careful fracture risk data in addition to your T-score and Z-score analysis, which may lag behind the changes that one might see in bone fractures.

**Dr. Lønning:** I completely agree with you that there is a need for long-term follow-up. A 2-year study like this one is, I would say, the most one can do with a placebo control. We will get more information also when we do the follow-up to see what is actually happening 1 year after terminating the drug. I fully agree with you that you need to be careful about extrapolating from 2 to 5 years. The problem is that all evidence we had previously was based on 12-week assessment of biomarkers.

**Dr. Stephen Johnston:** Your study was done with placebo; in cross-comparing to the nonsteroidal aromatase inhibitors, what they are doing to these biomarkers? In other words, where would exemestane sit if you did a randomized comparison versus anastrozole?

**Dr. Lønning:** All the evidence we have about nonsteroidal aromatase inhibitors is what Paul Goss has presented, first in San Antonio and now at ASCO. The take-home message is that when you look at the assessment of bone synthesis, there was clearly a difference between the exemestane and the two nonsteroidal inhibitors, but that study is ongoing.

**Dr. Johnston:** With ATAC, there has been some data presented on the bone parameters, but the comparison is with tamoxifen.

**Dr. Lønning:** In all the therapeutic trials, there will be a comparison to a third arm. That is important because you are addressing two therapeutic approaches. But if you are asking the scientific question, what does the aromatase inhibitor do, even in the MA.17, where it is against a placebo, the problem is that the patients have been exposed to tamoxifen before, and the hangover of tamoxifen will last for months. So, all of these are different settings. But we will get all of these data in due time.

**Dr. Carlos Arteaga:** Is there any reason to suspect that the preventive effect of AIs, or exemestane in this case, would be a function of the level of estradiol? In other words, the preventive effect might be easier to detect or detectable in those women who have a high estradiol level to begin with.

**Dr. Lønning:** When you look at the degree of estrogen suppression, all the third-generation aromatase inhibitors are so potent. They inhibit estrogen production by 98% or more in nearly all patients.

**Dr. Santen:** In the MORE trial, they divided people in five quintiles by plasma estrogen concentration. Those in the highest quintile had the greatest relative risk reduction of breast cancer—it was ~0.8—whereas in the individuals with the lowest estradiol levels, raloxifene did not seem to prevent breast cancer at all. So, the preexisting estrogen level, at least in that trial, tended to predict who was going to respond to breast cancer prevention.

**Dr. Lønning:** You could think that the higher estrogen levels you have, the more likely you are to develop clinical estrogen receptor–positive breast cancer. So, that would explain why you get the highest preventive effect if you have the highest estrogen levels.

**Dr. Arteaga:** That may not negate the possibility that you are also benefiting the other group but that it takes longer to see the effect. If you have an estrogen-primed preneoplastic that is well on its way toward becoming a full-blown clinical cancer, you may well be able to see a change in its natural history much sooner.

**Dr. Douglas Yee:** You probably can’t answer this with your data set, but I wonder if anybody can: Do you think that the fracture and bone density changes seen on aromatase inhibitors are equivalent in all racial groups? Most of the data were probably in Caucasians. I wonder if they have the same risk for Africans and Asians, because the natural history of osteoporosis is different in non-Caucasians.

**Dr. Lønning:** That is a good question but as long as we don’t have the data, it is difficult to speculate.

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