The Potential for Aromatase Inhibition in Breast Cancer Prevention

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Abstract

Although SERMs are currently being evaluated and are approved for breast cancer prevention in several countries, aromatase inhibitors and inactivators may represent interesting options in this setting. The encouraging results revealing these drugs to be superior to conventional therapy in metastatic breast cancer confirm their therapy efficacy and suggest that they may also have a role in adjuvant therapy and even for breast cancer prevention. Second, whereas the bulk of “high-risk” breast cancer patients with confirmed founder mutations in the BRCA1 or BRCA2 genes develop their cancers earlier in life (during the premenopausal period), 75–80% of all breast cancers, in general, develop in postmenopausal women. Thus, in considering prevention of breast cancer in moderate-risk groups, strategies for prevention in postmenopausal women may play an important role. Also, among high-risk patients who have not developed breast cancer by the time of the menopause, aromatase inhibition could be a feasible option. Considering the potential hazards of long-term use of SERMs, switching to an aromatase inhibitor or inactivator in this setting may be beneficial. Finally, the observation that postmenopausal estrogen levels are related to subsequent risk of breast cancer in the general population underlines the potential for estrogen suppression as a preventive strategy. Results from ongoing studies examining the toxicity of aromatase inhibitors and inactivators in postmenopausal women will set the stage for future trials that explore them as preventive treatment options.

Introduction

Breast cancer remains a major health threat to women, in particular in western countries. It represents the most frequently diagnosed form of cancer in most of these countries and the second leading cause of death from cancer. Although mammographic screening (1) as well as implementation of adjuvant treatment strategies (2, 3) have been shown to reduce breast cancer mortality, many patients will subsequently develop metastases for which no cure is currently available. Accordingly, there is a need for alternative strategies to limit the number of breast cancer deaths.

The problem of breast cancer prevention is complex. Whereas the role of estrogen effects in breast cancer development has been well documented (see section “Aromatase Inhibitors and Inactivators for Breast Cancer Prevention: Endocrine Rationale”), the diverse biology of breast cancer questions the hypothesis of a uniform etiology. In a recent study (4) that analyzed breast tumor samples with microarrays, some estrogen receptor-negative tumors were found to express genes associated with basal cells, which suggested a different origin and, probably, etiology of development, compared with the larger group of receptor-positive tumors expressing luminal cell genes.

In addition to plasma estrogen levels, the concentration of plasma IGF-1 (5) has been correlated to breast cancer risk in premenopausal women (5). Although IGF-I is a potent mitogen to breast cancer cells in vitro (6) and most breast cancers express the IGF type I receptor, (7), its role in breast cancer therapy is poorly understood (8). In addition, the only therapeutic strategy apart from tamoxifen and estrogens (9) known to suppress plasma levels of IGF-I is the use of somatostatin analogues, which, thus far, have never been proven to have antitumor effects in humans (10). Other potential approaches, such as the use of synthetic retinoids (11), will not be discussed in this article.

Although conflicting results have been obtained with regard to implementation of tamoxifen as a preventive strategy (12, 13), the encouraging results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study (14) and with raloxifene in the Multiple Outcomes of Raloxifene Evaluation (MORE) study of fracture prevention (15) both showing a reduction in breast cancer risk, suggest that breast cancer may be partly prevented by endocrine manipulation. This viewpoint is further supported by studies showing tamoxifen to prevent subsequent tumor development in patients with ductal carcinoma in situ (16) as well as the overview data revealing tamoxifen to prevent the development of contralateral breast cancers (3).

Notably, for the high-risk patients with confirmed BRCA1 and BRCA2 mutations, there is a need for early interventions...
Steroidal Inactivators

Exemestane

Formestane

Nonsteroidal Inhibitors

Aminoglutethimide

Letrozole

Androgen Substrate

Androstenedione

Fig. 1 Structural formulas for the third-generation aromatase inhibitors anastrozole and letrozole and the third-generation aromatase inactivator exemestane together with the first- and second-generation compounds aminoglutethimide and formestane.

Aromatase Inhibitors and Inactivators: State of the Art

After the beneficial results obtained with novel aromatase inhibitors and inactivators compared with regular second-line therapy like megestrol acetate and aminoglutethimide in metastatic breast cancer (28–32), anastrozole as well as letrozole and exemestane have all been compared with tamoxifen as first-line therapy in metastatic disease. For anastrozole, data from two large international trials have shown this drug to be at least as
good as tamoxifen in this setting (33, 34). More convincing results were obtained with letrozole, for which significant superiority compared with tamoxifen was revealed in a large international study enrolling more than 900 patients (35). Ongoing results from a study comparing exemestane to tamoxifen are encouraging (36), although more observations are required before final conclusions may be drawn.

On the basis of the results obtained in second-line and, later, first-line, metastatic therapy, all three of the drugs are currently being explored in the adjuvant setting. Thus, different protocols are exploring these drugs as monotherapy (5 years) compared with tamoxifen, as well as combined treatment, or in sequence with tamoxifen (Fig. 2, a and b). The last option is particularly attractive. Thus, the finding of a lack of cross-resistance between SERMs and aromatase inhibitors/inactivators in metastatic disease suggests that some patients in the process of developing resistance to tamoxifen during adjuvant therapy could benefit from the alternative treatment option. The results from these studies may provide a basis to design future studies on aromatase inhibitors and inactivators as preventive agents. In addition, they may suggest the optimal design (monotherapy? sequential treatment? combined treatment?) for such treatment strategies. If sequential therapy proves successful, an interesting option may be to switch premenopausal patients who are receiving a SERM for breast cancer prevention to an aromatase inhibitor at the time of menopause. In addition to improving therapeutic efficacy, this strategy may reduce potential toxic effects of the SERM (e.g., endometrial changes). Notably, even among women running a high risk of breast cancer, such as patients with inherited BRCA1/2 mutations, a significant number will develop their breast cancer in the postmenopausal age (37).

Aromatase Inhibitors and Inactivators for Breast Cancer Prevention: Endocrine Rationale

The important contribution of estrogens to breast cancer development is well recognized. Thus, early loss of ovarian function is associated with a reduced risk of later breast cancer of about 75% (38, 39). A number of prospective studies have addressed potential correlations between plasma estrogen levels and subsequent risk of breast cancer in postmenopausal women. The results from these studies (40–44) have revealed a surprisingly uniform picture. Although the hazard ratio varies from study to study (the number of observations provide quite large confidence intervals), it seems clear that total estrogen levels as well as the concentration of free estradiol are risk markers for subsequent development of breast cancer. Thus, comparing the highest with the lowest quartile for plasma estrogen levels, a hazard risk ratio between 2 and 5 for subsequent development of breast cancer has been revealed. As mentioned above, the novel third-generation drugs have shown clinical superiority compared with megestrol acetate, aminoglutethimide, and, to some extent, tamoxifen. Notably, although the antitumor mechanism of action of megestrol acetate is not known, this drug, similar to aminoglutethimide, suppresses plasma estrogen levels (45), albeit to a significantly smaller degree compared with the third-generation inhibitors/inactivators anastrozole, letrozole, and exemestane, which in general inhibit aromatase activity by a mean of 97–99% (Refs. 21, 46–48; Table 1). This finding supports the concept that the degree of estrogen deprivation is related to clinical outcome in metastatic breast cancer. Accordingly, based on the fact that the normal variation in plasma estradiol could influence the subsequent risk of breast cancer in postmenopausal women by a factor of 2 to 5, it is reasonable to postulate that profound estrogen suppression with these novel antiaromatase agents may be associated with a significantly reduced risk of breast cancer.

### Table 1: Aromatase inhibition with different aromatase inhibitors/inactivators administered to patients in different doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Percentage inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rgletimide</td>
<td>Inhibitor</td>
<td>51/64/74</td>
</tr>
<tr>
<td>Formestane oral</td>
<td>Inactivator</td>
<td>62/70/57</td>
</tr>
<tr>
<td>Fadrozole</td>
<td>Inhibitor</td>
<td>82/93</td>
</tr>
<tr>
<td>Formestane i.m.</td>
<td>Inactivator</td>
<td>85/92</td>
</tr>
<tr>
<td>AG</td>
<td>Inhibitor</td>
<td>91</td>
</tr>
<tr>
<td>Formestane + AG</td>
<td>Inactivator/Inhibitor</td>
<td>94</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Inhibitor</td>
<td>98.4/98.9/99.1</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Inhibitor</td>
<td>96.7/98.1/97.9</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Inactivator</td>
<td>97.9</td>
</tr>
</tbody>
</table>

*Results obtained from studies outlined in references 21, 46–48, and 52–56.

* AG, aminoglutethimide.

Aromatase Inhibitors and Inactivators in Breast Cancer Prevention: The Problem of Toxicity

As mentioned above, the effect of estrogen deprivation on cardiovascular risk parameters and bone density in postmenopausal women who are not suffering from advanced cancer is not known. Thus, to evaluate the effects of aromatase inhibitors/inactivators on these parameters is mandatory in considering these agents for adjuvant therapy in low-risk patient groups as well as in the preventive setting. Notably, such effects may not be adequately evaluated in the therapeutic trials comparing these drugs with tamoxifen, because tamoxifen, as well as other SERMs, is known to influence all of these parameters. Evaluation of such parameters over time in uncontrolled studies may
also be of limited value, given the expected alterations over time in relation to aging. In a previous study, we found aminoglutethimide to elevate plasma homocysteine levels (49) in patients with metastatic breast cancer. Notably, aminoglutethimide, in addition to being an aromatase inhibitor, has a number of other biochemical effects (50) that could underlie such alterations.

In an ongoing study (protocol OXE 027) conducted by the Norwegian Breast Cancer Group in collaboration with Pharmacia, cardiovascular risk parameters as well as bone markers and bone mineral density are being evaluated in low-risk breast cancer patients. Each patient is randomized to treatment with exemestane 25 mg versus placebo for 2 years in a double-blind fashion, followed by an additional 1 year of follow-up (Fig. 3). Patients eligible are those with estrogen and/or progesterone receptor-positive stage I tumors (for T2 tumors, grade 1 only), who are not offered standard adjuvant therapy according to the Norwegian Breast Cancer Group. In addition, patients surgically treated for ductal carcinoma in situ are eligible. Study participants must be postmenopausal as strictly defined, either by a complete absence of menstruation for the last 5 years, amenorrhea for 1 year with serum follicle-stimulating hormone in the postmenopausal range, or serum FSH levels in the postmenopausal range in patients who have undergone hysterectomy within 5 years of enrollment. The upper age-limit is 75 years. Notably, patients with a pretreatment bone density below 2 SDs from the mean value for age 65 are excluded. Lipid profile (cholesterol triglyceride, high-density lipoprotein, low-density lipoprotein, apoAl, and apoB), together with bone markers, the coagulation profile, bone mineral density, and plasma homocysteine with folate and vitamin B12 status are assessed at baseline and at regular intervals during the treatment period and for the 1-year posttreatment follow-up interval. In the first part of the trial, we experienced a slow recruitment rate. Careful survey of potentially eligible patients revealed the cause to be the stringent medical exclusion criteria with respect to blood lipids, body mass index, and blood pressure (total cholesterol, >7.8; total cholesterol:high-density lipoprotein ratio, >6.5; triglycerides, >4.6; body mass index, >30; blood pressure, >160/95), although the majority of eligible patients accepted the invitation to participate. After amendment of these criteria, recruitment has reached the goal of 144 patients (October 2001).

It should be emphasized that toxicity data obtained with a steroidal aromatase inactivator like exemestane may not be interpreted as representative for aromatase inhibitors of the nonsteroidal classes. Thus, the 17-hydro metabolite of exemestane has been shown to have slight androgenic side effects in vivo as determined by a drop in plasma levels of sex hormone-binding globulin (51). Whether such effects may be of relevance to its impact on bone and lipids in patients undergoing estrogen deprivation is currently not known.

Summary and Conclusions
Endocrine manipulation offers interesting prospects for future prevention of breast cancer. The exciting results obtained with aromatase inhibitors and inactivators in metastatic disease have revealed their potency as antitumor agents, and results from ongoing adjuvant studies will assess their role in early breast cancer. Most importantly, we will also learn the toxicity of estrogen deprivation in relation to risk factors for other endocrine-related orders such as cardiovascular diseases and osteoporosis. Hopefully, these results will create a basis for potential future evaluation of these agents in the preventive setting.

Open Discussion
Dr. Paul Goss: There’s an emerging thought that estrogen is related directly to breast cancer risk. With an aromatase inhibitor, you can dial the level down 20, 40, 60%, whatever you choose.

Dr. Lonning: If you can show that it’s safe to suppress the estrogens by 95%, why not? Why should we suppress it to 70% if we get exactly the same side effects by suppressing it by 95%?

Dr. Matthew Ellis: Some of the effects of estrogen deprivation may remain very subtle in the neurocognitive domain. I think there’s plenty of space for different strategies here, but it remains a hypothesis that to get your maximal effect you have to go to extremely low estrogen levels in the prevention setting.

Dr. Carlos Arteaga: You mentioned Cox-2 and I wonder what you think about the criticism that in chemoprevention strategies we start with tumor targets, i.e., retinoic acid receptors, Cox 2, etc., and we make the presumption that those targets are going to be present and functional in the preneoplastic and in the normal cell before transformation occurs. For estrogen, there’s no question because we know that’s important for the normal breast epithelial cell also.

Dr. Lonning: I fully agree with you, with therapy and prevention it’s not always that simple. I tried to illustrate that with the IGF story, which is really complicated. Because there you get a correlation, at least in premenopausal women, between the IGF levels and subsequent risk of breast cancer. But at the same time, thus far it’s very difficult to link alterations in IGF levels to a therapeutic outcome in the breast cancer.

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References


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