Commentary (Harvey): Nonsteroidal and Steroidal Aromatase Inhibitors in Breast Cancer

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Anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are members of the third generation of aromatase inhibitors that has now replaced aminoglutethimide (Cytadren), the progestins, and tamoxifen.

Hormone-dependent disease is an important and prevalent subtype of breast cancer. It is recognized by the presence of a functional estrogen-receptor apparatus, an indolent clinical course, a greater frequency in older women, and clinical responses to the sequential use of hormonal therapies. Antiestrogens, primarily tamoxifen (Nolvadex), have been the mainstay of hormonal therapy for metastatic disease, preinvasive disease, and as adjuvant treatment, and more recently, as chemoprevention. However, the aromatase inhibitors now provide an additional therapeutic approach for patients who remain candidates for hormonal therapy with disease progression in the face of antiestrogen therapy. The article by Hamilton and Volm presents a timely and succinct review of the biology of aromatase and the current status of aromatase inhibitors as treatment for breast cancer.

Biology of Aromatase

Aromatase is a cytochrome P-450-dependent enzyme system that catalyzes the conversion of androgens to estrogens in muscle and adipose tissue and is the major pathway of estrogen biosynthesis in postmenopausal women. Effective inhibitors of aromatase thus provide the potential for treatment of hormone-dependent breast cancer. Their mechanism of action is fundamentally different from that of antiestrogens. A drug such as tamoxifen may lead to an incomplete blockade of the estrogen receptor so that estrogen-mediated effects are still possible. Potent aromatase inhibitors, however, can reduce circulating estrogen levels to negligible amounts and almost completely prevent estrogen stimulation of cancer cell growth.

The authors also discuss the potential physiologic role of intratumoral aromatase. This source of estrogen could provide a mechanism for autocrine and paracrine growth stimulation.[1] The most potent of the third-generation aromatase inhibitors seem capable of inhibiting aromatase activity both in peripheral sites as well as decreasing the intratumoral synthesis of estrogens. This is a likely explanation of their greater clinical activity when compared with older agents. The authors describe exemestane (Aromasin) as a steroidal, irreversible inactivator of aromatase. However, they cite no evidence to support this mechanism of action or to indicate what clinical advantage this action might confer.

Clinical Trials of Third-Generation Aromatase Inhibitors

Until recently, megestrol acetate was considered the second-line hormonal treatment of choice following progression of disease on tamoxifen. The authors cite three large prospective, randomized clinical trials that independently compared anastrozole (Arimidex), letrozole (Femara), and exemestane with megestrol acetate and showed them to be of equal or greater efficacy when compared to the progestin. In each of these trials, the aromatase inhibitor was better tolerated. These data, therefore, provide clinicians with a better choice of second-line agents.[2]

The results from these studies also provide a rationale for directly comparing aromatase inhibitors with tamoxifen as first-line treatment in advanced disease. The authors summarized the results of three important, large clinical trials demonstrating that anastrozole was at least equal to tamoxifen, and that letrozole was superior to tamoxifen. Unfortunately, these trials were not restricted to patients known to have only estrogen- or progesterone-receptor-positive tumors. Nevertheless, these
two aromatase inhibitors have now successfully challenged tamoxifen as the gold standard of hormonal therapy in advanced breast cancer.

No data are yet available from various trials testing aromatase inhibitors as adjuvant therapy in breast cancer, although the large ATAC (Arimidex, Tamoxifen Alone and Combination) trial has now completed accrual of more than 9,000 patients. The authors adequately describe the design and rationale of other ongoing adjuvant therapy studies utilizing aromatase inhibitors.

**Frequently Asked Questions**

The article addresses several questions frequently asked by clinicians concerning the use of these new aromatase inhibitors. For example, the authors discuss the theoretical limitations of inhibiting aromatase in the ovary. In light of these limitations, the use of aromatase inhibitors to treat metastatic breast cancer in premenopausal patients should be limited to well-designed clinical trials.

The authors point out that combined hormonal therapy, although an attractive idea, has seldom led to any clinical advantage over the same agents used in sequential fashion for the treatment of metastatic breast cancer. This lack of enhanced effect could be explained by the possibility that these agents target the same subset of cells in the tumor, or perhaps they undergo some unfavorable pharmacokinetic interaction. As a pragmatic matter, patients with metastatic disease are probably best served by a longer duration of response when these agents are used in sequence. In the adjuvant setting, the issue of a combined-treatment arm was somewhat premature at the inception of the ATAC study, since there was no information available on the activity of the combination of anastrozole and tamoxifen in metastatic disease and little information on possible drug-drug interactions.

In discussing the lack of cross-resistance among aromatase inhibitors, the authors cite a study by Lonning et al, who reported further clinical responses to exemestane in patients with disease progression following treatment with aminoglutethimide (Cytadren) or anastrozole. It should be pointed out that this conclusion is based on a relatively small subset of patients from the original study population and that the objective response rate in this group only reached 7%. Larger, better-designed studies are needed before this question can be considered settled.[3]

**Unresolved Clinical Issues**

The authors allude to several unresolved issues concerning the clinical use of aromatase inhibitors. In the adjuvant and chemopreventive settings, for example, what would be their long-term effect on serum lipids and bone mineral density?

The article does not provide the clinician with a clear choice among the three approved drugs. Perhaps such a choice will not be obvious until the results of head-to-head comparisons among these agents are available. Nevertheless, it is clear that the greater potency of third-generation agents, compared with aminoglutethimide, has resulted in greater clinical efficacy. It seems likely that, in similar fashion, the more potent of the newer agents might also show clinical superiority. Currently, however, potency can only be determined by biochemical estimates of the degree of aromatase inhibition. The fact that letrozole causes 98% inhibition compared to 90% for anastrozole suggests, but by no means confirms, that it would be the more clinically effective agent.

The authors adduce a good rationale for future studies of aromatase inhibitors in the chemoprevention of breast cancer. Indeed, some clinical investigators have suggested that aromatase might be an oncogene. Furthermore, since aromatase inhibitors are devoid of estrogen activity, they are less likely than tamoxifen to induce endometrial carcinoma.

**Conclusions**

Because metastatic breast cancer is an incurable condition, effective and durable palliation with simple and nontoxic therapies should be the goal of treatment. The currently available aromatase inhibitors are well tolerated and easily administered, making them particularly well suited for older patients. These agents should now become first-line therapy for estrogen-receptor-positive
metastatic disease in postmenopausal women, relegating older drugs such as megestrol acetate and androgens to later therapy.

The place of newer selective estrogen-receptor modulators (SERMs) and the new class of estrogen-receptor downregulators will need to be established through carefully designed studies in patients with biologically indolent and estrogen-receptor-positive tumors. In the interim, aromatase inhibitors should be further studied in adjuvant, neoadjuvant, and chemopreventive approaches to breast cancer. However, tamoxifen and other SERMs should remain the current standard of care in the adjuvant treatment of estrogen-receptor-positive breast cancer, in the management of ductal carcinoma in situ, and as therapy to reduce breast cancer risk in women who would have met the criteria for inclusion in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 trial.

The article by Drs. Hamilton and VoM convincingly makes the case that the availability of the new generation of potent, safe, and effective aromatase inhibitors increases our therapeutic options in the management of hormone-responsive breast cancer.

**References:**


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