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Aromatase inhibitors in breast cancer: Current and evolving roles

ABSTRACT

The aromatase inhibitors are established first-line drugs for treating metastatic breast cancer in postmenopausal women, and are gaining acceptance as adjuvant treatment as well.

KEY POINTS

Aromatase inhibitors block conversion of androstenedione and testosterone to estrone and estradiol, the final step in estrogen synthesis.

In metastatic breast cancer, aromatase inhibitors have been proven to be as good as or better than tamoxifen.

New data in the adjuvant setting suggest that these agents will become important in the treatment of early breast cancer as well.

Available aromatase inhibitors are anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara).

Issues such as the optimal choice of agents, duration, sequencing, and their potential role in breast cancer prevention need further study.

This paper discusses treatments that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

AROMATASE INHIBITORS are finding new uses. Already approved for treating metastatic breast cancer in postmenopausal women, these estrogen-blocking drugs seem to be good alternatives to tamoxifen when used as adjuvant therapy (ie, after surgery) early in the course of the disease, and studies are testing their usefulness in preventing breast cancer in women at risk.

This review outlines the evolution of these drugs, their current clinical indications, pending studies, and unanswered questions about their utility.

2 MILLION WOMEN HAVE BREAST CANCER

Breast cancer is the most common malignant disease in women in the United States, with 205,000 new cases anticipated in 2002.[1] Considering that more than 2 million women are living with a current or previous diagnosis of breast cancer, their ongoing care remains a major public health issue not only for oncologists but also for primary care physicians and other specialists.

EARLY EFFORTS AT HORMONAL MANIPULATION

Like other types of cancer, breast cancer is treated with surgery, radiation, and chemotherapy—and also with hormonal manipulation.

Epidemiologic studies suggest that estrogens play an important role in initiating and promoting breast cancer.

Before menopause, most estrogen is produced in the ovaries, and as early as the 1890s, Beatson[2] observed that breast cancer

in premenopausal women sometimes regressed after bilateral oophorectomy.[2] Later, DeCourmellers[3] found that radiation therapy to the ovaries could have the same effect.[3] These observations indicated that estrogen deprivation could lead to regression of breast cancer.

After menopause, however, estrogen production by the ovaries becomes insignificant. Instead, estrogen is primarily produced in peripheral tissues, including adipose tissue, skin, and muscle. At these sites, androgens produced by the adrenal glands are converted to estrogens via a single enzyme, aromatase.[4]

Therefore, surgical or radiation ablation of the ovaries would not be effective for blocking estrogen in postmenopausal women. However, several decades ago, surgical adrenalectomy was shown to yield responses in patients with metastatic breast cancer.[5]

Targeting hormonal therapy to receptor-positive tumors

Early studies indicated that more than one third of cases of metastatic breast cancer would respond to hormonal manipulation. Why not more?

Tamoxifen has a dual action: estrogen agonist and antagonist

A key discovery was that the cancerous cells in many—but not all—cases of breast cancer have receptors for progesterone and estrogen. This discovery, and the development of sensitive assays to detect these receptors, have allowed clinicians to identify patients who are likely to benefit from hormonal manipulation.

Specifically, response rates with hormonal manipulation are much higher for women whose tumors have estrogen receptors, progesterone receptors, or both, ranging from 60% to 80% in previously untreated disease.[6]

Approximately 60% of premenopausal and 75% of postmenopausal patients have hormone receptor-positive tumors.[4]

We now have a range of hormonal therapies for breast cancer, including some drugs that block the effects of estrogens and others that inhibit estrogen production. Initially shown to be valuable in metastatic breast cancer, these agents were subsequently shown to be beneficial as adjuvants to surgery and, more recently, as preventive treatment.

Tamoxifen

In this country, tamoxifen has been the most widely used hormonal therapy for breast cancer.

Tamoxifen has a dual action: in some organs, such as the uterus and bones, it has agonist effects on estrogen receptors. Importantly for our purposes, however, it has antagonist effects on estrogen receptors in breast cancer cells, thus inhibiting the proliferative effect of estrogens.

Tamoxifen has proven clinical benefit:

- In women with receptor-positive metastatic breast cancer
- In the adjuvant treatment of receptor-positive tumors regardless of menopausal status, in which using tamoxifen for approximately 5 years reduces the annual odds of recurrence by 50% and the annual odds of death by 28%
- In preventing breast cancer in women at high risk, in whom using tamoxifen for 5 years reduces the risk by nearly 50%.[6]

Although many women with breast cancer benefit from tamoxifen treatment, newer approaches to hormonal manipulation could further improve the outcomes for all stages of breast cancer.

THE ROLE OF AROMATASE IN ESTROGEN SYNTHESIS

Estrogen, like other steroid hormones, is synthesized in a complex sequence of chemical transformations starting with cholesterol. The final step is the conversion of androstenedione and testosterone to estrone and estradiol by an enzyme called aromatase, a member of the cytochrome P450 class.[7]

This last step occurs in the ovaries of premenopausal women and in peripheral tissues—including breast adipose tissue—of postmenopausal women. Interestingly, while normal epithelial cells of breast ducts seem to lack aromatase, epithelial cells that have undergone malignant transformation express high levels of the enzyme.

Circulating levels of estrogen are quite low in postmenopausal women, but circulating levels do not tell the whole story. Breast cancer cells can also be stimulated by estrogen produced locally, either by nearby cells (paracrine influence) or by the cancer cells

themselves (autocrine influence).[4] Studies have documented that the more aromatase activity that breast cancer cells have, the greater their proliferative capacity,[8] suggesting that local aromatase activity and estrogen production are important in breast cancer.

Aromatase is a suitable and attractive target for breast cancer therapy, since it catalyzes the final step of estrogen synthesis. Any substance that could selectively inhibit aromatase without affecting the synthesis of other steroid hormones would be ideal for blocking the influence of estrogen in breast cancer cells.[9]

AMINOGLUTETHIMIDE, AN EARLY AROMATASE INHIBITOR

Knowing that surgical adrenalectomy is effective in treating metastatic breast cancer, researchers began to try to mimic this effect medically.

At first, they tried giving high doses of corticosteroids to cause adrenal atrophy. This treatment produced some responses, but the required doses often caused severe side effects.

Aminoglutethimide, originally developed as an anticonvulsant, was also noted to produce adrenal insufficiency and became the subject of breast cancer research.

Early phase 1 studies[5] proved that aminoglutethimide could produce responses in metastatic breast cancer. This agent was subsequently shown to powerfully inhibit steroid biosynthesis, but nonspecifically: it inhibits aromatase, but other enzymes as well.

Several studies[6] compared aminoglutethimide with tamoxifen in metastatic breast cancer. Response rates were at least as high with aminoglutethimide as with tamoxifen, but aminoglutethimide did not confer any significant benefit in survival, and its toxic effects, including addisonian crises, were more frequent and severe.

Despite the use of supplemental corticosteroids to alleviate some of the side effects of treatment, the toxicity of aminoglutethimide has generally limited its use to those whose cancer has progressed on tamoxifen and megestrol. However, the experience with this agent was key in understanding the potential of targeting the aromatase enzyme.

SELECTIVE AROMATASE INHIBITORS

Needed were agents that inhibit aromatase—and only aromatase. In theory, these would not cause the side effects associated with nonselective inhibitors such as aminoglutethimide, and, hopefully, could provide an effective treatment option.

P450 inhibitors

A group of azole compounds that reversibly inhibit fungal P450 enzymes also inhibit aromatase. Though these agents are intrinsically nonspecific and inhibit a variety of P450 subtypes, several have been developed that are highly specific for the aromatase P450 complex. This specificity should prevent any action against other P450 subtypes or interference with the synthesis of other steroid hormones.

Two such agents that are available as oral preparations are **anastrozole** (Arimidex) and **letrozole** (Femara).[9]

Androstenedione analogues

Other compounds have structural similarities to androstenedione, the major substrate of aromatase. These agents irreversibly bind to aromatase, inactivating it permanently. Owing to their structural homology with androstenedione, they are highly specific for aromatase and do not alter the production of other steroid hormones.[9]

Exemestane (Aromasin) is the first aromatase inhibitor in this class available in the United States. This drug, given orally, has been shown to suppress estrone and estradiol levels by up to 95%.[6] Owing to differences in mechanisms of action, exemestane may be effective in women in whom cancer has progressed on one of the reversible inhibitors, such as letrozole or anastrozole.

Exemestane binds irreversibly to aromatase, inactivating it permanently

TRIALS OF SELECTIVE INHIBITORS IN METASTATIC BREAST CANCER

Compared with aminoglutethimide

These new, more-selective inhibitors of aromatase quickly made aminoglutethimide obsolete for treating breast cancer. Several trials demonstrated their superiority over aminoglutethimide, consistent with the obser-

TABLE 1

Aromatase inhibitors vs megestrol in metastatic breast cancer after tamoxifen had failed

INVESTIGATORS	AGENT AND DAILY DOSE	SIGNIFICANT FINDINGS
Buzdar et al[11]	Anastrozole (Arimidex) 1 mg	Longer median survival
Dombernowsky et al[12]	Letrozole (Femara) 2.5 mg	Higher response rate and longer time to treatment failure
Bajetta et al[13]	Exemestane (Aromasin) 25 mg	Longer survival

vation that these agents are much more potent inhibitors of aromatase.

One such study[10] compared letrozole with aminoglutethimide in postmenopausal women with advanced breast cancer that was resistant to tamoxifen. Letrozole had a significantly higher response rate and was associated with an 8-month improvement in median survival.

Compared with megestrol

Selective aromatase inhibitors have proven to be effective in postmenopausal women with metastatic breast cancer that has progressed despite treatment with tamoxifen (TABLE 1).

Many consider aromatase inhibitors the agents of choice for metastatic breast cancer

Anastrozole,[11] letrozole,[12] and exemestane[13] have all been compared with megestrol in randomized trials in this setting. (Megestrol, a progestational agent, is used in advanced breast cancer after tamoxifen has failed.)

Anastrozole (1 mg daily) did not significantly differ from megestrol in the response rate, but the median survival time was significantly longer with anastrozole, 26.7 vs 22.5 months. Anastrozole was also associated with significantly less weight gain.[11]

Similarly, letrozole (2.5 mg daily) was superior to megestrol in its response rate, duration of response, and time to treatment failure. There was also a trend toward longer survival with letrozole, along with better quality of life and fewer thromboembolic complications.[12]

Exemestane (25 mg daily) was also shown to improve survival and quality of life when compared with megestrol in advanced disease.[13]

Compared with tamoxifen

More recently, aromatase inhibitors have established a role as a first-line treatment of hormone-sensitive, advanced breast cancer in postmenopausal women, ie, as an alternative to tamoxifen, the usual drug to be used first in this situation (TABLE 2).

A phase 3 randomized trial of letrozole vs tamoxifen in this setting showed the aromatase inhibitor to have a superior response rate, time to progression, and duration of response.[14]

An analysis of two trials of anastrozole vs tamoxifen, in more than 1,000 postmenopausal women with advanced breast cancer, found that women receiving either drug had an equivalent time to progression. However, a subgroup analysis showed that anastrozole provided a 4-month longer time to progression in patients who were estrogen receptor-positive, progesterone receptor-positive, or both. Anastrozole also caused fewer thromboembolic complications and less vaginal bleeding.[15]

In a smaller phase 2 trial,[16] exemestane was similarly superior to tamoxifen in terms of response rate and time to progression.

Currently, aromatase inhibitors constitute an established alternative to tamoxifen in first-line treatment of hormone-sensitive advanced breast cancer in postmenopausal women and are considered by many to be the agents of choice in this setting.

TRIALS OF AROMATASE INHIBITORS AS ADJUVANT THERAPY

With evidence that aromatase inhibitors might be superior to tamoxifen in metastatic breast cancer, the next logical situation in which to study these agents was the adjuvant (postoperative) treatment of early-stage disease, a setting in which tamoxifen has long

TABLE 2

Aromatase inhibitors vs tamoxifen in metastatic breast cancer

INVESTIGATORS	AGENT AND DAILY DOSE	SIGNIFICANT FINDINGS
Mouridsen et al[14]	Letrozole (Femara) 2.5 mg	Higher response rate Longer time to progression and time to treatment failure
Bonneterre et al[15]	Anastrozole (Arimidex) 1 mg	Longer time to progression in estrogen receptor-positive and progesterone receptor-positive patients
Paridaens et al[16]	Exemestane (Aromasin) 25 mg	Higher response rate Longer time to progression

been the standard of care in women with estrogen or progesterone receptor-positive tumors.

Several randomized trials are currently testing aromatase inhibitors alone, in combination with tamoxifen, or before or after tamoxifen.

The ATAC study: Anastrozole, tamoxifen, or both

Encouraging early data from a trial of anastrozole in the adjuvant setting were recently presented at professional meetings.

The ATAC (Arimidex, Tamoxifen, and the Combination) trial enrolled more than 9,000 patients who were randomized to receive 5 years of adjuvant therapy with either tamoxifen, anastrozole, or both drugs in combination. After a median follow-up of over 33 months, the single-agent anastrozole group showed a small but significant advantage in disease-free survival compared with the groups receiving either tamoxifen or the combination. The aromatase inhibitor also compared favorably with tamoxifen in terms of early toxicity end points, including lower rates of hot flashes, endometrial cancer, and thromboembolic events.[17]

Why isn't the combination superior to single-drug therapy, at least so far? One possible reason: earlier studies demonstrated that tamoxifen can reduce anastrozole levels by up to 30% when given simultaneously.[18] Another possible reason: tamoxifen may exert more estrogen agonist activity in the very low estrogen environment produced by the aromatase inhibitors.

Sequential therapy

Perhaps it would be better to give tamoxifen and then an aromatase inhibitor (or vice versa), a strategy called sequential therapy.

The Italian Cooperative Group[19] performed a trial in which postmenopausal breast cancer patients received adjuvant tamoxifen for 3 years and were then randomized to receive therapy for 2 additional years with either tamoxifen or aminoglutethimide. Overall survival was significantly longer in the aminoglutethimide group, even though more patients in that group had to stop therapy because they could not tolerate it. Though this study used aminoglutethimide, a drug now considered obsolete, it provided evidence that sequential treatment might be beneficial.

In a large international intergroup trial led by the **National Cancer Institute of Canada Clinical Trials Group,** patients will take tamoxifen for the standard 5 years and then will be randomized to take either letrozole or placebo for an additional 5 years.

The Breast International Group/ Femara-Tamoxifen (BIG/FEMTA) study is comparing four adjuvant hormonal regimens: 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, and 2 years of letrozole followed by 3 years of tamoxifen.[18]

Trials of exemestane are also underway. **The EXACT trial**, conducted by the International Cancer Collaboration Group, will compare 5 years of adjuvant tamoxifen vs 3 years of tamoxifen followed by 2 years of exemestane.

Anastrozole alone appears to be superior to anastrozole plus tamoxifen

Similarly, the **National Surgical Adjuvant Breast and Bowel Project B-33 trial** is examining the value of adding 2 years of exemestane therapy after 5 years of tamoxifen.

The use of sequential therapy with tamoxifen and anastrozole is being studied through a collaborative trial with **the Austrian Breast Cancer Study Group and the German Adjuvant Breast Cancer Group**.[18]

Together, these trials should provide important information about the sequential use of tamoxifen and selective aromatase inhibitors in the adjuvant setting.

Role as adjuvant therapy: Promising but preliminary

Although the initial findings of the ATAC trial are exciting, prolonged follow-up is needed to fully understand the significance of the results, potential long-term side effects of the aromatase inhibitors, and their ultimate impact on survival. Completion and continued follow-up of all these trials will provide important information about the optimal use of aromatase inhibitors in the adjuvant setting and how these drugs should be used in relation to tamoxifen.

Tamoxifen is still standard adjuvant therapy, says a recent expert panel

At the May 2002 meeting of the American Society of Clinical Oncology, an expert panel issued a consensus statement regarding the use of aromatase inhibitors in the adjuvant setting. The panel concluded that tamoxifen should still be considered standard adjuvant hormonal therapy for the majority of patients with hormone receptor-positive breast cancer. While aromatase inhibitors may be considered for use in patients who have a contraindication to tamoxifen, such as a prior thromboembolic event or cerebrovascular disease, recommendations for their widespread adjuvant use await longer follow-up of ongoing clinical trials.

FUTURE DIRECTIONS

Can aromatase inhibitors prevent breast cancer?

The role of aromatase inhibitors in preventing breast cancer is yet to be elucidated, but some early data show that studies are clearly warranted.

Tamoxifen, used as adjuvant therapy, reduces the risk of new contralateral breast cancers, but the recently reported ATAC trial found that anastrozole reduces the risk even more. In fact, in the early analysis of this study, the odds ratio of contralateral breast cancer in patients receiving anastrozole compared with tamoxifen was 0.42 (P = .0068).[17]

Long-term follow-up will clarify the significance of this observation, as will forthcoming randomized trials in the setting of primary prevention.

What are the risks of long-term use?

Another issue that must temper enthusiasm for aromatase inhibitors is the risks associated with long-term estrogen deprivation, which are not fully understood. As these drugs begin to be used in women who are expected to survive long-term, it will be important to understand their effects on such health concerns as bone density, lipid metabolism, and cognition.

The ATAC data showed clearly that anastrozole was associated with less vaginal bleeding and discharge, thromboembolic complications, and hot flashes than tamoxifen. However, the aromatase inhibitor was inferior to tamoxifen in terms of musculoskeletal events, including fractures.[17]

Several small studies evaluating the effects of aromatase inhibitors on bone and lipid metabolism have yielded conflicting results, with one human study associating letrozole with an increase in bone turnover but no effect on lipids.[20] Another study in rodents using the steroidal aromatase inhibitor exemestane actually showed a decrease in bone loss and a favorable effect on lipid profiles.[21] These issues should become clear with results of larger trials.

What is the optimal duration of treatment?

Another important question that needs to be addressed is the optimal duration of treatment with aromatase inhibitors in the adjuvant setting. This class of drugs will likely differ from tamoxifen in this respect.

Studies have shown that a 5-year course of tamoxifen is more effective than shorter durations, while tamoxifen given for more than 5 years is actually associated with decreased disease-free survival.[22] This phenomenon is thought to be related to tamox-

ifen's ability to act as both an estrogen agonist and antagonist. During the first 5 years of treatment, the antagonistic effect prevails. After this, either through up-regulation or supersensitization of the estrogen receptor, tamoxifen may become stimulatory. Tumor cells may also up-regulate the aromatase enzyme in the setting of prolonged estrogen blockade, thus providing themselves with increased autocrine stimulation.[18]

The lack of estrogenic activity of the aromatase inhibitors suggests that these drugs may be useful for longer periods of time and reinforces the rationale for using them in the adjuvant treatment of hormone receptor-positive breast cancer patients.

Are some aromatase inhibitors more effective than others?

Another unanswered question concerns the relative efficacy of the various available aromatase inhibitors. In a recent crossover study[23] in 12 postmenopausal women with metastatic breast cancer, letrozole suppressed aromatase activity and estrogen levels significantly more than anastrozole did. Further studies are needed to confirm this observation and determine its clinical significance.

The risks of long-term estrogen deprivation are not fully known

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