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AROMATASE INHIBITORS (AIs)

Aromatase is the enzyme that synthesizes estrogen from testosterone, which is synthesized from the adrenal hormone DHEA. Synthesis occurs in the ovaries, but also in many non-ovarian tissues. Breast cancer tumor cells may also contain local aromatase activity, which AIs appear to effectively block. Since estrogen + breast cancers require estrogen in order to grow, aromatase inhibitors are used to treat active breast cancer and to prevent breast cancer recurrences.

POST-MENOPAUSAL AND PRE-MENOPAUSAL SOURCES OF ESTROGEN.

In post-menopausal women, estrogen production from aromatase activity comes from a variety of non-ovarian tissues, including subcutaneous cells, fat, liver, muscle, brain, normal breast, and breast cancer cells, and a few regions within the brain. Estrogen is produced and acts locally via action of the aromatase enzyme in these tissues, but any circulating estrogen is the result of estrogen escaping local metabolism and spreading to the circulatory system. The activity of the enzyme is increased by alcohol, advanced age, obesity, insulin, and gonadotropins.

Aromatase inhibitors result in up to a 95% decrease in endogenous estrogen levels. Women who are on AIs should have their estrogen levels checked after 9 months of AI therapy, as a small percentage may experience increased estrogen levels even if their levels were decreased at 3 and 6 months.[1]

In premenopausal women, 95% of the estrogen comes from the ovaries. AIs generally are not used in premenopausal women, because when estrogen levels are lowered, the body compensates by increasing the ovarian production of estrogen. Studies are currently looking at the role of tamoxifen and AIs in women who are perimenopausal.

TYPES OF AROMATASE INHIBITORS

In the United States, there are currently three AIs available for clinical use: (*a*) anastrozole (Arimidex); (*b*) letrozole (Femara); and (*c*) exemestane (Aromasin).

There are 2 types of aromatase inhibitors (AIs) approved to treat breast cancer:[1]

- Irreversible steroidal inhibitors, such as exemestane (Aromasin), forms a permanent and deactivating bond with the aromatase enzyme. Exemestane has weak androgenic properties, and its use at higher doses has been associated with steroidal-like side effects such as weight gain and acne.

- Non-steroidal inhibitors, such as anastrozole (Arimidex) and letrozole (Femara), inhibit the synthesis of estrogen via reversible competition for the aromatase enzyme.

PREVENTION OF BREAST CANCER RECURRENCE

Overall, AIs have been shown to be more effective than tamoxifen in post-menopausal women with ER+ breast cancer in terms of better disease-free survival, reductions in the occurrence of early distant metastasis as well as improvement of overall survival.

For example, in a study of close to 10,000 patients, the 5 year recurrence rate was 9.6% for AIs and 12.6% for tamoxifen. There was also a non-significant decrease in mortality (4.8% vs. 5.9%). For 9,000 women who started with Tamoxifen, and then either stayed with tamoxifen or changed to AIs, there was a decreased recurrence (5.0% versus 8.1%%) and mortality rate (1.7% vs. 2.4%) with AIs three years after the therapies diverged (and 5-years after hormonal therapy was started). Neither age, nodal status, tumor grade, or progesterone status appeared to have any effect.

However, in it has been pointed out that in women with node negative disease with tumors less than 2 cm (pT1, pN0) there is no difference in either disease-free or overall survival at 5 years between tamoxifen and Femara.[2] Colleonia and Giobbie-Hurder suggest, "In the meanwhile, for patients at low risk of relapse or with co-morbidities that raise concern about the safety of AIs, adjuvant tamoxifen alone remains a reasonable alternative, and may be an economically viable option in many situations" (p.vii110).[2]

Effect of Body Mass Index: The effectiveness of AIs may also depend upon one's weight. Women who have a higher body mass index do not fare as well as thin women with Arimidex. However, thin women do not do as well as heavier women with Aromasin.[3]

Effect of vitamin D: According to one source[4]:

> Vitamin D influences aromatase activity (in which androgen is converted to estrogen in the body). A study presented at the June 2011 American Society of Clinical Oncology (ASCO) Meeting reported that high circulating vitamin D levels were associated with higher estrogen levels among aromatase inhibitor users (but not among women using tamoxifen or not using any anti-estrogen treatment). If replicated, this finding has implications for breast cancer survivors receiving aromatase inhibitors. In the mean time, we suggest that breast cancer survivors have their circulating vitamin D levels checked and use vitamin D supplementation only as required in combination with exposure to sunlight and consumption of vitamin D-rich foods to bring their levels to normal.

USE IN ADVANCED BREAST CANCER

In women with advanced breast cancer, estrogen can come from outside of the tumor or from within the tumor, or both. The actual percentage may vary among tumors. For some women, 80-90% of estrogen may come from within the tumor. In other women, it may all come from outside the tumor. Even patients whose tumors do not make estrogens may respond to AI therapy.

In one study of 713 women, there appeared to be somewhat better clinical benefit from Femara than from Arimidex, although time to progression, to treatment failure, and survival were similar. In patients with ER+ disease, the antitumor activity of the two drugs was similar, while in those with unknown ER status, the Femara had better objective response rates.

ADVERSE EFFECTS

Most studies have clearly shown that AIs are generally better tolerated than tamoxifen, and that the side effect profile is also different. AIs do not cause the endometrial proliferation that can be seen with tamoxifen. Also, AIs are less likely to cause blood clots (strokes, pulmonary embolism, and deep venous thrombosis).

HOT FLASHES

AIs are known to cause hot flashes in roughly 35% to 85% of women, but is considered to be less than tamoxifen. However, the differences between AIs and tamoxifen may not be that great. In one trial, 35.7% of women treated with Arimidex experienced hot flashes, versus 39.7% of women on tamoxifen. In another trial the rates were 32.8% for Femara versus 37.3% for tamoxifen. There was no difference in hot flash occurrence in patients taking Aromasin (exemestane) versus tamoxifen.

Natural treatment of hot flashes: While population studies suggest that black cohosh is not contraindicated with tamoxifen, similar studies with AIs don't yet exist. At this point, only one animal study exists using AIs and black cohosh, which suggests that no contraindication exists.[5] It's important to remember that black cohosh has not been found to have estrogenic activity.[6-7]

OSTEOPOROSIS

Women with breast cancer already have an increased risk of breast cancer, possibly due to premature menopause caused by chemotherapy. One study showed a 31% increased risk of fractures in women with breast cancer, and a 5-fold increased risk of vertebral compression fractures. AIs have been shown to increase fracture risk by 7.7% to 11%.

Before starting AI therapy, it is important to check your baseline bone mass, and then to follow-up every 1-2 years. According to Files, et al (2010):

> Regular follow-up assessment of bone density and awareness of and adherence to nonpharmacologic therapies, such as lifestyle changes, adequate calcium and vitamin D intake, physical activity, and fall prevention, should also be encouraged. Vitamin D levels should be measured routinely and optimized throughout the patient's lifetime (p. 562)

Eight risk factors for bone fractures have been identified in women with breast cancer: AI therapy, age over 65 years, thin (body mass index less than 20), family history of hip fracture, personal history of a fragility fracture after age 50, oral corticosteroid use over 6 months, and smoking.[8] Another issue is the use of SSRIs (a class of antidepressants), which may be prescribed to control hot flashes. SSRIs may exacerbate bone loss after menopause[9] and in a study of almost 8,000 people over 55 years old, increased fracture risk by as much as 2-fold, which increased further with prolonged use.[10]

MUSCULOSKELETAL

Muscle and joint pain and stiffness are among the most common side effects of AIs and occur in up to 60% of all patients.[11] Approximately 20% of patients will choose to discontinue AIs due to these effects. Low levels of vitamin D may make these problems worse, and indeed taking enough vitamin D to reach a minimum level of 40 ng/mL has been associated with decreased symptoms.[12] The most serious symptoms appear to occur in the first 6 months of therapy and may improve with continued use. Sometimes a switch to a different AI may help. Acupuncture may be helpful as well. One study showed that women who had 6 weeks of acupuncture had significant improvement in joint pain and stiffness.

HEART DISEASE & BLOOD CLOTS

Blood clots: All studies have shown a decrease in the risk of venous clots in women taking Arimidex and Femara versus tamoxifen.

Heart disease: There appears to be some cardioprotection with tamoxifen. Arimidex has no impact on plasma lipid levels, while Femara and Aromasin are considered to have unfavorable effects. Nevertheless, no significant difference in cardiovascular risk has been noted after 5 years of Femara versus tamoxifen.

UROGENITAL

As with menopause, the further reduction of circulating estrogen with AIs can exacerbate genitourinary symptoms, such as vaginal erosion. Vaginal lubricants can provide comfort and lubrication with intercourse (we like the all-natural "Good Clean Love" brand.)

Local Estrogen: Using local application of estrogen (such as an estrogen ring, creams, or suppositories) to help treat moderate to severe symptoms of genitourinary atrophy is becoming more accepted in clinical practice. Frequent urinary tract infections may also respond to increasing estrogen in vaginal tissues. Such treatments are controversial. One recent study showed that after systemic estrogen levels initially increased, they eventually decreased to post-menopausal levels after 12 weeks of therapy in 6 out of the 7 women studied. Nevertheless, these authors concluded that women on AIs should not use local estrogen therapy. In another small study, the risk of breast cancer recurrence did not increase with vaginal estrogen therapy.

Clearly, the decision to use localized estrogen therapy needs to be carefully considered and the pros and cons discussed with your medical team. There are no long term studies on using localized therapy and breast cancer recurrence. According to Files et al., smaller, consistent doses may be more desirable than intermittent use because the healing of the tissues may actually allow less estrogen to be systemically absorbed.

Local DHEA and Testosterone: While the use of local estrogens may be questionable, local application of either testosterone or DHEA appears to be a promising treatment for vaginal erosion. In one very small early trial, 4 weeks of topical intra-vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to AI therapy without increasing estradiol or testosterone levels.[13] The use of intra-vaginal DHEA may also be

beneficial, as it has been effective for vaginal erosion in women without breast cancer.[14] More and longer studies are needed for both of these options.

COGNITIVE FUNCTION

Studies in this area are conflicting, some showing worse cognitive function with tamoxifen versus Arimidex, and others showing the opposite. At this point, more studies are needed to clarify this issue.

FOODS THAT ENHANCE THE EFFECTIVENESS OF AROMATASE INHIBITORS[4]

The following foods (or major bioactive components) have been found to inhibit aromatase or to enhance the effectiveness of aromatase inhibitors and are recommended during treatment:

Arugula
Black tea
Blueberries
Broccoli
Brussels sprouts
Cabbage
Cauliflower
Celery
Cherries, sour
Collard greens
Cranberries
Grapes, red
Grape juice, purple (limit quantities, as the sugar can increase insulin levels)
Horseradish
Kale
Kefir
Mushrooms, white button
Mustard
Mustard greens
Peas
Pomegranate juice (limit quantities, as the sugar can increase insulin levels)
Tomatoes
Watercress

TO SOY OR NOT TO SOY

While large scale population studies make it fairly clear that soy products work synergistically with tamoxifen to reduce breast cancer recurrence, this may not be true of soy and AIs. While soy isoflavones, such as genistein, act in a similar manner to tamoxifen (possibly augmenting the effect), soy does not act the same as AIs, which reduce estrogen levels in a variety of tissues and the circulation. One study in cell culture model has suggested that genistein may actually increase the risk of breast cancer recurrence when used with AIs.[15] However, cell culture results may not reflect real world effects. For example, soy products were thought to increase breast cancer risk because of cell culture results, when in fact, population studies indicate a decrease in breast cancer risk. One thing to remember is that genistein from soy and certain other phytoestrogens tend to stimulate ERbeta receptors over ERalpha receptors, with breast cancer cells expressing ERalpha (versus beta) receptors. Clearly more research is needed. In the meantime, one should not overdo soy products, but it is not clear that one should totally avoid them, either.

Drugs That Induce CYP 3A4

In a pharmacokinetic interaction study of 10 healthy postmenopausal volunteers pretreated with potent CYP 3A4 inducer rifampicin 600 mg daily for 14 days followed by a single dose of

exemestane 25 mg, the mean plasma Cmax and AUC 0–∞ of exemestane were decreased by 41% and 54%, respectively.
Significant pharmacokinetic interactions mediated by inhibition of CYP isoenzymes therefore appear unlikely. Co-medications that induce CYP 3A4 (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's wort) may significantly decrease exposure to exemestane. Dose modification is recommended for patients who are also receiving a potent CYP 3A4 inducer [see **DOSAGE AND ADMINISTRATION**].

Recommended Dose
The recommended dose of AROMASIN in early and advanced breast cancer is one 25 mg tablet once daily after a meal.

- adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy.
- the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

Dose Modifications
For patients receiving AROMASIN with a potent CYP 3A4 inducer such as rifampicin or phenytoin, the recommended dose of AROMASIN is 50 mg once daily after a meal.

Pharmacodynamics
Effect on Estrogens
Multiple doses of exemestane ranging from 0.5 to 600 mg/day were administered to postmenopausal women with advanced breast cancer. Plasma estrogen (estradiol, estrone, and estrone sulfate) suppression was seen starting at a 5-mg daily dose of exemestane, with a maximum suppression of at least 85% to 95% achieved at a 25-mg dose. Exemestane 25 mg daily reduced whole body aromatization (as measured by injecting radiolabeled androstenedione) by 98% in postmenopausal women with breast cancer. After a single dose of exemestane 25 mg, the maximal suppression of circulating estrogens occurred 2 to 3 days after dosing and persisted for 4 to 5 days.
Effect on Corticosteroids
In multiple-dose trials of doses up to 200 mg daily, exemestane selectivity was assessed by examining its effect on adrenal steroids. Exemestane did not affect cortisol or aldosterone secretion at baseline or in response to ACTH at any dose. Thus, no glucocorticoid or mineralocorticoid replacement therapy is necessary with exemestane treatment.
Other Endocrine Effects
Exemestane does not bind significantly to steroidal receptors, except for a slight affinity for the androgen receptor (0.28% relative to dihydrotestosterone). The binding affinity of its 17-dihydrometabolite for the androgen receptor, however, is 100-times that of the parent compound. Daily doses of exemestane up to 25 mg had no significant effect on circulating levels of androstenedione, dehydroepiandrosterone sulfate, or 17-hydroxyprogesterone, and were associated with small decreases in circulating levels of testosterone. Increases in testosterone and androstenedione levels have been observed at daily doses of 200 mg or more. A dose-dependent decrease in sex hormone binding globulin (SHBG) has been observed with daily exemestane doses of 2.5 mg or higher. Slight, nondose-dependent increases in serum luteinizing hormone

(LH) and follicle-stimulating hormone (FSH) levels have been observed even at low doses as a consequence of feedback at the pituitary level. Exemestane 25 mg daily had no significant effect on thyroid function [free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH)].

Coagulation and Lipid Effects

In study 027 of postmenopausal women with early breast cancer treated with exemestane (N=73) or placebo (N=73), there was no change in the coagulation parameters activated partial thromboplastin time [APTT], prothrombin time [PT] and fibrinogen. Plasma HDL cholesterol was decreased 6–9% in exemestane treated patients; total cholesterol, LDL cholesterol, triglycerides, apolipoprotein-A1, apolipoprotein-B, and lipoprotein-a were unchanged. An 18% increase in homocysteine levels was also observed in exemestane treated patients compared with a 12% increase seen with placebo.

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