

Precautions for Patients Taking Aromatase Inhibitors

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Abstract

Aromatase inhibitors are the drug of choice for the treatment of estrogen receptor- or progesterone receptor-positive breast cancer in postmenopausal women. Aromatase is an enzyme that catalyzes the final and rate-limiting step in the biosynthesis of estrogen. Inhibitors of this enzyme are an effective therapy for breast cancer. The benefits of these agents have been clearly shown through various clinical trials, yet adherence may be challenging for some patients due to issues of drug interactions, proper first dose education, and adverse effects. Education to prevent and treat adverse effects is of the utmost importance to promote adherence.

Aromatase inhibitors (AIs) are now U.S. Food & Drug Administration approved and have been shown to be more effective than the antiestrogen drug tamoxifen in the postmenopausal population. There are three medications that are second-generation AIs, including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). Estrogens are known to be important in the growth of breast cancers in both pre- and postmenopausal women. Although estrogens are no longer made in the ovaries after menopause, the body continues to make estrogen from other sources that could stimulate tumor growth. The clinical outcomes continue to improve in

breast cancer treatment. Educating patients and providers will increase patient compliance and ultimately patient response.

RESEARCH

A significant amount of research has gone into determining whether there are benefits for breast cancer patients who receive AIs compared with the previous standard of care, tamoxifen. Tamoxifen, a selective estrogen receptor modulator (SERM) with antiestrogenic activity in the breast tissue, was the previous standard of care for both pre- and postmenopausal, estrogen receptor-positive breast cancer patients. However, the drug's efficacy was limited by the rate of breast

cancer recurrence. Aromatase inhibitor research has demonstrated improved survival in postmenopausal women, postmenopausal women with metastasis, and premenopausal women under the age of 35 with ovarian ablation. Aromatase inhibitors are also effective in the preventative setting.

The following review of research has demonstrated significantly prolonged disease-free survival, time to recurrence, and reduced distant metastases and contralateral breast cancers by 40% with the use of AIs. Early studies such as “Arimidex, Tamoxifen, Alone or in Combination (ATAC)”, “A Comparison of Letrozole and Tamoxifen in Postmenopausal Women With Early Breast Cancer (BIG 1-98)”, and “Adjuvant Tamoxifen and Exemestane in Early Breast Cancer (TEAM)” have shown a reduction in the recurrence of breast cancer in the postmenopausal population (Breast International Group [BIG] 1-98 Collaborative Group, 2005; Derks et al., 2017; Howell et al., 2005). In the extended adjuvant setting (therapy for 5–10 years), the MA.17 study showed that in the group that continued letrozole, there was a statistically significant reduction in recurrence, particularly in the node-positive population (Burstein et al., 2018; Goss et al., 2016). Premenopausal women under the age of 35 also have a reduction in recurrence with the use of AIs and ovarian ablation as reflected in the subset analysis of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT; Francis et al., 2018).

Women with metastatic breast cancer continue to experience improved progression-free survival with nonsteroidal AIs (anastrozole or letrozole) alone or in combination with various drugs such as CDK4/6 or mTOR inhibitors as reported in the MONALESSA, PALOMA, and MONARCH trials (Cristofanilli et al., 2016; Johnston et al., 2019; Slamon et al., 2018). Additionally, the ExCel and IBIS-II trials reported that exemestane and anastrozole (respectively), significantly reduce invasive breast cancer in postmenopausal women who are at moderately increased risk for a new breast cancer (Cuzick et al., 2014). As the population of breast cancer survivors continues to grow, attention to supporting patients is paramount to providers’ practice.

PATIENT COMPLIANCE

The effectiveness of AIs is well documented, but they are not without concerns. There are safety and efficacy issues when taking AIs. Patient education reduces complications and improves AIs effectiveness, resulting in improved long-term survival. The patient teaching sheet, “Precautions for Patients Taking Aromatase Inhibitors” (see Appendix A), serves as a reference for patients and providers on which medications and supplements to avoid while taking AIs.

Patient education is imperative for medication adherence and the improvement of long-term survival. Adherence rates of 55% to 88% have been reported in year 1 and a drop to 62% to 79% in year 3 (Atkins & Fallowfield, 2006; Partridge et al., 2008). Meeting with oncology providers, including advanced practitioners (nurse practitioners, physician assistants, and clinical pharmacists) on a regular basis promotes patient adherence, addresses patient concerns, educates patients on new research reports, and supports healthy behaviors. Clinical pharmacists spend more time than ever in direct patient contact. They reinforce treatment goals, address compliance, medication interactions, possible adverse effects, and ensure safe and effective use of medications. Literature surrounding positive outcomes associated with pharmacist-driven oral chemotherapy programs continues to grow (Quinones et al., 2016).

ADVERSE EFFECTS

While AIs are generally well tolerated, side effects may limit adherence in a number of women. Education to prevent and treat adverse effects is of the utmost importance to promote adherence.

The three most commonly encountered adverse effects are joint pain, bone loss, and vaginal symptoms. Additional adverse effects include flushing or hot flashes, edema, headaches, fatigue, and night sweats. Most of these side effects are reduced with acupuncture (Hershman et al., 2018) or manageable through multiple methods.

Arthralgias

The prevalence of AI-associated arthralgias ranges between 20% and 70% in studies (Niravath, 2013; Younus & Kligman, 2010). Correction of low vitamin D may improve musculoskeletal symptoms in

women with breast cancer (Khan et al., 2017; Singer et al., 2014). The actual cause of AI-related joint symptoms is not well understood. Two common theories of AI-related joint symptoms include that a drop in estrogen decreases the pain threshold in the brain or leads to cytokine release causing bone loss and pain (Coleman et al., 2008).

The proposed management of these symptoms includes weight loss and exercise. Weight loss causes less stress on the musculoskeletal system. An additional significant benefit of weight loss is the reduction of adipose tissue, one of the extragonadal organs that is a major source of estrogen (other sites include adrenal glands, brain, skin, and pancreas; Barakat, Oakley, Kim, Jin, & Ko, 2016). After these steps have been exhausted, the patient should be referred for acupuncture, which may be effective in managing AI-induced arthralgias (Bae et al., 2015). If these steps are not successful, there are several pharmacologic interventions, including the use of glucosamine/chondroitin (Greenlee et al., 2013), acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs; Younus & Kligman, 2010).

Bone Loss

Bone health is an important educational topic for patients. Women on AIs experience a two- to four-fold increase in bone loss compared to the normal rate associated with menopause, and as a result, they are at a heightened risk for fractures (Muslimani et al., 2009). All patients initiating AI treatment should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess osteoporosis and then have scans repeated every 2 years. Patients should be encouraged to implement a 150-minute exercise program, including a twice weekly core-strengthening program as recommended by the American Society of Clinical Oncology and the National Comprehensive Cancer Network (ASCO, 2018, NCCN, 2019). It is also recommended that women begin taking calcium supplements at 1,200 mg and vitamin D supplements at 1,000 IU every day (see age-specific recommendations per the Centers for Disease Control and Prevention).

Vaginal Symptoms

Aromatase inhibitors block peripheral estrogen production, which impacts vaginal symptoms and

sexual dysfunction. Women should be counseled on methods that may help alleviate these symptoms. For example, the use of vaginal lubricants, moisturizers, and vaginal massage with coconut oil are some examples of treatments that may benefit women who experience vaginal dryness or pain (Lee et al., 2011). A referral to a pelvic physical therapist can be valuable and complement symptom management. Dyspareunia may impact patients' quality of life. If the above are not effective, low-dose vaginal estrogen is currently recommended. Recent practice recommendations deem low-dose vaginal estrogen as safe to use (American College of Obstetricians and Gynecologists, 2018; Melisko et al., 2017). If the above recommendations are not effective, a vaginal dilator may ease dyspareunia. A reputable website, www.vaginismus.com, may offer additional vaginal symptom relief options.

Other Adverse Effects

Aromatase inhibitors are also associated with a potential for a higher risk of cardiovascular disease, as evidenced by hypercholesterolemia. Patients taking anastrozole or exemestane should have their blood pressure (BP) monitored closely. If there is an elevation, the AI should be held and the BP level checked at regular intervals, and if the BP returns to normal, the patient should be switched to letrozole. Patients taking letrozole may benefit from periodic lipid panel assessments, and if there is an elevated cholesterol, providers should consider switching to anastrozole or exemestane.

Side effects that impact quality of life may require an AI drug holiday for 2 weeks and switching to another AI. For example, letrozole may cause hair thinning that may be reversed when switched to anastrozole or exemestane. Additionally, mood alterations may be significant. Holding the AI for 2 weeks with the resolution of a bothersome side effect is an indication of the need to switch to another AI. The half-life of anastrozole is 50 hours, letrozole 48 hours, and exemestane 24 hours. In our practice, patients have been known to try all three AIs and start back on the original AI without side effects. Management of side effects requires providers' thorough assessment, establishing trust, and follow-up so that patients will be invested in their medication management.

INTERACTIONS

Many patients are on medications that may interfere with the effectiveness of AIs. For the estrogen receptor–positive breast cancer patient who will be starting nonsteroidal AI therapy such as anastrozole or letrozole, the list of major interactions is short and largely manageable by monitoring. One of the interactions that can be seen in this population is the concurrent use of methadone for chronic pain control. CYP19, an aromatase enzyme, theoretically plays a role in the metabolism of methadone. The inhibition of this enzyme by AI therapy leads to increased levels of methadone in the body, increasing the risk of potential serious side effects such as respiratory depression and QTc prolongation (Lu, Thong, & Flockhart, 2012; see Appendix A).

Exemestane is a steroidal AI with drug interactions that health-care providers should consider. Exemestane is extensively metabolized by CYP3A4, one of the major enzymes responsible for the metabolism of medications in our body. Any drug that induces the activity of CYP3A4 will decrease levels of exemestane in the body, and the patient could potentially lose some of the clinical benefit of the drug. Conversely, any medication that inhibits CYP3A4 will prevent the metabolism of exemestane, increasing serum concentrations, which may lead to increased side effects. Patients and providers should be aware of any estrogen-containing products the patient is taking. These products should be avoided while on hormone deprivation therapy, as they could potentially counteract the benefits from AIs.

Some herbal products contain compounds known as phytoestrogens, which have various degrees of estrogen activity, while other herbal products could help stimulate estrogen production (Zava, Dollbaum, & Blen, 1998). The use of some supplements can counteract the effectiveness of AIs. Some of the more problematic supplements are commonly found in over-the-counter herbal preparations marketed to help with signs and symptoms of menopause in women. Patients should also be instructed to read labels before taking high-protein exercise drinks that may contain Whey protein, which is a phytoestrogen (see Appendix A).

EDUCATION

Patient education provides patients with the necessary tools to guide their AI management. Medication management is challenging for patients who don't have the pharmacologic knowledge to understand drug interactions. Integrating a team-based approach to patient education including clinical pharmacists and nursing staff give patients the optimal information and tools for informed decision-making. Reinforcing verbal education with a resource such as the "Precautions for Patients Taking Aromatase Inhibitors" handout provides a quick reference for patients and staff. ●

Disclosure

The authors have no conflicts of interest to disclose.

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Appendix A. Precautions for Patients Taking Aromatase Inhibitors

Aromatase inhibitors are the gold standard medication for postmenopausal women with breast cancer. Daily use of an AI has been shown to improve survival and reduce the risk of a second invasive breast cancer by 40%.

Medications to Avoid or Use With Caution While Taking Anastrozole or Letrozole

Estrogen derivatives, such as estradiol, should be avoided while taking letrozole or anastrozole because they may reduce the effectiveness of letrozole or anastrozole and provide less protection against breast cancer.

Other medications should be used with caution while taking letrozole or anastrozole because of a higher risk of side effects caused by using an AI with one of the below medications:

- Antiseizure medications such as aripiprazole (Abilify) and pimozide (Orap)
- Heart medications such as dofetilide (Tikosyn)
- Pain medications such as hydrocodone (Vicodin) or methadone (Dolophine)

Medications to Avoid or Use With Caution While Taking Exemestane

Certain medications should be avoided or used with caution while taking exemestane because they lower the effectiveness of exemestane and provide less protection against breast cancer.

- Estrogen derivatives such as estradiol
- Anti-infective medications such as efavirenz (Sustiva), nevirapine (Viramune), rifampin (Rimactane), and rifabutin (Mycobutin)
- Antidepressants such as St John’s wort
- Antiseizure medications such as carbamazepine (Tegretol), phenobarbital, and phenytoin (Dilantin)

Other medications should be used with caution while taking exemestane because of a higher risk of side effects caused by using an AI with one of the below medications:

- Diabetes medications such as saxagliptin (Onglyza)
- Pain medications such as hydrocodone (Vicodin) and methadone (Dolophine)

Supplements

Some herbs, supplements, and other products can be dangerous if taken during your cancer treatment, or with other medicines and supplements. Talk with your doctor or health-care team if you are taking any of the products. The products listed below may cause problems with breast cancer or breast cancer treatment when taken in high doses such as in supplement form. These products are not normally harmful if they are found in the food that you eat as part of your regular diet.

Always tell your doctor or health-care team all the medications, herbs, supplements, vitamins, and minerals that you are taking.

Aletris	Alfalfa	Androstenediol
Androstenedione	Anise	Black/Blue cohosh
Chasteberry	Deer velvet	Diindolylmethane (DIM)
Dong quai	Fennel	Flaxseed
Ginseng	Guggul	Isoflavones/plant estrogens
Hu zhang	Kudzu	Licorice (plant)
Maca	Milk thistle	Noni juice
Panax ginseng	Red clover	Red raspberry leaf
Resveratrol	Saw palmetto	Scarlet Pimpernel
Star anise	Wild yam	Valerian

Note. AI = aromatase inhibitor. Generic drug names and common trade names listed only. Please consult your health-care provider for more information. Reprint permission granted. © 2020 Mary Heery, Stephen Farley, Rhett Sparkman, John Healy, William Eighmy, George Zahrah, and Richard Zelkowitz.