REVIEWS

The Expanding Use of Third-Generation Aromatase Inhibitors: What the General Internist Needs to Know

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BACKGROUND: Breast cancer patients represent the largest group of adult cancer survivors in the US. Most breast cancers in women 50 years of age and older are hormone receptor positive. Third generation aromatase inhibitors (AIs) are the newest class of drugs used in treating hormone responsive breast cancer. It is often during start of adjuvant hormone therapy that the breast cancer patient establishes (or reestablishes) close follow-up with their general internist.

OBJECTIVE: Given the large numbers of breast cancer patients in the US and the increasing use of third generation AI's, general internists will need to have a clear understanding of these drugs including their benefits and potential harms. Currently there are three third generation aromatase inhibitors FDA approved for use in the US. All have been shown to be superior to tamoxifen in disease free survival (DFS) in the treatment of both metastatic and early breast cancers.

RESULTS: While the data on side effects is limited, AI (compared to tamoxifen) may result in higher rates of osteoporosis and fractures, more arthralgias, and increased vaginal dryness and dysparuenia. Limited information on their effects on the cardiovascular system and neuro-cognitive function are also available. Patient's receiving adjuvant hormone therapy are generally considered disease free or disease stable and require less intensive monitoring by their breast cancer specialist.

CONCLUSIONS: In situations where patients experience significant negative side effects from AI therapy, discussions to discontinue treatment (and switch to an alternative endocrine therapy) should involve the cancer specialist and take into consideration the patient's risk for breast cancer recurrence and the impact of therapy on their quality of life. In some cases, patients may choose to never initiate AI treatment. In other cases, patients may choose to prematurely discontinue therapy even if therapy is well tolerated. In both settings increased knowledge by the general internists will likely facilitate discussions of risks versus benefits of therapy and possibly improve compliance to adjuvant hormone therapy.

KEY WORDS: breast cancer; aromatase inhibitors; adjuvant hormone therapy.
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INTRODUCTION

An estimated 60% to 75% of breast cancers in women over 50 years of age in the United States are hormone responsive.[1] Breast cancers are considered hormone responsive if there is expression of either estrogen receptors, progesterone receptors, or both.[2] For decades, tamoxifen therapy for 5 years has been considered first-line treatment for hormone responsive breast cancer. However, an estimated 30% of hormone responsive breast cancers are initially resistant to tamoxifen and a further 40% will develop eventual resistance.[3–5] Alternative hormone therapies used to treat tamoxifen-resistant breast cancer have included fulvestrant (a pure estrogen antagonist that downregulates estrogen receptors), megesterol acetate (that interferes with progesterone receptors), and aromatase inhibitors (AIs). Large clinical trials have found AIs to be superior to tamoxifen both in disease-free survival (DFS) and adverse side effects.[6–8] The observation of lower rates of contralateral breast cancers suggests a potential role in chemoprevention and studies are currently underway.[9] This paper focuses on third-generation AIs including benefits and potential harms, especially as they relate to care of breast cancer survivors by general internists.

BACKGROUND

AIs inhibit the cytochrome P450 enzyme aromatase, responsible for the peripheral conversion of androgens to estrogens. In postmenopausal women, this peripheral conversion is the major source of estrogen. Aromatase activity is highest in breast tissue with hormone-responsive breast cancer, although it is also found in adipose tissue, muscle, bone, brain, and skin. Three generations of AIs have been developed. The first- (aminoglutethimide) and second-generation AIs (e.g., fadrozole and vorozole) were less selective and decreased aldosterone and cortisol production in addition to aromatase. Both were poorly tolerated and had limited clinical efficacy.[5] Third-generation AIs are highly selective for the enzyme aromatase and are fairly well

tolerated. Currently, three third-generation AIs are approved for use in the United States. Both anastrozole (Arimedex®) and letrozole (Femara®) are nonsteroidal inhibitors that reversibly bind aromatase. Exemestane (Aromasin®) is a steroidal AI that irreversibly binds aromatase. All AIs reduce systemic estrogen levels by as much as 98%.[10] A 2007 Cochrane review of 25 studies comparing AIs to other endocrine therapies in the treatment of metastatic breast cancer showed a significant survival benefit of AIs (HR = 0.89; 95% CI, 0.82–0.96).[11] Although there does not appear to be a benefit in combining tamoxifen with AIs, studies of AIs given before, after, or in place of tamoxifen for the treatment of early-stage breast cancer found AIs to be superior to tamoxifen monotherapy in DFS (Table 1).[6–8,12–15] Consequently, current guidelines recommend the use of AIs at some time during treatment of hormone-responsive postmenopausal breast cancer. Head-to-head AI trials are ongoing and should provide information on clinical efficacy among the different third-generation AIs. The optimal duration of therapy with an AI remains to be determined. Although studies have shown the use of tamoxifen beyond 5 years increases harm, the National Cancer Institute of Canada Clinical Trial MA.17 (MA.17) of letrozole use for 5 years after 5 years of tamoxifen use suggests increasing clinical efficacy of AIs with increasing duration.[14,16] Future recommendations may prolong adjuvant hormone therapy beyond 10 years.

BONE HEALTH: THE IMPACT OF BREAST CANCER AND AI THERAPY

Patients with breast cancer have higher rates of osteoporosis and fractures. In the Women's Health Initiative Observational Study (WHIOS) cohort, women with breast cancer had a 31% increased risk of fractures compared to women without breast cancer, even after adjustment for other known risk factors.[17] In another study, women with breast cancer and no bone metastases were found to have a nearly 5-fold increased risk of vertebral fractures compared with healthy age-matched controls.[18] The mechanism for this increased fracture risk may be due to premature menopause induced by breast cancer therapy and/or the direct toxic effects of the cancer therapies on bone.[19] Whereas tamoxifen in postmenopausal women is protective, all three third-generation AIs negatively affect bone health.[20–22] Furthermore, an estimated 50% of patients with breast cancer have considerable bone loss before initiation of therapy with an AI.[23] AIs suppress both systemic estrogen levels as well as aromatase activity within osteoblasts.[21] Studies of third-generation AIs versus tamoxifen found a statistically significant increase in fracture rates for the AI group (Table 2). Although data on fracture types are limited, evidence suggests higher rates of fractures in the spine.

All patients should have bone mineral density testing (BMD) before the initiation of AI therapy. Deciding when to initiate treatment with bisphosphonates varies depending on the guidelines being followed. According to the 2003 American Society of Clinical Oncology (ASCO) recommendations for the management of bone loss in postmenopausal women on AIs, bisphosphonate therapy should be considered for women with T scores of -2.5 or lower.[24] However, data from the National Osteoporosis Risk Assessment Study (NORA), which involved more than 200,000 postmenopausal women without breast cancer, found that 82% of bone fractures occurred in women without osteoporosis (T-scores greater than -2.5).[25] Because women with a breast cancer history are at increased risk for osteoporosis and osteoporosis-related fractures, ASCO recommendations may undertreat most women on AIs who are at increased risk for fractures.

In 2008, the National Osteoporosis Foundation (NOF) expanded their recommendations for bisphosphonate therapy to include anyone with osteopenia (T scores between -1.0 and -2.5) and at increased risk for fracture (as calculated by having a 10-year probability of a hip fracture $\geq$ 3% or a 10-year probability of a major osteoporosis-related fracture $\geq$20%) using the World Health Organization Fracture Risk Assessment tool (FRAX®).[26,27] Although the FRAX algorithm takes into consideration risk factors seen in patients with breast cancer such as premature menopause and glucocorticoid exposure, it is unclear whether these recommendations will result in fracture reductions in patients with breast cancer on AIs. Limited studies suggests that upfront bisphosphonate use at the initiation of AI therapy can prevent AI-induced bone loss; however, not all patients on AIs will experience significant bone loss.[28] More studies are needed to identify those patients on AIs with the highest risk for continued bone loss and fractures.

Continued monitoring of BMD for all women on AIs is important for identifying women at increased risk for bone loss and fracture risk related to AI therapy. Current recommendations are to perform BMD testing every 2 years (or annually if

Table 1. Aromatase Inhibitor Trials of Early Breast Cancer Treatment

Trial	AI	Duration (months)	N	Disease-free survival (Hazard Ratio, 95% CI)
Concurrent trials (tamoxifen vs. AI)				
ATAC[6]	Anastrozole	30.7	9366	Stopped due to lack of benefit
Head to head trials (tamoxifen vs AI)				
ATAC[6]	Anastrozole	47	6241	0.86 (0.76–0.99)
BIG 1–98[13]	Letrozole	41	8028	0.82 (0.71–0.95)
Switch trials (tamoxifen for 5 years vs. tamoxifen for 2–3 years followed by AI for 2–3 years)				
Meta-analysis[12]	Anastrozole	30	4006	0.59(0.48–0.74)
IES[7]	Exemestane	30.6	4724	0.67(0.56–0.82)
Extended adjuvant trials (tamoxifen for 5 years followed by AI for 5 years vs. placebo for 5 years)				
NCIC CTG MA.17[8]	Letrozole		5187	0.58(0.45–0.76)
NSABP[15]	Exemestane		1598	1.20 (0.57–2.52)

AI aromatase inhibitor, ATAC Arimidex, Tamoxifen Alone or in Combination trial, BIG 1-98 Breast International Group 1-98 trial, IES Intergroup Exemestane Study, NCIC CTG National Cancer Institute of Canada Clinical Trials Group, NSABP National Surgical Adjuvant Breast and Bowel Project B-33 trial.

Table 2. Fracture and Cardiovascular Event Rates in Aromatase Inhibitor Versus Tamoxifen Studies

Study	Drug	N	Duration (months)	Fractures		Cardiovascular events	
				%	(N)	%	(N)
ATAC[64]	Anastrozole	3125	100	16.6	(521)*	1.9	(60)
	Tamoxifen	3116		12.0	(377)	1.9	(61)
BIG 1–98[43]	Letrozole	2448	40	8.0	(196)*	5.7	(140)
	Tamoxifen	2447		5.4	(132)	5.2	(127)
IES[65]	Exemestane	2320	55	4.3	(100)*	16.4	(382)
	Tamoxifen	2338		3.1	(73)	15.0	(350)

* $P < 0.05$.
ATAC Arimidex, Tamoxifen Alone or in Combination trial, BIG 1-98 Breast International Group 1-98 trial, IES Intergroup Exemestane Study.

patients are at high risk for fractures as defined by a previous history of fragility fracture). Patients with reduced BMDs should be evaluated for secondary causes of bone loss such as vitamin D deficiency.[29] Although studies have demonstrated higher rates of bone biomarkers (such as deoxypyridinoline, urine N-telopeptide, serum C-telopeptide, and bone alkaline phosphatase) among women on AIs versus tamoxifen, as in the nonbreast cancer patient, there is no role for the use of bone biomarkers in identifying patients at increased fracture risk. Although evidence-based guidelines on the optimal time to initiate bisphosphonate therapy are lacking, ongoing studies should eventually provide additional guidance. In the meantime, bisphosphonate therapy should be initiated for all women on AIs (without other contraindications) with osteoporosis ($T \leq -2.5$) and/or a previous history of fragility fracture (regardless of their T score). Anyone who experiences significant negative changes in their BMD should also be considered for treatment. Treatment decisions for patients on AIs with osteopenia and without other established risk factors for osteoporosis-related fractures should be individualized, based on discussions regarding risks and benefits.

ARTHRALGIAS DUE TO AI USE

Arthralgias were first reported to be associated with AIs in 2001.[30] Subsequent studies have found increased arthralgias with all third-generation AIs.[31] Surveys suggest that nearly 50% of women on AIs experience some joint discomfort with 25% reporting significant joint discomfort.[32]

Arthralgias associated with AI use can occur at any time but occur most commonly within the first 6 months of therapy.[31] Joint involvement is symmetric and most commonly affects the knees, hands, wrists, and shoulders.[31] Patients typically report early morning pain and stiffness. AI use may be associated with a syndrome characterized by joint discomfort, stiffness, and mild soft-tissue swelling. In most cases of AI-related arthralgia, symptoms improve over time, even with continued AI use.[31] For some patients; however, the symptoms may be severe enough to require cessation of therapy. In these cases, the symptoms generally resolve within a few weeks after cessation of AI therapy. It is unclear whether patients who are intolerant to one AI can tolerate another AI; however, most patients are able to tolerate tamoxifen. Symptomatic treatment includes high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors. Heat, transcutaneous electrical stimulation, biofeedback, relaxation training, and acupuncture have been investigated but data are limited.[31] Although small studies suggest a link between inadequate 25-hydroxyvitamin D levels and AI-induced joint symptoms, the role of vitamin D replacement is unclear.[33,34] Studies are also ongoing to evaluate the role of bisphosphonate as an analgesic in AI-induced arthralgia.[35]

Given the variability in both the timing and severity of AI-associated arthralgias, general internists should consider AIs in the differential diagnosis for new joint symptoms. More extensive evaluation should be based on the patient's history and physical examination. Initial management should include over-the-counter and/or prescription pain medications as well as reassuring the patient that the symptoms generally improve with time. Patients who experience severe, debilitating symptoms, will need to discuss options for alternative adjuvant hormone therapy with their cancer specialist.

GYNECOLOGIC EFFECTS OF AROMATASE INHIBITORS

Compared to tamoxifen, AIs are associated with lower rates of endometrial cancer, vaginal discharge, and bleeding.[36] Not surprisingly, however, the potent reduction in systemic estrogen levels by AIs leads to an increase in gynecologic symptoms including vaginal dryness, decreased libido, dyspareunia, and decreased sexual functioning.[7,37,38] For AI-induced vaginal dryness, treatment includes the use of nonhormonal water-based lubricants. Although data on breast cancer survivors are lacking, small studies suggest a possible benefit for vitamin E suppositories for vaginal atrophy.[39] Professional organizations such as the Society of Gynecologists and Obstetricians recommend regular vaginal coital activity as a way to increase blood flow to the pelvic organs.[36] Products that are potentially irritating to the vulva should be avoided. The safety of even poorly absorbed intravaginal estrogens such as vaginal estradiol in women with hormone-positive breast cancer is unknown. As in patients without breast cancer, little is known about treatments to improve decreased libido in women.

AROMATASE INHIBITORS AND THE HEART

The impact of estrogen on the cardiovascular system is complex. The Women's Health Initiative (WHI) trial demon-

strated higher rates of cardiovascular events among hormone users compared to nonusers.[40] Subsequent studies, however, demonstrated lower coronary calcium scores for women between the ages of 50 to 59 years on estrogen therapy.[41] Women in this study were younger than women in the WHI trial. If estrogen has a differential effect on the cardiovascular system at different ages, what are the long-term cardiovascular consequences of near complete estrogen deprivation by AIs?

Data on the effect of AIs on cardiovascular disease is limited. Trials involving anastrozole and exemestane were underpowered for cardiovascular events (Table 2). The Breast International Group (BIG 1–98) trial was designed to review the potential effects of letrozole on cardiac risk. At 30 months of follow-up, more severe and fatal cardiovascular events were seen in the letrozole arm compared to the tamoxifen arm.[42] An updated analysis of the BIG 1–98 trial found higher rates of cardiac events in the letrozole arm versus the tamoxifen arm, specifically for women between the ages of 65 and 74 years.[43] Several additional trials are ongoing to evaluate the effect of AIs on cardiovascular risk.[44]

The effects of AIs on lipid levels may explain the association with cardiovascular events reported in some trials. While tamoxifen has a positive effect on lipid profiles with decreases in both total cholesterol and low-density lipoprotein cholesterol (LDL-C), results from studies evaluating third-generation AIs have been mixed.[45] The Tamoxifen or Arimedex Randomized Group Efficacy and Tolerability trials found no effect on nonfasting lipids in either the anastrozole or tamoxifen arms.[46] Results from studies on the effect of letrozole on lipid levels have conflicted. Although overall cholesterol levels were higher for letrozole compared to tamoxifen in the BIG 1–98, this was not seen in the lipid substudy involving letrozole (MA 17L).[46,47] Similarly, both positive and negative effects have been reported for exemestane.[48,49] Results from two other trials comparing AI to placebo have been reported in abstract form and neither trial observed lipid effects.[45,50]

The effect of AIs on other cardiovascular risk factors such as weight gain and physical activity are unknown. However, studies show that both increases in weight and decreases in physical activity are observed in women after breast cancer treatment. Weight gain is commonly reported during the first year after a breast cancer diagnosis. This weight gain has been linked to both chemotherapy and adjuvant hormone therapy use (tamoxifen and megesterol acetate).[51] In addition, studies involving breast cancer survivors have shown increased negative lifestyle behaviors after diagnosis. In the Health, Eating, Activity, and Lifestyle (HEAL) study, significant decreases in physical activity were observed among women after a breast cancer diagnosis.[52]

Postmenopausal women are at high risk for coronary heart disease (CHD). It is possible that AIs may increase the risk for cardiovascular events. As in all patients, women should have appropriate evaluation and modification of cardiovascular risk factors. An interesting finding from the WHI was a decreased incidence in breast cancer among women using hydrophobic statins (e.g., simvastatin, lovastatin, or fluvastatin) (HR = 0.82; 95% CI, 0.70–0.97).[53] Given the known association of increased risk for breast cancer recurrence with both obesity and decreased physical activity, extra emphasis should be placed on these lifestyle interventions.[54]

AROMATASE INHIBITORS AND COGNITION

Estrogen receptors have been identified in many areas of the brain including the hypothalamus, pituitary, hippocampus, cerebral cortex, midbrain, and brainstem.[55] Although initial observational studies suggested that estrogen replacement therapy may exert a protective effect on cognition, recent studies have contradicted this finding.[56] Subjects in the Women's Health Initiative Memory Study (WHIMS), had higher rates of cognitive decline and dementia with estrogen and estrogen plus progesterone therapy.[57,58] The consequences of long-term suppression of endogenous estrogen production by AIs on cognition are unknown.

Cognitive dysfunction after breast cancer treatment is reported in up to one-third of breast cancer survivors.[59] Most studies have linked this finding to chemotherapy use.[60] It is also possible that the long-term suppression of endogenous estrogen may effect cognitive function. Preliminary, limited findings from the aromatase trials are conflicting. In a 2007 study of 62 women with early stage breast cancer, those receiving anastrozole (n = 31) had poorer verbal and visual learning and memory problems compared to women receiving tamoxifen (n = 31).[61] The International Breast Intervention Study (IBIS II) found no difference in cognition among women randomly assigned to anastrozole (n = 111) versus placebo (n = 116). Both studies have numerous flaws that limit their results.

It is possible that AIs may have some effect on neurocognitive function. As in any patient who reports changes in neurocognitive function, evaluation should begin with a thorough history and physical examination. Underlying depression and/or substance abuse should be ruled out. In some cases, patients may benefit from additional testing such as a formal neuropsychiatric evaluation, neuroimaging studies and/or laboratory tests.

AROMATASE INHIBITORS AND THROMBOEMBOLIC EVENTS

Compared to tamoxifen, all three of the third-generation AIs are associated with lower rates of thromboembolic events.[62,63] The risk of thromboembolic events with AIs compared to placebo is unknown. Data from the MA-17 trial that looked at 5 years of letrozole versus placebo after 5 years of tamoxifen have not been released.[8] Currently thromboembolic events are listed as a potential complication of these agents and general internists need to aware of this potential side effect for women on AIs.

CONCLUSION

Third-generation AIs are the newest class of drugs used to treat hormone-responsive breast cancer. In the future, their use may expand to include the prevention of breast cancer in women at high risk. Discussions with patients on risks versus benefits of AIs are currently being conducted by cancer specialists. However, as care for these patients transitions to their primary care physicians, general internists will likely find themselves continuing these discussions. Little conclusive evidence of side effects and significant harms beyond increased rates of arthralgias, vaginal dryness, and fractures for AIs

compared to tamoxifen exists at this time. However, internists need to be aware of ongoing studies evaluating other potential harms. In situations where patients experience significant negative side effects from AI therapy, discussions to discontinue treatment (and switch to an alternative endocrine therapy) should involve the cancer specialist and take into consideration the patient's risk for breast cancer recurrence and the effect of therapy on their quality of life. In some cases, patients may choose to never initiate AI treatment. In other cases, patients may choose to prematurely discontinue therapy even if the therapy is well tolerated. In both settings, increased knowledge by the general internists will likely facilitate discussions of risks versus benefits of therapy and possibly improve compliance with adjuvant hormone therapy.

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