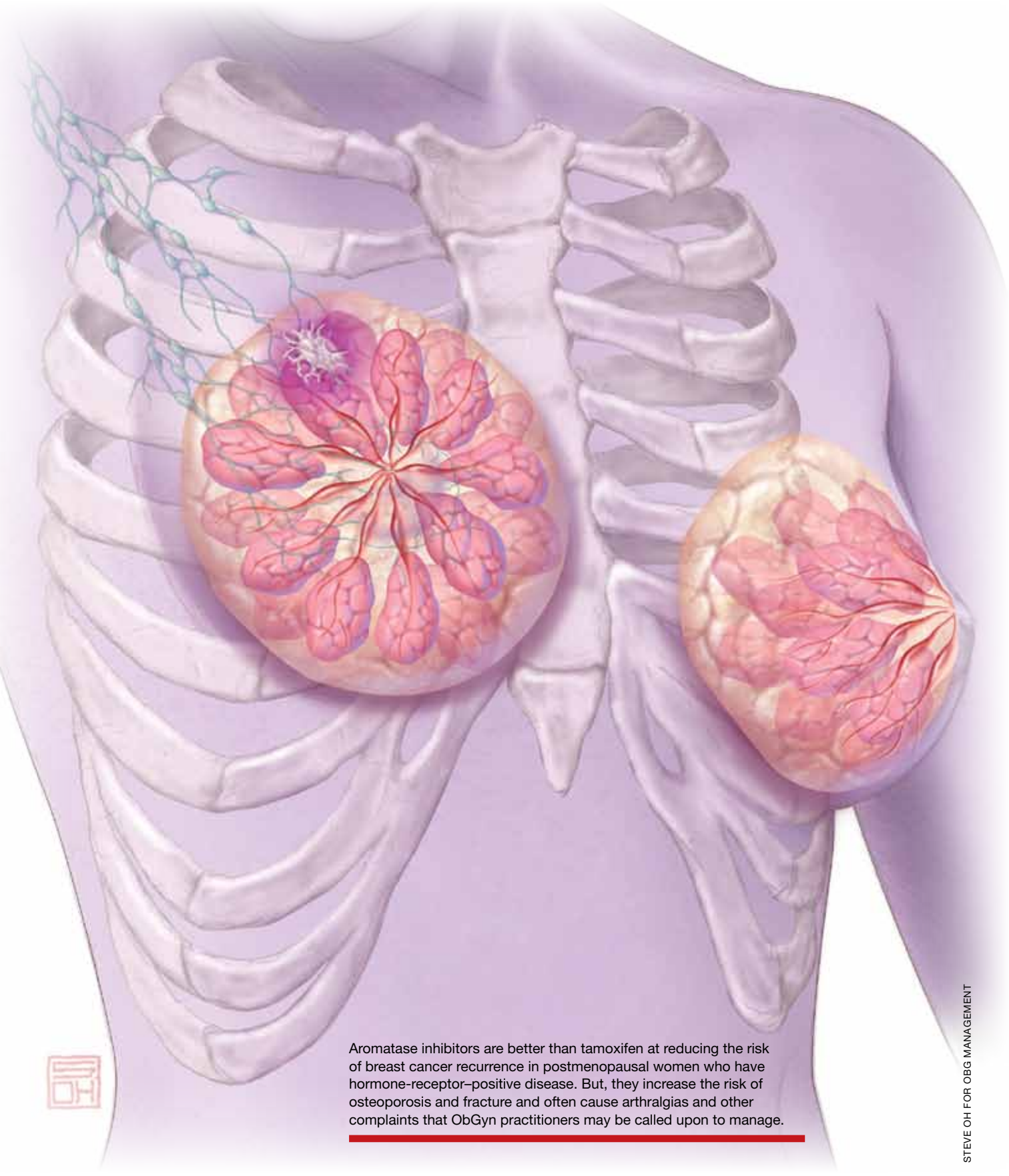

Aromatase inhibitors are better than tamoxifen at reducing the risk of breast cancer recurrence in postmenopausal women who have hormone-receptor–positive disease. But, they increase the risk of osteoporosis and fracture and often cause arthralgias and other complaints that ObGyn practitioners may be called upon to manage.

STEVE OH FOR OBG MANAGEMENT

Q&A WITH ANDREW M. KAUNITZ, MD

An ObGyn's guide to aromatase inhibitors as adjuvant therapy for breast CA

You may not prescribe anastrozole, letrozole, or exemestane, but there's a strong possibility that some of your patients are taking one of these medications. Here's what you need to know to encourage compliance and ease their ill effects.

Janelle Yates
Senior Editor, OBG MANAGEMENT

Think breast cancer survivors are unlikely to show up in your practice? You should think again.

At last official count, 2.5 million women in the United States had a history of breast cancer.[1] Most of them are now free of malignancy, but others are still grappling with the disease in some form or fashion.[2] All need continuing health care.

Roughly two thirds of women who have breast cancer have disease that is hormone-receptor–positive.[2,3] Recently updated guidelines from the American Society of Clinical Oncology (ASCO) recommend that adjuvant therapy for postmenopausal women who have hormone-positive breast cancer include an aromatase inhibitor (AI) (see a summary of these guidelines on page 36). That makes it likely that a good number of breast cancer survivors who visit your practice are taking one of these medications: anastrozole (Arimidex), letrozole (Femara), or exemestane (Aromasin). These drugs are antiestrogens, given to postmenopausal women to reduce the likelihood of disease recurrence and progression.

The antiestrogenic properties of these drugs are what make them lifesavers. But the same qualities can create a range of health issues, from increased risk of osteoporosis and fracture to vasomotor and joint symptoms. And although ObGyns are not the physicians who prescribe these drugs, you may be the provider one of these women consults about their side effects and related issues.

To find out the latest on the management of women who are taking one of these agents, we inserted ourselves into the busy schedule of Andrew M. Kaunitz, MD, who agreed to address some fundamental—and some not so basic—questions about the drugs. In this extended Q&A, Dr. Kaunitz touches on mechanism of action, benefits versus risks, common side effects, compliance with therapy, and the ill effects of early discontinuation.

OBG MANAGEMENT: What is the overall aim of adjuvant endocrine therapy in the setting of breast cancer?

Dr. Kaunitz: Endocrine therapy—specifically,

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IN THIS ARTICLE

Key points about AIs in breast Ca

- The American Society of Clinical Oncology recommends that adjuvant therapy for postmenopausal women who have hormone-positive breast cancer include an aromatase inhibitor (AI).
- AIs are not recommended for use in premenopausal women.
- By blocking the aromatase enzyme, AIs reduce endogenous estrogen levels by as much as 95%.[4]
- AIs are more effective than tamoxifen at preventing recurrence in the first 2 years after breast cancer surgery. Postmenopausal women taking an AI have a longer disease-free survival and time to recurrence than do women taking tamoxifen. They also have a lower incidence of contralateral breast cancer.
- The most prominent side effects of AI therapy include arthralgias and hot flushes, while the most serious health impact appears to be a decrease in bone mineral density (BMD). However, endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events, and hot flushes all are less common among women taking an AI than among those taking tamoxifen.
- The FDA strongly discourages the use of estrogen therapy—systemic or local—in women who are taking an AI. Accordingly, bisphosphonate therapy is recommended as first-line treatment of low bone mineral density. Vaginal lubricants and moisturizers are the mainstay strategy for symptomatic genital atrophy. And gabapentin, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors are the mainstay of therapy for vasomotor flushes.
- Roughly 50% of women who are prescribed adjuvant endocrine therapy with tamoxifen or an AI discontinue the drug early.[32] Early discontinuation is associated with an increase in mortality.[33]

use of an AI—prevents the stimulation of breast cancer cells by endogenous estrogen. In other words, aromatase inhibitors suppress the growth of cancer cells that have estrogen receptors. These drugs also inhibit aromatase near any breast tumor and reduce estrogen levels in breast tissue.

OBG MANAGEMENT: What is the mechanism of action of adjuvant endocrine therapy?

Dr. Kaunitz: In postmenopausal women, androgens are converted to estrogens via the aromatase enzyme, which is present in adipose tissue and other sites. By blocking this enzyme, AIs reduce endogenous estrogen levels by as much as 95%.[4]

OBG MANAGEMENT: How does that differ from the mechanism of action of tamoxifen, another drug used in breast cancer patients?

Dr. Kaunitz: Tamoxifen is a selective estrogen receptor modulator (SERM). It blocks estrogen in breast tissue selectively, by competitively binding to estrogen receptors.[5] However, tamoxifen has estrogenic effects in the uterus, bone, and liver, as well as other tissues.

The efficacy of AIs in preventing breast cancer recurrence in the first 2 years after breast cancer surgery is higher than that of tamoxifen. And unlike tamoxifen, the AIs do not increase the risk of venous thromboembolism or cause endometrial disease.

OBG MANAGEMENT: What effects do aromatase inhibitors have in premenopausal women?

Dr. Kaunitz: These agents are not recommended for use in premenopausal women because, in that population, the lion's share of estrogen production takes place in the ovary rather than in adipose tissue and muscle. If you were to administer an AI to a premenopausal woman, the reduced hypothalamic and pituitary estrogen feedback could lead to ovarian stimulation—which could *increase* ovarian steroid production.

OBG MANAGEMENT: What about women who become amenorrheic as a result of chemotherapy or other cancer treatment? Do most oncologists assume that they are postmenopausal and prescribe an aromatase inhibitor?

Dr. Kaunitz: Clinicians should not assume that chemotherapy-induced amenorrhea signals permanent cessation of ovarian function. It is common for ovarian function to return in this setting. Accordingly, follicle-stimulating hormone (FSH) and estradiol levels should be assessed before an AI is considered as adjuvant therapy. Some investigators have suggested that the use of an AI in women who have chemotherapy-induced amenorrhea may actually *increase* the likelihood that ovarian function will return.[6]

OBG MANAGEMENT: Do all AIs produce the same effects?

Dr. Kaunitz: The AIs used in women with breast cancer are third-generation drugs. These AIs are classified as steroidal (type 1; exemestane) or nonsteroidal (type 2;

CONTINUED ON PAGE 35

anastrozole, letrozole). Exemestane, a steroid derived from androstenedione, inhibits the aromatase enzyme irreversibly. The nonsteroidal AIs are reversible.

Although all three AIs have numerous similarities, there are other distinctions between them in pharmacokinetics, mechanism of action, and toxicity—so they are not completely interchangeable.[7] However, from our perspective as ObGyns caring for breast cancer survivors, we can assume that all three AIs will have similar effects on skeletal health and produce similar side effects in postmenopausal women.

How much do we know about these drugs?

OBG MANAGEMENT: How long does a woman typically take an AI?

Dr. Kaunitz: At present, in women treated for early-stage, hormone-positive breast cancer, the optimal duration of treatment is unknown. Most oncologists prescribe an AI for 5 years, the length of treatment in a prominent trial of the drugs.[8]

OBG MANAGEMENT: Is that duration likely to increase as more data come in?

Dr. Kaunitz: The optimal duration of adjuvant AI therapy will be determined by the findings of long-term clinical trials. The National Surgical Adjuvant Breast and Bowel Project B-42 trial may provide new insights into optimal duration of AI treatment after initial tamoxifen therapy.[9]

OBG MANAGEMENT: How thoroughly have AIs been studied in regard to their use in breast cancer survivors and women who have early-stage disease? How would you characterize the quantity and quality of data that we have so far?

Dr. Kaunitz: AIs have been extensively studied. The most important clinical trials of AIs in this setting, including the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial (over 6,000 participants, median follow-up of 100 months) and the Breast International Group (BIG) trial (almost 5,000 participants, median follow-up of 76 months) have been detailed in the recent ASCO report.[10] These two large landmark trials, in particular, formed the basis for ASCO's recommendations to routinely incorporate AIs into the therapy of postmenopausal women who have hormone-receptor–positive breast cancer.

OBG MANAGEMENT: In treating breast cancer, what other applications are AIs used for?

Dr. Kaunitz: AIs appear to be slightly more effective than tamoxifen in treating postmenopausal women who have metastatic breast cancer.[11]

They are approved as *first-line* therapy for breast cancer in:

- postmenopausal women who have hormone-receptor–positive disease
- postmenopausal women who have locally advanced disease when the hormone receptor is unknown
- postmenopausal women who have metastatic disease.

In addition, they are approved as *second-line* treatment of advanced breast cancer in postmenopausal women who have disease progression following tamoxifen therapy.[12]

How effective is AI therapy?

OBG MANAGEMENT: What do we know about the efficacy of these drugs?

Dr. Kaunitz: Most of the studies that have explored efficacy compare an AI with tamoxifen rather than with placebo. In the ATAC trial, after a median follow-up of 33 months, women who were taking anastrozole for early-stage breast cancer had longer disease-free survival and time to recurrence and a lower incidence of contralateral breast cancer than did women taking tamoxifen.[8]

After 4 years of follow-up in the ATAC trial, women taking anastrozole continued to have more favorable disease-free survival (86.9% vs 84.5% for anastrozole and tamoxifen, respectively; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.76–0.99; $P = .03$).[13] They also had a more favorable time to recurrence than did women taking tamoxifen (HR, 0.83; 95% CI, 0.71–0.96; $P = .015$). And women taking anastrozole had a lower incidence of contralateral breast cancer, as well, although

FAST TRACK

All third-generation aromatase inhibitors have similar effects on skeletal health and produce similar side effects in postmenopausal women

this different did not achieve statistical significance (HR, 0.62; 95% CI, 0.38–1.02; $P = .062$).[13]

In the BIG study, women taking letrozole had a 5-year disease-free survival estimate of 84.0%, compared with 81.4% for women taking tamoxifen.[14] In addition, women taking letrozole were significantly less likely than those taking tamoxifen to experience an event that ended a period of disease-free survival (HR, 0.81; 95% CI, 0.70–0.93; $P = .003$), especially the event of distant recurrence (HR, 0.73; 95% CI, 0.60–0.88; $P = .001$).[14]

And a phase-3 study of exemestane versus tamoxifen in women who had *metastatic* breast cancer found that the AI produced a superior response rate (46% vs 31% for exemestane and tamoxifen, respectively; odds ratio [OR], 1.85; 95% CI, 1.21–2.82; $P = .005$). In addition, median progression-free survival was greater with exemestane (9.9 months; 95% CI, 8.7–11.8 months) than with tamoxifen (5.8 months; 95% CI, 5.3–8.1 months). However, there was no difference between arms in progression-free survival or overall survival.

FAST TRACK

All major phase-3 trials of adjuvant use of AIs in women who have early breast cancer found an increased risk of fracture

How well tolerated are AIs?

OBG MANAGEMENT: What adverse effects are associated with AIs?

Dr. Kaunitz: Although AIs, overall, are safe medications, their use is associated with a number of adverse events. The most prominent side effects include arthralgias and hot flushes, while the most serious health impact appears to be a decrease in bone mineral density (BMD).

However, the drugs are generally perceived as being easier to tolerate than tamoxifen. That's because endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events, and hot flushes all are less common among women taking an AI than among those taking tamoxifen.[8,13]

For overweight women, who face an elevated baseline risk of thromboembolism, the availability of AIs represents a major advantage over tamoxifen. Similarly, AIs offer advantages over tamoxifen for women who have an intact uterus. In addition, postmenopausal women who are taking a selective serotonin reuptake inhibitor (SSRI) such as paroxetine should take an AI rather than tamoxifen, because the concomitant use of SSRIs attenuates the efficacy of tamoxifen.[15]

What can be done about the most prominent risks?

OBG MANAGEMENT: Let's focus on what's probably the best-known adverse effect of AIs—the heightened risk of osteoporosis and fracture. How significant is this effect?

Dr. Kaunitz: Because use of an AI is associated with a profound reduction in endogenous estrogen levels, it also decreases BMD and can lead to osteoporotic fractures. All major phase-3 trials of adjuvant use of AIs in women who have early breast cancer found an increased risk of fracture, with no significant differences between AIs.[16]

Fortunately, bisphosphonate therapy (oral or intravenous) has been found to reduce bone loss associated with AI therapy.[17,18]

Assessing baseline BMD is important as women initiate AI therapy. Although no consensus exists regarding follow-up BMD assessment in the setting of AI use, an interval of 2 years is prudent, with the follow-up study preferably performed at the same imaging center and by the same technician as the first. If baseline osteoporosis is observed at the lumbar spine or hip, bisphosphonate therapy is appropriate. If a woman taking an AI has low bone mass (osteopenia) but not osteoporosis, bisphosphonate therapy should be considered if any of the following risk factors are present:

- advanced age
- history of fracture
- glucocorticoid therapy
- parental history of hip fracture
- low body weight
- current smoking status
- excess alcohol consumption
- rheumatoid arthritis
- known risk factors for secondary osteoporosis.[19]

In breast cancer survivors initiating or

ASCO guidelines emphasize the importance of aromatase inhibitors

Postmenopausal women who have hormone-receptor–positive breast cancer should consider taking an aromatase inhibitor (AI) to lengthen disease-free survival and lower the risk of recurrence. That's one of the recommendations in updated guidelines issued earlier this year by the American Society of Clinical Oncology (ASCO). The guidelines suggest a duration of AI therapy of 5 years. In the event that a woman discontinues AI therapy before 5 years are up, she should consider using tamoxifen to bring the total duration of treatment to 5 years.

Other recommendations in the guidelines include:

- Women who have taken tamoxifen for 5 years stand to benefit from switching to an AI for as long as 5 additional years.
- When advising a woman about adjuvant therapy with an AI, clinicians should consider the potential adverse effects, which include osteoporosis, fracture, and arthralgias.
- The third-generation AIs on the market today have not been found to have clinically important differences between them. A woman who cannot tolerate a particular AI should consider switching to a different AI.
- Switching from an AI to tamoxifen (or vice versa) may be an appropriate option for patients who cannot tolerate a drug's adverse effects. In the event of a switch to tamoxifen, the clinician should counsel the patient about its adverse effects, which include venous thromboembolism and endometrial polyps, hyperplasia, and cancer.

The full guidelines can be accessed at http://jco.ascopubs.org/content/early/2010/07/12/JCO.2009.26.3756.full.pdf.

—Andrew M. Kaunitz, MD

continuing AI therapy, it is also appropriate to check a serum vitamin D level and ensure that intake of this nutrient is adequate.

Bisphosphonates may offer oncologic benefits, as well; preliminary evidence suggests that the drugs may prevent recurrence of the cancer and prolong survival.[20]

OBG Management: What can an ObGyn offer to a woman who complains of significant AI-related arthralgia?

Dr. Kaunitz: Bone and joint symptoms, including aches, pain, and stiffness that is bilateral and not associated with other evidence of rheumatologic disorders, are among the most common side effects of AI therapy. On the plus side of the equation, these symptoms are more likely to be mild to moderate than severe. On the negative side, no specific treatment has been found to be effective in relieving these symptoms, which usually resolve within 2 months or so after discontinuing AI therapy.[10]

OBG Management: Do AIs have a negative impact on cardiovascular health?

Dr. Kaunitz: Unlike tamoxifen, AIs do not increase the risk of thromboembolic disease. Although the use of an AI may modestly increase the risk of ischemic cardiovascular disease (and lipid changes), compared with tamoxifen, AIs do not appear to increase cardiovascular risk compared with placebo.[21,22]

OBG Management: Do the antiestrogenic effects of AIs have a significant impact on vaginal health and sexual desire?

Dr. Kaunitz: A review of published reports did not find that the use of AIs has a predictable impact on vaginal dryness or sexual desire.[10] However, symptomatic genital atrophy is common in postmenopausal breast cancer survivors, whether or not they use adjuvant therapy.

Although the FDA considers the use of any estrogen (systemic or vaginal) following a diagnosis of breast cancer to be contraindicated, some breast cancer survivors who have symptomatic genital atrophy express an interest in the use of vaginal estrogen. Use of 25-µg estradiol tablets (Vagifem) is associated with a short-term increase in serum estradiol levels.[23] This finding has reinforced caution among medical oncologists about the safety of vaginal estrogen in breast cancer survivors. (The 25-µg tablets are no longer marketed.) The lowest dosage of vaginal estrogen available for the treatment of genital atrophy is found in 10-µg estradiol tablets (Vagifem) and the estradiol (2-mg) 3-month vaginal ring (Estring). Nonetheless, in the absence of data, oncologists will likely continue to be concerned that even the lowest dosage of vaginal estrogen could attenuate the favorable impact of AIs on breast cancer. Accordingly, use of vaginal lubricants and moisturizers are the mainstay strategy for symptomatic genital atrophy.

OBG Management: What about the ubiquitous hot flush? Vasomotor symptoms may be

more common in women who take tamoxifen, but women on AIs are also bothered by flushes. What are the alternatives to estrogen therapy?

Dr. Kaunitz: Both nonprescription and prescription alternatives are available. Nonprescription options include soy extract and red clover isoflavones, black cohosh, and Chinese herbs. However, none of these over-the-counter approaches has been found to be more effective than placebo in the treatment of menopausal hot flushes.[24–26]

As for prescription nonhormonal options, ObGyns should recognize that all such treatments are off-label and that none attain the efficacy of hormone therapy in the treatment of vasomotor symptoms. The best-studied and most effective medications include gabapentin, SSRIs (especially paroxetine), and serotonin-norepinephrine reuptake inhibitors (venlafaxine and desvenlafaxine).[24,27]

OBG Management: Is there any evidence that AIs impair cognitive function in postmenopausal women?

Dr. Kaunitz: Because estrogen is important for cognition, one might anticipate that the profound reduction in background estrogen associated with AI use would impair cognition. Fortunately, the evidence to date is reassuring. Substudies of the BIG trial and the Tamoxifen and Exemestane Adjuvant Multinational Trial indicate that, compared with tamoxifen (which is associated with declines in cognitive function in postmenopausal women), letrozole and exemestane do not diminish cognitive function.[28,29]

OBG Management: Overall, what is the typical impact of an AI on a woman's quality of life?

Dr. Kaunitz: Most women do very well on an AI, finding it easier to tolerate than tamoxifen, as we have discussed. However, a significant minority of women is seriously bothered by the adverse effects, with arthralgias usually leading the pack of complaints.[30,31]

OBG Management: Do some women discontinue adjuvant endocrine therapy because of adverse effects?

Dr. Kaunitz: Regrettably, the answer is "Yes." A recent study from Kaiser Permanente of northern California found that roughly 50% of women who are prescribed adjuvant endocrine therapy with tamoxifen or an AI discontinue the drug early.[32]

OBG Management: What can an ObGyn do to encourage compliance with and completion of AI therapy?

Dr. Kaunitz: First, it is critical that patients understand that AIs are lifesaving drugs. As a recent paper points out, early discontinuation or noncompliance with AI therapy is associated with higher mortality.[33]

Clinicians should also help breast cancer patients understand what common side effects to anticipate with these medications.

Finally, clinicians who understand the financial toll a breast cancer diagnosis and treatment can take are better positioned to help women overcome challenges that may interfere with long-term compliance with AI therapy.

OBG Management: Do you expect the use of AIs in breast cancer survivors to become more commonplace?

Dr. Kaunitz: Given how common breast cancer is, and given the new ASCO guidelines and the extensive literature upon which they are based, ObGyns will be seeing more women using AIs. Although we are not the physicians who prescribe AIs, we need to remain up to date on their benefits and side effects. This important class of drugs is positioned to improve outcomes for postmenopausal women with breast cancer.

FAST TRACK

Early discontinuation or noncompliance with aromatase inhibitor therapy is associated with higher mortality

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