Caring for women on adjuvant therapy for breast cancer:

Role of the NP in the primary care setting

By Rachel Gorham, MSN, WHNP-BC, AGN-BC

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners and other healthcare providers who provide primary care for women.

CE approval period: Now through February 28, 2022

Estimated time to complete this activity: 1 hour

CE approval hours: 1 contact hour of CE credit, including 1 contact hour of pharmacology content

Goal statement: Primary care providers will increase their knowledge about the indications for, mechanism of action, side effects, and potential risks associated with breast cancer adjuvant therapies so they can be aware of specific problems and concerns that may arise with patients on these medications and manage care appropriately.

Needs assessment: Breast cancer therapies are ever evolving. Survival rates continue to improve following initial treatment. Because the number of breast cancer survivors is growing, healthcare providers need to understand potential post-treatment effects that these patients may experience, particularly with regard to the adverse effects of prescribed adjuvant therapy. Although nurse practitioners in women's health and/or primary care—other than those who specialize in oncology—do not prescribe or manage this adjuvant therapy, they need to understand the rationale for it and the effects of it on their patients.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Describe indications and mechanisms of action for breast cancer adjuvant therapies.
2. Discuss potential risks associated with the use of breast cancer adjuvant therapies.
3. Describe strategies to reduce potential risks associated with the use of breast cancer adjuvant therapies.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH) and has been approved for 1 contact hour of CE credit, including 1 contact hour of pharmacology content.

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Breast cancer therapies are ever-evolving. Survival rates continue to improve following initial treatment. Because the number of breast cancer survivors is growing, healthcare providers need to understand potential post-treatment effects that these patients may experience, particularly with regard to the adverse effects of prescribed adjuvant therapy. Although nurse practitioners in women's health and/or primary care—other than those who specialize in oncology—do not prescribe or manage this adjuvant therapy, they need to understand the rationale for it and the effects of it on their patients.

KEY WORDS: **breast cancer, adjuvant endocrine therapy, tamoxifen, aromatase inhibitors, targeted gene therapy, primary care, survivorship**

Breast cancer, the most common noncutaneous cancer in the United States, can affect women of any age, ethnicity, or socioeconomic status. In 2018, approximately 63,960 cases of in situ disease and 266,120 cases of invasive disease were diagnosed.[1] About 40,920 breast cancer-related deaths occurred in 2018, which represents 6.7% of all cancer-related deaths.[2] Female breast cancer is most common in middle-aged and older women; median age at diagnosis is 62 years.[2] In 2016, more than 3.5 million women were breast cancer survivors.[3] The lifetime risk of developing breast cancer in the United States is 12.4% (1 in 8 women).[3]

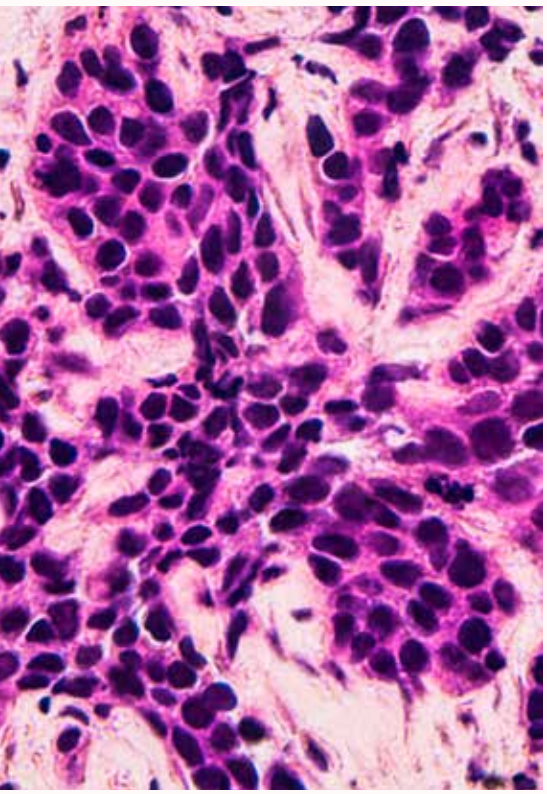
Breast cancer treatments continue to evolve. Although oncologists make the decisions regarding prescribing and managing adjuvant therapy, primary care providers (PCPs), including women's health nurse practitioners (WHNPs) and other advanced practice registered nurses caring for women, need to understand the indications for these medications, as well as their mechanism of action, duration of use, side effects, potential interactions with other medications, and potential harms. Choice of adjuvant therapy depends on lymph node involvement, hormone receptor status, human epidermal growth factor receptor-2 (HER2) overexpression, and the patient's age and menopausal status.[4]

Adjuvant endocrine therapy

Hormone receptor–positive tumors represent 75% of all breast cancer diagnoses.[5] Adjuvant endocrine therapy, also known as adjuvant hormonal therapy, is appropriate for most patients with a hormone receptor–positive tumor.[5] Endocrine therapy stops or slows growth of a hormone-sensitive tumor by preventing breast cancer tumor cells from receiving stimulation from endogenous hormones. If breast cancer tumor cells contain an estrogen receptor, the cancer is labeled estrogen-receptor (ER) positive. If these tumor cells have a progesterone receptor, the cancer is labeled progesterone-receptor (PR) positive.[6] The two main types of adjuvant endocrine therapy are tamoxifen, which is a selective estrogen receptor modulator (SERM), and aromatase inhibitors (AIs).

Tamoxifen

Tamoxifen is the only endocrine therapy used to treat ER-positive breast cancer in premenopausal women.[7] Although generally a weak estrogen agonist, tamoxifen is an antagonist of estrogen activity in the breast.[8] In premenopausal women, tamoxifen can reduce the risk of breast cancer recurrence by 30%



to 50% and the risk of contralateral breast cancer by 50%.[8]

In addition, tamoxifen is used to debulk a breast cancer tumor prior to surgery, slow or stop the growth of advanced (metastatic) breast cancer, or reduce the risk of developing a primary breast cancer in women with a higher-than-average breast cancer risk.[9] Pregnancy is not recommended during tamoxifen therapy or for 2 months after its completion.[10] Premenopausal women treated with chemotherapy are at an increased risk for premature ovarian failure and should use a nonhormonal contraceptive until menopause is confirmed.[10]

Although the use of tamoxifen as adjuvant endocrine therapy has many benefits, it also entails certain risks:

Endometrial cancer

Studies have shown that tamoxifen users, compared with age-matched populations, have a 2 to 3 times greater relative risk of developing endometrial cancer.[11] In asymptomatic tamoxifen users, routine screening for endometrial cancer with transvaginal ultrasound and endometrial biopsy has not been shown to be effective.[11] However, if a premenopausal or postmenopausal patient experiences irregular vaginal bleeding while taking tamoxifen, further evaluation is warranted with an endometrial biopsy, hysteroscopy, and/or transvaginal ultrasound.

Hot flashes

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are the classes of drugs used for hot flushes therapy in breast cancer patients and their efficacy has been proven in randomized clinical trials. Selective serotonin reuptake inhibitors (SSRIs) have been shown to reduce the occurrence of tamoxifen-induced hot flashes by inhibiting the activity of CYP2D6.[12] Because SSRIs that are strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine) can adversely affect the efficacy of tamoxifen, moderate CYP2D6 inhibitors such as sertraline and duloxetine are preferred.[12] Venlafaxine has also been studied and may be used as an effective treatment of hot flashes in breast cancer patients taking tamoxifen. Other drugs, such as clonidine and gabapentin, have also been shown to significantly reduce the frequency of hot flashes. There have been reports that a dose of 400 IU of vitamin E twice daily can improve hot flashes. Hot flashes are reported in up to 80% of patients taking tamoxifen; thus finding an effective nonhormonal treatment is essential to improve quality of life.[13]

Ocular pathologies

Women on tamoxifen should undergo an annual eye examination because this SERM is associated with a 3.7% increased risk of developing cataracts.[13] In addition, reports have described reversible corneal pigmentation and irreversible retinal deposits, which are associated with macular edema and vision loss in tamoxifen users.[13]

Fatty liver disease

There have been reports of fatty liver disease in one-third of women taking tamoxifen. These patients are advised to continue tamoxifen therapy unless their liver function test values are twice the upper limit of normal. In patients with documented tamoxifen-induced fatty liver disease, liver function tests are recommended every 3 to 6 months.[13]

Venous thromboembolism

Tamoxifen users, as compared with age-matched women in the general population, have a 2 to 3 times greater risk of developing a venous thromboembolism.[13] The risk is further pronounced when tamoxifen users have extended therapy to 10 years. Certain risk factors for a tamoxifen-induced venous thromboembolism include prior surgery, fracture, immobilization, and being a carrier of heterozygous factor V Leiden.

Sexual dysfunction

Of patients on tamoxifen, 30% to 40% report sexual complaints (eg, decreased libido, vaginal dryness, dyspareunia).[14] Nonhormonal treatments such as vaginal moisturizers have been shown to be effective.[14] For example, a vaginal pH-balanced gel reduces vaginal pH and promotes vaginal maturation, which improves vaginal dryness and dyspareunia.[14] Polycarbophil vaginal moisturizers have been found to improve vaginal dryness and complaints of dyspareunia.[14] Aqueous lidocaine has been shown to improve penetrative dyspareunia and reduce vulvar vestibular pain.[14] One study

showed that vaginal pH-balanced gels containing lactic acid are significantly more efficient than placebo in decreasing vaginal pH and increasing the mean maturation value, thereby relieving symptoms of vaginal atrophy.[15]

Other options for managing dyspareunia are vaginal lubricants and vaginal dilators. Vaginal exercise and pelvic floor physical therapy, as part of a multimodal treatment, have been shown to be effective in treating sexual dysfunction.[16] In the OVERcome [Olive Oil, Vaginal Exercise, and MoisturizeR] trial, 25 women with dyspareunia were instructed to perform pelvic floor muscle exercises twice daily, use a polycarbophil vagina moisturizer 3 times per week, and use olive oil as a lubricant during sex. This treatment regimen resulted in significant improvements in dyspareunia scores, sexual function, and quality of life. Among study participants, 92%, 88%, and 73% rated the pelvic floor exercises, vaginal moisturizer, and olive oil, respectively, as beneficial. These results have suggested that improving sexual health can rely on a multimodal approach.[16]

Urinary dysfunction

Women on tamoxifen may present with urinary frequency, urgency, incontinence, and frequent urinary tract infections.[17] These infections may respond to local estrogen therapy. However, decisions to institute therapy with local estrogen must be made collaboratively with patients and their oncology team, calculating the risks and benefits for each individual.

Aromatase inhibitors

Most breast cancers that occur in women older than age 50 years are ER- and/or PR-positive and are treated with adjuvant endocrine therapy.[18] The goal of adjuvant endocrine therapy is to prevent breast cancer cells from receiving endogenous estrogen, which prevents ER/PR-positive cancer cells from growing and spreading.[18] AIs work by blocking aromatase, which is responsible for conversion of androstenedione to estradiol. These drugs are not administered to premenopausal women because the hypothalamic–pituitary–ovarian axis becomes activated in response to low systemic levels of estrogen. This activation causes an increase in gonadotropin secretion and ovarian production of estrogen, androgen, and aromatase.[18] The three most commonly used AIs are anastrozole, letrozole, and exemestane.

As is the case with tamoxifen, the use of AIs as adjuvant endocrine therapy has many benefits, but it also entails certain risks:

Effect on bone health

Compared with tamoxifen, AIs cause significantly greater bone loss, which increases fracture risk.[18] As such, AI users have a 5-fold increased risk for vertebral compression fractures. Experts differ regarding their recommendations for treating osteopenia and osteoporosis in women receiving adjuvant endocrine therapy. The American Association of Clinical Oncology and Economical Aspects of Osteoporosis and Osteoarthritis advises clinicians to start bisphosphonate therapy for prevention of fragility fractures in all patients with a T score below –2.5.[19] By contrast, the National Osteoporosis Foundation recommends bisphosphonates only for patients who have a diagnosis of osteopenia and a 10-year risk of a hip fracture exceeding 3% or of a major fracture exceeding 20%.[20] Estimates are calculated using the World Health Organization fracture risk assessment tool.[21]

Measurement of baseline bone mineral density is recommended prior to initiation of AI therapy and every 1 to 2 years thereafter.[22,23] To reduce fracture risk, PCPs should ensure that patients institute lifestyle changes as needed: smoking cessation, reduction of alcohol intake, intake of adequate calcium and vitamin D (supplements of calcium 1,200 mg/day and vitamin D 800 IU/day as needed), regular exercise, and fall prevention measures.[23]

Musculoskeletal complaints

These complaints, including joint pain and stiffness, are among the most common adverse effects associated with AI use, with rates as high

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as 36%.[23,24] The most serious symptoms seem to occur during the first 6 months of therapy.[24] Relief can be provided by exercise, massage therapy, acupuncture, a switch to a different AI, or use of an NSAID.[24] The precise etiology of these musculoskeletal symptoms is unclear. AIs do not cause permanent joint or muscle damage.

Vasomotor and genitourinary dysfunction

The same information and recommendations regarding vasomotor and genitourinary dysfunction that appear in the tamoxifen section apply to AIs.

Cardiovascular risk

AIs can cause adverse cardiometabolic effects, whereas tamoxifen is favorable in this regard because of its estrogen agonist effects.[25] To understand a patient's individualized risk of cardiometabolic effects with the use of an AI, PCPs need to consider other contributing factors such as age, time from menopause until the AI is initiated, and the degree of pre-existing cardiovascular disease. AI treatment, whether upfront or sequenced after tamoxifen, is associated with an increased risk of cardiovascular events. Compared with tamoxifen, however, it poses a decreased risk of venous thromboembolism. PCPs need to be proactive with cardiovascular risk assessment and identification of risk factors. Women with breast cancer must be educated on lifestyle modifications such as smoking cessation, healthful nutrition, and exercise. Cardiovascular monitoring should be consistent with clinical standards for other high-risk populations. Pharmacologic management should follow recommendations for patients with breast cancer and with general population guidelines.[25]

Cognitive dysfunction

The data are conflicting regarding the effects of endocrine therapy on cognitive function in AI users. AIs inhibit the enzyme aromatase, which leads to a decrease in circulating estrogen throughout the body.[26] Estrogen receptors are spread throughout the brain. Some studies have shown that estrogen can promote neuron growth and provide neuroprotective activity, which raises the question of whether AIs may influence cognitive function. Some patients experience difficulty concentrating and forgetfulness. The main cognitive impairment is verbal episodic memory and executive impairments, suggesting that memory deficits are associated with estrogen suppression signaling.[27]

In dealing with cognitive dysfunction in breast cancer survivors taking AIs, PCPs should focus on awareness, education, and monitoring. Awareness involves recognizing risk factors for impaired cognitive function such as older age, lower educational attainment, psychological distress, diabetes, hypertension, fatigue, sleep problems, and poor general health.[28] Patients and their family members need education about the potential cognitive effects of cancer and AI use, which include problems in attention, memory, processing speed, and executive function. Patients and family members need to regularly monitor and report any observed difficulties with cognitive function to the PCP, who can then take further action if needed.[28]

More information about adjuvant endocrine therapy

Despite the proven benefits of adjuvant endocrine therapy, about 33% of patients do not take their medication as prescribed.[29] This lapse can raise the risk for breast cancer recurrence and death. Women who do not take their medication as prescribed or who discontinue it before completion of the fifth year may have a shorter disease-free interval, a reduced survival rate, increased healthcare costs, and a lower quality of life.[29]

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The American Society of Clinical Oncology recommends an extended duration of treatment in breast cancer survivors as follows: AIs for up to 10 years; tamoxifen for 2 to 3 years followed by an AI for 7 to 8 years; tamoxifen for 5 years followed by an AI for 5 years; or tamoxifen for 10 years.[30] Women placed on long-term endocrine therapy may experience ongoing adverse effects that

can affect their overall quality of life. As such, an individualized approach to treatment duration is best. Treatment decisions should be based on cancer status, risk for late recurrence, tolerability of therapy, and adverse effects of treatment. Women who have certain prognostic factors, such as nodal involvement, larger tumors, or other adverse prognostic features of the cancer would benefit substantially from extended endocrine therapy for 10 years. Women who have stage I disease with lower-risk features might consider discontinuing therapy after 5 years unless concern for contralateral and/or second breast cancer exists.[30]

Adjuvant endocrine therapy significantly improves long-term survival in patients diagnosed with hormone receptor–positive disease.[31] Several large randomized trials have shown AIs to be superior to tamoxifen with respect to disease-free survival in postmenopausal women who have been diagnosed with early-stage breast cancer.[31] Patients have an improved disease-free survival when AIs are initiated after 2 to 3 years of taking tamoxifen.[31]

HER2-targeted therapy

This article mainly covers adjuvant endocrine therapies, such as tamoxifen and aromatase inhibitors, but it is essential to offer a few words about HER2-targeted therapy. HER2-targeted therapy is recommended for women with breast cancers found to have HER2-positive gene amplification.[32] Targeted cancer drugs can block the growth and spread of cancer by interfering with certain target molecules responsible for the growth, spread, and progression of cancer. One limitation of targeted therapies is that cancer cells can become resistant to them. Resistance can occur when the target itself changes through a mutation (the therapy will no longer interact well with it) and/or the tumor finds a new pathway to grow that does not depend on the target. As such, targeted therapies work best in combination.[32]

Overexpression of the HER2 gene causes 15% to 30% of breast cancers.[33] HER2 is one of the human epidermal growth receptors that regulate cell growth, cell survival, and cellular proliferation and differentiation. HER2-positive breast cancers are typically more aggressive than other breast cancers and, in previous years, had a poorer prognosis.

Options for targeted treatment of HER2-positive breast cancer tumors include trastuzumab, pertuzumab, and trastuzumab emtansine, with other drugs in this class still being evaluated in clinical trials.[33] Trastuzumab is the most common first-line therapy. In 2017, neratinib was approved for patients with early-stage HER2-positive breast cancers following treatment with trastuzumab. Lapatinib, a tyrosine kinase inhibitor, may also be used after treatment with trastuzumab or other HER2 therapies.[33] HER2-positive breast cancer is more likely than HER2-negative cancer to metastasize to the brain and liver. Trastuzumab and pertuzumab appear to pass through the blood–brain barrier and reduce the size of the brain tumor metastases.[33] Duration of chemotherapy with these drugs is at least 6 months or until a maximum response occurs. In patients with metastatic HER2 positive cancers, HER2-positive targeted therapies may continue until the time of progression or unacceptable toxicities.[34]

Managing breast cancer survivor care

Many breast cancer survivors continue to see their oncologists, although this option is becoming more

difficult as the survivor population grows. As such, many survivors transition their care to the primary care setting.[35] WHNPs and other PCPs must address five key areas in breast cancer survivorship: surveillance for breast cancer recurrence, screening for second primary cancers, assessment and management of physical and psychosocial long-term effects of treatment, health promotion, and care coordination.

Primary care providers should individualize breast cancer follow-up based on each patient's age, specific diagnosis, and treatment protocol.[36] PCPs should inform and counsel breast cancer survivors about signs and symptoms of recurrence and screen for other cancers as they would for women in the general population. Survivors should be counseled on ways to reduce the risk for lymphedema. PCPs should help them deal with concerns with body image/appearance and advise them to maintain a healthy weight, exercise regularly, limit alcohol consumption, and quit smoking if applicable.[36]

For all breast cancer survivors, a history and physical examination should be performed every 3 to 6

months for the first 3 years, followed by every 6 to 12 months for an additional 2 years, and then annually thereafter. Women who have had a unilateral mastectomy should have a yearly mammogram of the contralateral breast for surveillance. Women who have undergone a lumpectomy should have an annual bilateral mammogram. PCPs should assess each patient's family cancer history and refer her for genetic counseling as needed. Genetic testing should be performed if a patient meets the appropriate criteria, which can help determine whether she is at risk for a hereditary cancer syndrome.[37]

Conclusion

As the number of breast cancer survivors increases, more and more of them will transition into the primary care setting for treatment. As such, WHNPs and other PCPs need to understand the rationale regarding adjuvant endocrine therapy and HER2-directed therapy. PCPs need to be aware of specific problems and concerns that affect breast cancer survivors and how to manage their care appropriately.

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(continued from page 12)

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