You Asked for It! CE
Advanced Breast Cancer Management: Clarifying Guidelines and the Community Pharmacist's Role

ABSTRACT: The treatment for breast cancer is based on two main factors: the stage of disease at diagnosis and the molecular assessment of the tumor. Hormonal therapy is a mainstay of treatment in early-stage disease and in advanced, metastatic breast cancer. The U.S. Food and Drug Administration has approved five classes of drugs that are incorporated into treatment guidelines for secondary prevention and for treatment of advanced, recurrent and metastatic breast cancer. Each of these classes is discussed in this continuing education unit. Overall, these drugs are well tolerated, but appropriate, early identification and management of side effects is critical to prevent polypharmacy and to achieve optimal outcomes. The community pharmacy team has a critical role in caring for patients with breast cancer. They must reinforce education about proper use of the hormonal therapy; identify side effects and recommend treatment appropriately; and identify and resolve potential drug-drug and drug-food interactions.

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INTRODUCTION
Breast cancer is the most common cancer diagnosed and leading cause of cancer-related death in women around the world. The cause of breast cancer is unknown but several risk factors have been identified, including female gender, increasing age, family history of breast cancer at a young age, early menarche, late menopause, late age at first childbirth, prolonged hormone-replacement therapy, previous exposure to chest irradiation, benign breast disease, increased mammographic density, and genetic mutations such as BRCA1/2 mutations. However, most of these risk factors, except age and female gender, explain only a small portion of breast cancers diagnosed. What this means is that most people diagnosed with breast cancer do not have significant or obvious risk factors. The treatment for breast cancer is based upon two main factors: the stage of disease at diagnosis and the molecular assessment of the tumor.
As with many solid tumor cancers, the stage of breast cancer is based upon the American Joint Committee on Cancer (AJCC) TNM Staging System. This staging system uses the size of the tumor, the presence of disease spread to lymph nodes, and the presence of disease spread to other areas of the body. Patients with smaller tumors and the presence or absence of diseased lymph nodes are typically treated with surgery with or without radiation therapy and adjuvant systemic treatment. Patients whose disease has spread beyond the lymph nodes are considered to have stage IV or metastatic disease, sometimes referred to as advanced breast cancer. These patients will only receive systemic therapy; for these patients, the disease has spread too far for radiation or surgery to be helpful.

Oncologists select the type of adjuvant systemic therapy for local disease (stages I-III) or systemic therapy for metastatic disease (stage IV) based on the molecular assessment of the tumor. Breast cancer is a molecularly diverse cancer and has three main therapeutic subgroups:

- Hormone-receptor positive (tumors that express estrogen receptors [ER], progesterone receptors [PR], or both but normal HER2 expression)
- HER2 positive (tumors with any HER2 gene amplification or overexpression even if some ER/PR+ present)
- Triple-negative breast cancers (those who have very low numbers or absence of hormone receptors and no HER2 alterations).

Worldwide, approximately 65% of breast cancers are hormone-receptor positive, 25% are HER2 positive, and 15% are triple negative.

In early-stage breast cancer, those with ER and/or PR positive disease should receive hormonal therapy following surgery with or without radiation therapy as adjuvant systemic therapy. They also need secondary prevention of breast cancer regardless of patient age, lymph node status, and whether or not chemotherapy is to be administered. Those with HER2 positive disease may not be as sensitive to the effects of hormonal therapy as secondary prevention, but at this time, patients with HER2 positive disease should still continue to receive hormonal therapy.

Systemic treatment of advanced or recurrent breast cancer prolongs survival and enhances quality of life, but is not curative. Therefore, treatments are aimed at providing minimal toxicity. The mainstay of treatment in these patients is the use of hormonal therapy. The exception might be in patients with symptomatic visceral disease (i.e., disease in their liver). In these patients with more symptomatic visceral disease, chemotherapy or HER2 directed therapy is more appropriate. For the most part, hormonal treatment includes use of orally administered medications that are available in retail pharmacies. Therefore, it is important for community pharmacists and pharmacy technicians to be familiar with the disease and treatment options to optimize care.

**Sidebar: Helpful Definitions**

**Adjuvant therapy:** The use of anticancer drugs after or in combination with another form of cancer treatment, as after apparently complete surgical removal of cancer cells. Adjuvant therapy is used when there is a significant risk that micrometastasis may still be present.

**Cell cycle:** The precise cycle of biochemical and morphological events occurring in a reproducing cell population:
- First, DNA is synthesized in the S phase
- Second, the cell enters the relatively quiescent G2 phase
- Third, the cell undergoes the four phases of mitosis in the M phase
- Last, the cell enters the G1 phase of interphase, which lasts until the S phase of the next cycle

**Clinical benefit:** All patients who respond partially, completely and who did not progress.

**Disease-free survival:** The period after successful treatment in which there is no appearance of the symptoms or effects of the disease.

**Intolerance:** The inability to tolerate the side effects of treatment, which may create a need to reduce doses, switch treatments, or stop treatment altogether.

**Ovarian suppression:** Treatment that stops or lowers the amount of estrogen made by the ovaries. Types of ovarian suppression include surgery to remove both ovaries, radiation therapy, and the use of certain drugs.

**QT prolongation:** The QT interval is a tracing on an electrocardiogram that tracks each heart beat; the portion called "the QT interval" tracks activity in the heart's lower chambers (the ventricles). A QT interval longer than 0.45 milliseconds is usually caused by treatment with anti-arrhythmic drugs, such as amiodarone and sotalol, or a number of other drugs. It can cause fainting, palpitations, or in severe cases, torsades de pointes and possibly death.

**Progression:** Cancer that continues to grow or spread.

**Secondary prevention:** The second level of prevention, provided at the earliest possible identification and treatment of cancer so that adverse sequelae (especially recurrence) can be prevented. (Contrast this to primary prevention, which is designed to prevent cancer from developing at all.)

**Tumor flare:** A temporary worsening in symptoms (e.g., pain, tumor size, redness around the tumor, or new lesions). Hormonal therapies can cause a "flare" reaction shortly after they are started. It may be a sign that the hormonal treatment is working and is often followed by a positive response. Clinicians should monitor patients closely the first few weeks after beginning treatment and manage side effects as needed.
Menopausal Status
The type of hormonal therapy selected depends on whether the patient is premenopausal or menopausal (Figure 1).

Premenopausal Women
More than 60% of breast cancers in premenopausal women are hormone-receptor positive. The main source of estrogen in premenopausal women is circulating estrogen from aromatization of exogenous and endogenous androgens. This is different from those who are postmenopausal, in whom circulating estrogen comes from peripheral estrogen production. Thus, the therapy directed at treatment of hormone-receptor positive breast cancer in pre- and postmenopausal women is different.

Women who are premenopausal will be treated with a hormone therapy and ovarian suppression (with use of a gonadotropin-releasing hormone [GnRH] analogue), as this combination has shown to improve overall outcomes when compared with single-agent hormonal therapy. Tamoxifen and ovarian suppression is the most well studied; however, the combination of aromatase inhibitor (AI) and ovarian suppression can be considered as first- or second-line treatment and in patients younger than 35 years old. These agents result in response in more than 60% of patients.

Limited data supports use of fulvestrant and ovarian suppression. Tamoxifen alone is still considered an option for those patients in whom ovarian suppression is not desired. For example, the American Society of Clinical Oncology (ASCO) guidelines recommend that women with small tumors (T1a or T1b) should not receive ovarian suppression. Furthermore, some women do not like the side effects of ovarian suppression and prefer to avoid it. However, outcomes are better with the combination.

Used as adjuvant or secondary prevention, five years of therapy is recommended. If after five years of tamoxifen therapy, the woman becomes menopausal, guidelines recommend considering an additional five years of AI therapy. When using for advanced or metastatic disease, guidelines recommend continuing hormonal therapy until progression or intolerance occurs. When progression occurs, switching to an alternative hormonal therapy with a different mechanism of action is reasonable.

Types of Hormonal Therapy
Table 1 lists the available hormonal therapies used to treat breast cancer, their common doses, appropriate administration, common side effects and monitoring, common drug and food interactions and patient counseling points. This next section, organized by drug class, describes each of the drugs in more detail.

Aromatase Inhibitors (AIs)
AIs decrease estrogen production by blocking the aromatase enzyme that converts androgens to estrogen in the peripheral tissue, such as the breast. The nonsteroidal AIs, anastrazole and letrozole, reversibly bind to aromatase; whereas exemestane, a steroidal AI, irreversibly binds to aromatase. AIs are a standard therapy in early breast cancer and are administered for five to ten years after surgery. In the metastatic setting, no randomized clinical trials have compared the three available AIs as first-line therapy. However, results from the studies show that efficacy and tolerability appear to be similar. In women with no prior hormonal treatment in the past 12 months, AI appear to produce better results than SERMs, providing a clinical benefit of 50% to 60%. In those with recurrent disease or who progressed on hormonal therapy, responses are similar to SERMs and estrogen receptor antagonists, with clinical benefits of 30% to 40%. The most common side effects are musculoskeletal symptoms, hot flashes, vaginal dryness, and an increase in loss of bone mineral density and bone fractures.
Cyclin-Dependent Kinases 4 and 6 (CDK4/6) Inhibitors

The CDK are a large family of serine threonine kinases that along with cyclins (regulatory proteins) assist orderly and controlled progression of the cell cycle in the G1/S transition phase. The cyclin/cyclin-dependent kinase/retinoblastoma pathway is often dysregulated in breast cancers. CDK4/6 inhibitors cause G1 arrest in sensitive cells. The first generation CDK inhibitors were nonselective, pan-CDK blocking agents and produced disappointing results in the treatment of breast cancer. However, the second-generation, selective CDK4/6 inhibitors have been shown to be effective, and they also have a synergistic effect with endocrine therapies. Three selective CDK4/6 inhibitors are commercially available at this time: abemaciclib, palbociclib, and ribociclib.

Both palbociclib and ribociclib are approved in combination with an AI as options as first-line treatment in hormone therapy-naïve patients with hormone-receptor positive, HER2 negative, advanced or metastatic breast cancer. Palbociclib is also approved in combination with fulvestrant for those who have progressed on hormonal therapy. Abemaciclib is also indicated for patients who have progressed on hormone therapy, and can be administered alone or in combination with fulvestrant.

When used as a first-line therapy, palbociclib and ribociclib in combination with letrozole, a clinical benefit rate of 68% to 80% is achieved. The combination of palbociclib and letrozole improved objective response rates by 11% and prolonged disease-free progression (DFS) by 10 months when compared with letrozole alone or placebo. Although not yet approved, abemaciclib in combination with either letrozole or anastrozole is also effective at improving outcomes compared with AI alone. Abemaciclib and an AI produce a clinical benefit rate of 78%, improve objective response rates by 15%, and improve disease-free survival rates (although median DFS rates were not reached at time of the publication) when compared with AIs alone. Abemaciclib and fulvestrant resulted in a 72% clinical benefit rate and improved response rates by 13% to 19% and DFS by five to seven months. Abemaciclib alone resulted in a 52% overall clinical benefit.

Unlike other hormonal therapies, CDK4/6 inhibitors cause reversible and noncumulative cytopenias, including anemia, leukopenia, neutropenia, and thrombocytopenia.

CDK4/6 inhibitors’ other common side effects include nausea, infection, fatigue, diarrhea, abdominal pain, and hair loss. Ribociclib is associated with hepatic toxicity, generally manifesting as rises in transaminases, and also QT prolongation. Venous thromboembolism (VTE) has also been reported in 5% of patients receiving abemaciclib and palbociclib. Both drug and food interactions occur with all three of these drugs. Table 1 provides detailed information about the types of interactions.

Gonadotropin-Receptor-Hormone (GnRH) Analogues

GnRH analogues block the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and sex steroids, such as estrogen and testosterone, through downregulation of the GnRH receptors and uncoupling of signal transduction pathways. Chronic administration of GnRH analogues initially causes an increase in FSH and LH levels and then eventually cause them to fall below castration levels. The initial rapid rise in FSH and LH levels causes a temporary elevation in estrogen. This in turn can result in a tumor flare, whereby the tumors respond to the rapid rise in estrogen and temporarily cause increased bone pain, swelling, or a release of calcium into the blood causing hypercalcemia. This flare resolves once the estradiol levels fall below castration levels. In premenopausal women, the reduction of hormone levels typically occurs within ten weeks and will result in amenorrhea. This castration and amenorrhea is reversible after GnRH analogue therapy cessation, although it may take months. Most commonly goserelin or leuprolide formulations are used. At this time, monthly doses are administered because the depot injections have not been fully investigated to confirm that estradiol suppression, safety and tolerability are similar to monthly injections. Clinicians should monitor FSH, LH, and estradiol levels regularly as amenorrhea is not a reliable marker for appropriate gonadotropin suppression.

Overall, most patients continue therapy with GnRH analogues despite experiencing some side effects. The side effects associated with GnRH analogues are a result of suppressed sex steroids. When used in combination with other hormonal therapies, these side effects are enhanced. Other than amenorrhea, hot flashes, depression, loss of sexual interest, insomnia, vaginal dryness, osteoporosis, myalgias, hypertension and glucose intolerance can occur. Studies comparing patients taking hormonal therapy alone versus combination of GnRH analogue with a hormonal therapy show that quality of life scores are no different between solo and combination treatments.

Pause and Ponder:
What is the impact of tumor flare in women treated with GnRH analogues, and how can you promote medication adherence?
### Table 1. Endocrine Therapies for Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
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<th>Drug &amp; Food Interactions</th>
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<tr>
<td><strong>Aromatase Inhibitors</strong></td>
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<tr>
<td>Anastrozole (Arimidex®)</td>
<td>1 mg po daily Take with or without food</td>
<td>□ Hot flashes, muscle weakness, musculoskeletal symptoms (arthralgia, myalgia)</td>
<td>□ Avoid estrogen, and tamoxifen</td>
<td>□ Women of reproductive potential should use effective contraception during therapy and for at least 4 weeks after the last dose</td>
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<tr>
<td>Exemestane (Aromasin®)</td>
<td>25 mg po daily Take after a meal</td>
<td>□ Hot flashes □ Monitor BMD</td>
<td>□ Avoid CYP3A4 inducers and estrogen-containing products □ Dose reduce if CYP3A4 strong inducers used concomitantly</td>
<td>□ Lactating women should not breastfeed while on aromatase inhibitors and for at least 4 weeks after the last dose</td>
</tr>
<tr>
<td>Letrozole (Femara®)</td>
<td>2.5 mg po daily Take with or without food</td>
<td>□ Hot flashes, muscle weakness, arthralgia, myalgia, hypercholesterolemia</td>
<td>□ None</td>
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<td><strong>Cyclin-Dependent Kinase 4/6 Inhibitors</strong></td>
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<tr>
<td>Abemaciclib (Verzenio®)</td>
<td>150 mg po BID (with fulvestrant) 200 mg po BID (single agent) Take with or without food No dose adjustment for renal or hepatic dysfunction</td>
<td>□ Diarrhea, neutropenia, nausea/vomiting, abdominal pain, infection, fatigue □ Monitor: CBC and LFTs and bilirubin at every 2 weeks for first 2 months, then monthly for 2 months, then as needed; VTE and PE throughout</td>
<td>□ Avoid strong CYP3A4 inducers and inhibitors □ Dose reduce abemaciclib with concomitant strong CYP3A4 inhibitor Avoid grapefruit and grapefruit juice</td>
<td>□ Signs and symptoms liver toxicity, neutropenia and neutropenic fever □ Avoid eating grapefruit and avoid drinking grapefruit juice □ Women of reproductive potential should use effective contraception during therapy and for at least 3 weeks after the last dose should have pregnancy test before treatment. □ Lactating women should not breastfeed while on cyclin-Dependent Kinase 4/6 Inhibitors and for at least 3 weeks after the last dose</td>
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<td>Goserelin acetate (Zoladex®)</td>
<td>□3.6 mg SC q 28 days Administer into the anterior abdominal wall below navel line □No dose adjustment for renal or hepatic dysfunction Reserved for premenopausal woman; use with AI or tamoxifen; depot versions should not be used because of unreliable LHRH suppression</td>
<td>□Hot flashes, headache, emotional lability, depression, acne vulgaris, decreased libido, vaginitis □Monitor hypercalcemia in those with bone metastases, BMD, abdominal wall bruising, blood glucose especially in those with diabetes</td>
<td>□None</td>
<td>□Menses return may be delayed after stopping therapy □Women of reproductive potential should use effective nonhormonal contraception during therapy and for at least 12 weeks after the last dose and should have pregnancy test before treatment □Lactating women should not breastfeed while on gonadotropin releasing hormone analogues</td>
</tr>
<tr>
<td>Leuprolide (Lupron®)</td>
<td>□3.75 mg IM q 28 days Administer into gluteal area, anterior thigh or deltoid □No dose adjustment for renal or hepatic dysfunction Reserved for premenopausal woman; use with AI or tamoxifen; depot versions should not be used because of unreliable LHRH suppression</td>
<td>□Hot flashes, headache, depression, insomnia □Monitor blood glucose especially in those with DM, QT interval in those with cardiac diseases, BMD</td>
<td>□None</td>
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### Mammalian Target of Rapamycin (mTOR) Inhibitors

Breast cancer patients frequently develop resistance to hormonal therapies. Activation of the mTOR pathway has been implicated as a method of resistance. Therefore, use of an mTOR inhibitor in combination with a hormonal therapy has been used in patients who are resistant to hormonal therapy. One available mTOR inhibitor, everolimus, has been used in combination with exemestane. Disease-free survival is prolonged from 4 months to 11 months with this combination. The side effects of this combination include stomatitis, infections, rash, pneumonitis, and hyperglycemia.

**PAUSE AND PONDER:** When a women hopes to become pregnant or is lactating develops breast cancer, what does the pharmacy care team need to consider?
Selected Estrogen Receptor Downregulator (SERD)

Fulvestrant is the only available selective estrogen downregulator available in the US. It is a pure estrogen receptor antagonist that competes with estrogen receptor and exerts selective estrogen receptor downregulation. This decreases the ER’s ability to activate or inhibit gene transcription. Its ER-binding capacity is 100 times greater than SERM’s. Fulvestrant is either administered as monotherapy or in combination with anastrozole as a first-line hormonal therapy or in combination with palbociclib, abemaciclib, or an AI as second- or higher-line therapy. Fulvestrant as first-line therapy improves DFS by 2 months and overall survival times by 6 months. In patients with relapsed or refractory disease, fulvestrant as a second-line therapy is reasonable as monotherapy or combined with abemaciclib or palbociclib. As described above in the CDK4/6 Inhibitor section, studies show a 72% clinical benefit rate with these combinations, response rates that improved by 13% to 19%, and DFS that was five to seven months longer.

Overall, fulvestrant is very well tolerated. When administered with anastrozole or alone, side effects occur in less than 10% of patients. The most common are injection-site reactions, nausea, bone pain, and arthralgia. When administered with palbociclib, side effects are more common but associated with the CDK4/6 inhibitor. Injection-site reactions can be minimized if

<p>| Table 1. Endocrine Therapies for Advanced Breast Cancer&lt;sup&gt;5-18&lt;/sup&gt; (continued from previous page) |</p>
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<td><strong>Selective Estrogen Receptor Modifiers</strong></td>
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<tr>
<td>Tamoxifen (Nolvadex®, Oltamox®)</td>
<td>□ 20 mg po daily □ Take with or without food □ No dose adjustments for renal or hepatic impairment</td>
<td>□ Hot flashes, vaginal discharge, fluid retention □ Monitor for new breast lumps, DVT, vaginal bleeding and annual gynecologic examination; periodic CBC and LFTs</td>
<td>□ No association between CYP2D6 subtype and outcome; but avoid drugs metabolized by CYP2D6 □ Avoid co-administration of AIs □ Avoid strong CYP3A4 inducers and inhibitors □ Avoid grapefruit and grapefruit juice</td>
<td>□ Signs and symptoms of endometrial cancer, DVT □ Women of reproductive potential should use effective nonhormonal contraception during therapy and for at least 2 months after the last dose □ Lactating women should not breastfeed while on tamoxifen and for at least 2 months after the last dose</td>
</tr>
<tr>
<td>Toremifene (Fareston®)</td>
<td>□ 60 mg po daily □ Take with or without food □ No dose adjustments for renal or hepatic impairment</td>
<td>□ Hot flashes, sweating, nausea, vaginal discharge □ Monitor K, Mg if CHF, hepatic impairment or electrolyte abnormalities; hypercalcemia if bone metastases, DVT, vaginal bleeding and annual gynecologic exam</td>
<td>□ Caution with drugs that decrease renal calcium excretion (eg, thiazide diuretics) as these drugs increase hypercalcemia in those with bone metastases □ Avoid QT prolonging agents; if needed closely monitor □ Avoid strong CYP3A4 inducers and inhibitors □ CYP2C9 substrate closely monitor levels (eg, warfarin)</td>
<td>□ Signs and symptoms of endometrial cancer, DVT □ Women of reproductive potential should use effective nonhormonal contraception during therapy and for at least 1 month after the last dose □ Lactating women should not breastfeed while on toremifene and for at least 1 month after the last dose</td>
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ABBREVIATIONS: BID, twice daily; BMD, bone mineral density; CBC, complete blood count; CHF, congestive heart failure; CYP, cytochrome P450; DM, diabetes mellitus; DVT, deep venous thrombosis; IM, intramuscular; K, potassium; LFT, liver function tests; Mg, magnesium; PE, pulmonary embolism; po, orally; SC, subcutaneous; VTE, venous thromboembolism.
Bone loss is less with SERMs than with AIs. In the rare cases of bone loss, the real reason is due to suppressed estrogen levels, the amount of deep venous thromboembolism (DVT). Although bone loss can be effective in treating cancer; it has only been proven effective in prevention of breast cancer in high-risk patients. SERMs bind to the estrogen receptor and ultimately inhibit receptor-mediated gene transcription, blocking estrogen’s effects on the body. However, they are tissue selective in their actions on the estrogen receptors; they have agonistic and antagonistic activity, depending on the tissue. For example, they have antagonist action on breast tissue but partial agonist activity on bone and uterus. The agonist effect on the bone is a positive effect because estrogen stimulates bone formation rather than the usual bone destruction that happens during menopause. However, the agonist effect on the uterus causes overstimulation on uterine cells, resulting in abnormal cell development, such as endometrial cancer.

Tamoxifen is one of the most firmly established therapies for treatment of early-stage breast cancer in both pre- and post-menopausal women, decreasing annual recurrence odds by 39%. Guidelines recommend patients receive at least five to ten years of tamoxifen therapy in early-stage disease. When a patient relapses or is diagnosed with metastatic breast cancer, tamoxifen or toremifene can be used. Tamoxifen tends to be the preferred agent if a SERM is selected because of clinicians’ familiarity with this drug. Both produce an overall clinical benefit of 30% to 50%.

Tamoxifen’s and toremifene’s side effects are similar to that experienced during menopause, with hot flashes, night sweats, vaginal dryness and bleeding/discharge as the most common side effects. Rare side effects include endometrial cancer and deep venous thromboembolism (DVT). Although bone loss can occur because of suppressed estrogen levels, the amount of bone loss is less with SERMS than with AIs. Nonetheless, guidelines recommend routine bone mineral density monitoring and regular annual gynecologic examinations. Tumor flare and hypercalcemia can occur, particularly in patients who have a large volume of disease and bone metastases, respectively. Tumor flare occurs in about 5% of women, but does not require discontinuation. Instead, prompt treatment is necessary.

Drug interactions are also important to consider in orally administered anti-cancer therapies.

The cytochrome P-450 enzyme CYP2D6 is involved with the conversion of tamoxifen to endoxifen. Conflicting evidence surrounds whether extensive metabolizers (those with wild type CYP2D6 alleles) have the same outcomes. At this time, guidelines do not recommend testing patients routinely for this genetic mutation. However, prescribers should avoid prescribing and pharmacists should monitor for concurrent drugs known to inhibit CYP2D6, however. Examples include paroxetine and fluoxetine, which are often used to treat hot flashes and/or depression in women.

**Selective Estrogen Receptor Modifiers (SERM)**

Three SERMs are available in the US: first-generation SERMS, tamoxifen and toremifene and the sole second-generation SERM, raloxifene. However, raloxifene has not been shown to be effective in treating cancer; it has only been proven effective in prevention of breast cancer in high-risk patients. SERMs bind to the estrogen receptor and ultimately inhibit receptor-mediated gene transcription, blocking estrogen’s effects on the body. However, they are tissue selective in their actions on the estrogen receptors; they have agonistic and antagonistic activity, depending on the tissue. For example, they have antagonist action on breast tissue but partial agonist activity on bone and uterus. The agonist effect on the bone is a positive effect because estrogen stimulates bone formation rather than the usual bone destruction that happens during menopause. However, the agonist effect on the uterus causes overstimulation on uterine cells, resulting in abnormal cell development, such as endometrial cancer.

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**Supportive Therapy: Bone Metastases**

Bone is one of the common sites of metastases in breast cancer, and when present, make the patient at higher risk of complications. Medications that target osteoclast activity have been proven beneficial in preventing skeletal-related events (SREs), including bone fractures, bone pain requiring radiation therapy, spinal cord compressions, and hypercalcemia. Available medications include bisphosphonates and RANK-ligand inhibitors. These agents should be used in women with bone metastases, especially if lytic lesions occur in weight-bearing bones and if expected survival is greater than three months.

Several randomized trials have evaluated bisphosphonates in patients with metastatic breast cancer. US trials have evaluated pamidronate and zoledronic acid. In each study, bisphosphonates have been shown to decrease SREs but no impact on overall survival times have been reported. Some studies have demonstrated zoledronic acid superiority to pamidronate in patients with lytic lesions. Pamidronate is dosed at 90 mg infused intravenously over 90 minutes, and zoledronic acid at 4 mg intravenously infused over 15 minutes. Typically, these doses are administered every three to four weeks for up to 2 years. However, recently a phase III study of zoledronic acid in women with breast cancer demonstrated that the rate of SREs did not differ when zoledronic acid was administered every 12 weeks or every 4 weeks. Furthermore, longer durations of bisphosphonates have been associated with no increase in toxicity. Both of these drugs do require serum creatinine monitoring before each dose and dose adjustment, and discontinuation in the presence of renal dysfunction.

Denosumab, a RANK-ligand inhibitor, is also an option in women with bone metastases. One non-inferiority randomized trial compared denosumab (120 mg IV q 4 wk) with zoledronic acid (4 mg IV q 4 wk) in women with metastatic breast cancer. All patients also received calcium and vitamin D supplementation. Denosumab was shown to be noninferior to zoledronic acid in delaying the time to the first and subsequent SREs. Adverse events were similar, and the optimal duration is unknown.

For both agents, calcium (1200-1500 mg/day) and vitamin D (400 to 800 international units/day) supplementation should be used concurrently. Clinicians should monitor serum calcium, magnesium, and phosphorous levels at baseline and throughout therapy to ensure prompt treatment of hypocalcemia, hypomagnesemia, and hypophosphatemia. All patients should undergo a dental examination and have required preventative dental procedures performed before starting either agent to reduce risk of the rare side effect of osteonecrosis of the jaw.
ENDOCRINE REFRACTORY PATIENTS
In patients who are hormone refractory—that is, they progress while on or within 12 months of stopping hormonal therapy—an additional type of hormonal therapy can be used successfully for further treatment. This is especially true if they have bone or soft tissue only metastases or asymptomatic visceral disease. For example, if a patient on an aromatase inhibitor progressed while on therapy, using palbociclib or abemaciclib + fulvestrant may be option. Or, a SERM or selective estrogen downregulator, or exemestane and everolimus are alternatives. Switching to another hormonal therapy can occur up to twice before the patient is considered hormone refractory. If the patient has visceral disease that is symptomatic, then systemic chemotherapy or HER2 directed therapy is indicated based on the patient’s HER2 status.

MANAGING SE OF HORMONAL THERAPY

Bone Loss
AI-associated bone loss is marked, with a 2- to 4-fold increase in bone loss compared with the bone loss experienced during the postmenopausal period. Therefore, patients are at high risk for fractures during therapy. In patients who have bone metastases, bone-modifying agents are recommended (see above) to prevent skeletal-related events. In those without bone metastases, evaluation of bone health is needed before therapy is initiated and throughout therapy. Both a physical exam and history is required to identify clinical risk factors for osteoporosis (eg, smoking, excessive alcohol, physical inactivity, and poor nutrition). Bone mineral density (BMD), using a dual energy x-ray absorptiometry (DEXA) scan of the lumbar spine and hip are also performed. If low BMD (T score below -2.5) is identified, other causes should be ruled out. It is prudent to have each woman, regardless of BMD result, consume 1200 mg and 800 international units of calcium and vitamin D each day and to increase weight-bearing physical activity. For those with no other causes of low BMD or history of fragility fracture, then pharmacologic therapy with a bisphosphonate or RANK-ligand should be initiated. Available drugs include alendronate 70 mg po weekly, risedronate 35 mg po weekly, zoledronic acid 4 mg intravenously (IV) every 6 months or 5 mg IV yearly or denosumab 60 mg subcutaneously every 6 months. During therapy, BMD should be measured every 2 years. Note that doses of bisphosphonates and RANK-L inhibitors used to prevent SREs are different than those used when treating SREs.

Although bone loss can occur with tamoxifen as well because of the suppressed estrogen levels, the amount of bone loss is less with SERMs compared with AIs. Nonetheless, routine BMD monitoring is a good idea.

Cytopenias
Cytopenias are an on-target effect of the CDK4/6 inhibitors, as CDK6 is responsible for promotion of hematologic precursor proliferation. In many cases, grades 3 or 4 neutropenia are dose-limiting and require dose adjustments and supportive care. However, febrile neutropenia is uncommon. This has been attributed to the fact that the bone marrow progenitor cells affected by CDK4/6 inhibitors are functional, unlike those affected by chemotherapy agents which die. The median time to onset of neutropenia is 15 days, (range 13-117 days), thus the intermittent dosing of these agents, often allows recovery between cycles. Complete blood counts with differential should be done at baseline, every 2 weeks during first 2 cycles and then at beginning of each subsequent cycle. Dose modifications are provided in the package inserts of each drug.

Endometrial Cancer
Prolonged use of tamoxifen is associated with endometrial cancer. Endometrial cancer can also occur with toremifene, but because this drug is not used as often, the incidence of endometrial cancer is not known. Endometrial cancer is more...
common in those women over age 50. Clinicians should instruct women to report any abnormal bleeding, discharge or spotting to their healthcare provider immediately. Women who take tamoxifen need regular annual gynecologic examinations.

Hepatic Dysfunction
Ribociclib is associated with hepatic toxicity, generally manifesting as rises in transaminases. In the pivotal MONALESSA-2 trial, grade 3 or 4 enzyme elevations occurred in 15% of patients, with the median time to onset of 57 days. Thus, monitoring is needed throughout therapy (see Table 1). This effect has also been observed with abemaciclib but not palbociclib.

Hot flashes
Hot flashes are the most common side effects associated with all of the hormonal agents except CDK4/6 inhibitors. They are five times more likely in breast cancer patients than women undergoing menopause. Breast cancer patients often complain about these recurring, transient episodes of flushing and sweating (often followed by chills). Accompanying anxiety can have significant impact on their quality of life. Little information has been published about the duration of hot flashes. It isn’t surprising then that women often seek treatment for hot flashes.

Most treatments are based upon affecting the physiology of the hot flashes. The decline in estrogen may affect the thermoregulatory system but the correlation of estrogen levels and hot flashes is poor, suggesting other mechanisms may be present. Neuroendoctrine pathways have also been implicated in the regulation of core body temperature and may involve complex interactions of neuromodulators (norepinephrine, serotonin), hormones (estrogen, testosterone), and endorphins.

Nonpharmacologic treatments are always preferred adding pharmacologic therapy. Lifestyle changes, such as dressing in layers, and using cotton clothing and bedding and fans and cooling aids can be helpful. Reducing alcohol use, smoking and caffeine can also help. If these are not successful after a two-week trial, then offering a 4-week trial of relaxation and paced respiration exercises is recommended.

When nonpharmacologic therapies fail, clinicians may prescribe a selective serotonin receptor inhibitor (SSRI) or selective norepinephrine receptor inhibitor (SNRI). Venlafaxine (37.5-75 mg po daily) and citalopram (20 mg po daily) can be used. It is important to note that these medications must be tapered when they are discontinued. Also, some SSRIs, particularly fluoxetine and paroxetine, can interact with tamoxifen by decreasing formation of endoxifen, 4-OH tamoxifen, an active metabolite of tamoxifen. This may impact tamoxifen’s efficacy. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. Alternatives to SSRIs/SNRIs include oxybutynin (2.5-5 mg po daily to BID), gabapentin (100-300 mg po TID) and clonidine (0.5 mg po BID). Caution should be used when considering herbal or complimentary alternative medications.

Although many are advertised to relieve hot flashes, they often contain estrogen or compounds that contain estrogen. These might decrease or negate hormonal therapies’ effects on breast cancer.

Musculoskeletal Effects
Musculoskeletal symptoms include joint and muscle aches that are often symmetrical; associated with early-morning stiffness and difficulty sleeping; and can occur in up to 50% of patients receiving AIs. Most commonly, the hands, feet, shoulders, lower back, and knees are affected. The presence of tenosynovial changes or intra-articular fluid has been documented in some patients. Most often these side effects occur during the initial months of therapy. They are often troublesome for patients and have resulted in suboptimal adherence in 20% to 30% of patients during their first year of treatment. Thus, patients often desire treatment for these symptoms. Acupuncture, exercise, and the use of complimentary alternative medications, such as soybean, have been used. Unfortunately, the quality of evidence of these studies is not strong, so no one treatment option is recommended. Exercise is often recommended based on positive results from one randomized trial. While other trials did not find a positive effect, the overall positive effects with exercise on general health make it a worthwhile treatment option. In fact, it is important to be careful of complimentary alternative medications because many of them contain estrogenic substances, which may impact the effectiveness of the AI therapy.

QT Prolongation
QT prolongation is a heart rhythm that can potentially cause fast or chaotic heartbeats and can be fatal. Patients receiving ribociclib must have their QT intervals assessed at baseline and during therapy. Prolongations of the QT interval of more than 60 milliseconds from baseline occur in approximately 3% of patients. This effect has not been reported with the other two CDK4/6 inhibitors. See Table 1 for specific monitoring instructions. QT prolongation has also been reported with leuprolide and toremifene and clinicians should consider monitoring patients receiving these drug and avoid other drugs that prolong the QT interval (see Table 2).

Table 2. Common non-cancer drugs known to prolong QT interval

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone, quinidine, sotalol</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Clarithromycin, ciprofloxacin, erythromycin, fluconazole, itraconazole, ketoconazole, levofloxacin, moxifloxacin</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, desipramine, imipramine, doxepin, fluoxetine, sertraline, venlafaxine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol, citalopram, risperidone, ziprasidone</td>
</tr>
<tr>
<td>Others</td>
<td>Cisapride, methadone, sumatriptin, zolmitriptan</td>
</tr>
</tbody>
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**COMMUNITY PHARMACIST’S ROLE**

The community pharmacy team often sees the patient more frequently than the breast cancer team because they dispense other medications and provide counseling and recommendations on over-the-counter (OTC) medications. Thus, it is vital for community pharmacists and technicians to also be knowledgeable about common hormonal treatments that these patients will receive for prolonged periods. They may have the most impact on assisting patients achieve optimal outcomes.

**Venous Thromboembolism**

VTE has been reported in 5% of patients receiving abemaciclib and palbociclib.\(^9,26\) Higher rates of deep venous thromboembolism (DVT), pulmonary embolism (PE), and stroke have been reported with prolonged use of tamoxifen. Thus, patients with a history of thrombotic event or disorder should not receive abemaciclib, palbociclib, ribociclib, or tamoxifen if alternative agents can be used. Furthermore, prescribers should consider alternative therapies or possible VTE prophylaxis in patients with risk factors for VTE. The National Comprehensive Cancer Network Guidelines for Venous Thromboembolism provide excellent guidance on which patients should receive prophylaxis and appropriate regimens, which may differ from those used in the non-cancer population.\(^51\) The community pharmacist team must be aware of signs of symptoms of VTE and direct patients for immediate attention if these are present. Common signs/symptoms of a DVT include pain, unilateral edema of a limb, and a feeling of heaviness in that area; edema of the face, neck, or supraclavicular space; and/or unexplained cramping. Signs and symptoms of PE include unexplained shortness of breath, chest pain, tachycardia, apprehension, tachypnea, syncope, and hypoxia. Stroke signs and symptoms include face drooping, arm weakness, speech difficulty but also difficulty walking or with coordination, blurred vision, or visual changes. If you witness a person with any signs of a stroke or PE, call 911 immediately. Refer patients with signs/symptoms of a DVT to their doctor immediately for further evaluation.

More than likely the patient may seek advice about OTC medications to alleviate some symptoms. Understanding the side effects and proper management can be critical for these patients to remain adherent and achieve the best possible outcomes. The community pharmacist can also help patients and/or caregivers understand the importance of adherence.

This is critical when patients have complex dosing schedules, which can be difficult for the patient to follow without appropriate education and healthcare provider support. Furthermore, patients are responsible for identifying and reporting side effects between clinic visits so the breast cancer team can provide optimal management. Having a thorough understanding about how to identify and report side effects is important for pharmacists. The community pharmacist can reinforce the education that is needed for patients to identify side effects and report them immediately.

Many of these hormonal agents are associated with drug–drug and drug–food interactions. The community pharmacist can identify these and contacting the healthcare provider to avoid use of interacting drugs, instruct patients to not use OTC medications that may interact, and counsel on how to best take this medication in relation to food.

**CONCLUSION**

Hormonal therapy is a mainstay of treatment in early-stage disease and in advanced, metastatic breast cancer. Overall, these drugs are well tolerated, but appropriate and early identification of management of side effects is critical to prevent polypharmacy and to achieve optimal outcomes. The community pharmacy team can play a critical role in caring for patients with breast cancer by reinforcing education about proper use of the hormonal therapy, identifying and appropriately recommending treatment of side effects, and identifying and resolving potential drug–drug and drug–food interactions.
REFERENCES