A Review of Common Oral Treatments for Breast Cancer: Improving Patient Safety in Nononcology Settings

What nononcology nurses need to know.

ABSTRACT: Breast cancer patients are living longer with the disease than ever before. According to the National Cancer Institute, more than 3 million women in the United States are currently living with a breast cancer diagnosis, and many seek care in nononcology settings, whether for treatment, acute symptoms and complaints related to their cancer diagnosis, or unrelated concerns. Yet many nononcology providers are unfamiliar with the various oral agents used to treat breast cancer, and their possible adverse effects and drug interactions. It is imperative that all providers be aware of these agents and know when a patient is currently taking or has taken them. This article provides an overview of the most common oral treatments for breast cancer and discusses common adverse effects and management.

Keywords: breast cancer, drug therapy, management, oral treatment, patient safety

Loretta Panko, a 72-year-old retiree, arrives for her annual examination with her gerontology NP. (Both this case and the one following are composites based on our experience.) The results of Ms. Panko's bone density evaluation indicate that she has osteoporosis. The NP considers which medical intervention is most appropriate for managing this condition. The patient had breast cancer three years ago. Should this history affect the NP's decision?

Ella Whalen, a 58-year-old bank manager, has metastatic breast cancer that has spread to her bones. She is being treated with palbociclib (Ibrance) and letrozole (Femara); she has been stable for the last 18 months on this regimen and continues to work full time. Her employer requires regular employee

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wellness assessments. After assessing Ms. Whalen, the wellness nurse plans to offer her a tetanus booster and the shingles vaccine. Are these recommendations appropriate? Could they pose undue risks to this patient's health?

These are just two examples of situations that may arise in a variety of health care settings. Breast cancer patients are living longer than ever with the disease, and many frequently receive treatment from nononcology providers. They need to be able to trust that care recommendations are based on sound knowledge. But nononcology providers aren't often sufficiently aware of the complex issues these patients face and may not be prepared to address their unique needs. This article will help nononcology nurses in any setting to identify essential information and know what questions to ask when they encounter breast cancer patients in their practice. It provides an overview of the most common oral treatments for breast cancer, describes common adverse effects and suggested management, and discusses other considerations for patients taking these agents.

BACKGROUND

Although the number of newly diagnosed breast cancer cases has remained fairly stable over the last 25 years, death rates are declining.[1,2] According to the National Cancer Institute, more than 3 million women in this country are currently living with a breast cancer diagnosis, including an estimated 180,000 with metastatic disease.[1] (The vast majority of all breast cancers occur in women; less than 1% occur in men.) Since 1985, the overall five-year relative survival rate for those diagnosed with breast cancer has climbed from 78% to 91%.[1] As these patients age, their medical needs become more complex than those of their healthy counterparts.

Breast cancer patients seek care from nononcology providers, including RNs and NPs, in a variety of settings for a multitude of reasons. They may present to the ED for cardiovascular issues, respiratory distress, fever, pain, dehydration, infection, or sepsis. They may see nononcology providers for annual wellness checks, treatment of comorbidities, and monitoring for recurrence of cancer.[3] It's also worth noting that an estimated 11% of patients in assisted living facilities and 4% of patients in home care are living with a cancer diagnosis (of all types).[4]

Before 2005, patients with breast cancer were limited to two oral treatment options, which were indicated only in patients with estrogen receptor–positive or progesterone receptor–positive (ER/PR-positive) disease. During the last decade, that number increased fivefold: at this writing, 10 oral treatments for breast

cancer have been approved by the U.S. Food and Drug Administration (FDA). (This article discusses nine of these drugs. The 10th, etoposide, is used less frequently; it's only used to treat metastatic breast cancer after other agents have been used and become ineffective.) Several additional therapies are currently being assessed in phase 3 trials and many more are in earlier phases of clinical development.[5] The rising use of oral treatments has added further complexity to the management of oncology patients.

Nononcology providers play an active role in managing treatment-related adverse effects. One study found that nononcology providers prescribed more analgesics, antiinfective agents, corticosteroids, dermatologic agents, gastrointestinal agents, and psychotropics for patients with active breast cancer diagnoses than they did for patients without cancer.[6] Other studies indicate that many cancer patients are prescribed antidepressants.[7,8] It's also been reported that 33% to 50% of oncology patients use herbal or "alternative" medicines, often without their physician's knowledge.[9,10] Cancer patients are at increased risk for drug–drug interactions because their treatment commonly involves multiple medications. Not all such interactions are predictable or even avoidable. But to lower the risk of adverse events, it's essential that nononcology providers be aware of which anticancer drugs their patients are taking and know their potential adverse effects and possible interactions.

AROMATASE INHIBITORS

Drugs in this class include anastrozole (Arimidex), exemestane (Aromasin), and letrozole.

Indications. Aromatase inhibitors are frequently used as adjuvant endocrine therapy in treating ER/PR-positive breast cancer and metastatic ER/PR-positive breast cancer in postmenopausal women.[11] The enzyme aromatase is involved in producing estrogen after estrogen production from the ovaries decreases; inhibitors of aromatase work by interfering with its action. For patients with early-stage breast cancer, aromatase inhibitor treatment is initiated after primary treatment (surgery, with or without chemotherapy and radiation) and is continued for five years. New research suggests that continuing treatment for 10 years may provide more benefit in decreasing the rates of recurrence.[12] For patients with metastatic breast cancer, aromatase inhibitors are continued through the progression of disease. If one aromatase inhibitor stops being effective, others within the class can be used as subsequent lines of therapy.

Common adverse effects and management. Common adverse effects of aromatase inhibitors include those consistent with estrogen deprivation during menopause, such as hot flashes (13% to 36%), vaginal dryness (4% to 32%), and headaches (4% to 13%), which are typically mild.[13-17] Aromatase inhibitors are also known for causing musculoskeletal symptoms, including arthralgias (15% to 59%) and myalgias (5% to 9%),[13,15-17] as well as decreased bone density (4% to 14%).[13,16-21] Decreased bone density can be compounded by bone loss resulting from premature ovarian failure related to chemotherapy.[22] Aromatase inhibitors have also been linked to hypercholesterolemia (9% to 52%), but data are lacking regarding risk of cardiovascular disease.[13,16,17,20,23]

Certain adverse effects of aromatase inhibitors mimic signs and symptoms of menopause. Some are readily manageable with lifestyle modifications (such as avoiding caffeine and alcohol to lessen hot flashes) or over-the-counter agents (such as nonhormonal moisturizers for vaginal dryness or antiinflammatories for arthralgias). Bone loss and hypercholesterolemia can have more serious health implications (such as increased risk of fracture and of cardiac events, respectively) and must be monitored and managed.

Patients treated with curative intent (as opposed to palliative intent) with an aromatase inhibitor should have a dual-energy X-ray absorptiometry (DXA) scan at menopause and every 24 months thereafter. If significant bone loss is seen or a major medical intervention has been initiated, then obtaining a follow-up DXA scan at 12 months "is reasonable."[22] Similarly, patients should undergo periodic monitoring of their lipid levels and should be started on lipid-lowering drug therapy as needed.[24] Such routine screenings and management are well within the scope of practice for nononcology providers. For patients with metastatic disease, decisions about whether such screenings are warranted in a given case are best left to the oncology team.

Drug interactions. Few drug–drug interactions are associated with aromatase inhibitors. That said, dosing modifications may be necessary in patients who also take the herbal supplement St. John's wort, as St. John's wort is a cytochrome P-450 (CYP) 3A4 inducer. (CYP inducers increase drug metabolism, thereby decreasing drug concentration; inhibitors

Table 1. Common CYP3A4 Inducers and Inhibitors[25,26,a]

	Inducers	Inhibitors
Strong	phenobarbital phenytoin (Dilantin, Phenytek) rifampin (Rifadin) St. John's wort	clarithromycin (Biaxin) ketoconazole, systemic nefazodone voriconazole (Vfend)
Moderate	efavirenz (Sustiva) etravirine (Intelence) nafcillin	atazanavir (Reyataz) fluconazole (Diflucan) grapefruit juice verapamil (Verelan and others)

CYP = cytochrome P-450.
[a]This list is not all-inclusive. Possible drug–drug interactions should be checked on a case-by-case basis.

decrease drug metabolism and can increase drug concentration.) For example, the manufacturer of exemestane recommends increasing the recommended dose from 25 mg per day to 50 mg per day in patients concurrently taking St. John's wort.[17] Dosing modifications may be necessary in the presence of other CYP3A4 inducers as well (see Table 1[25,26]). Where increased dosing isn't advisable, avoidance of CYP3A4 inducers is recommended.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Drugs in this class include tamoxifen (Soltamox) and raloxifene (Evista).

Indications. Selective estrogen receptor modulators (SERMs) were the first targeted oral therapies for breast cancer, with tamoxifen as the initial drug. Raloxifene, a second-generation SERM primarily indicated for the treatment of osteoporosis, is also approved for the prevention of breast cancer in postmenopausal, high-risk patients.[27] SERMs bind to estrogen receptors in cells, preventing estrogen from binding and thus blocking cell growth in cancers fueled by estrogen.

Tamoxifen is approved for the treatment of ER/PR-positive breast cancer in pre- and postmenopausal women (and in men) following primary treatment, prevention of breast cancer in high-risk patients, and treatment of ER/PR-positive metastatic breast cancer.[28] But since the development of aromatase inhibitors, tamoxifen is no longer the first line of treatment in postmenopausal women, except when the adverse effects of aromatase inhibitors contraindicate their use.[29]

Common adverse effects and management. Common adverse effects of SERMs include those consistent with estrogen deprivation, as with aromatase inhibitors, and they are managed in the same fashion. Hot flashes constitute the most common complaint among patients (19% to 80%).[30] Research indicates that breast cancer survivors tend to experience more severe hot flashes than healthy women, and that those with more severe hot flashes report a poorer overall quality of life.[31] The frequency and severity of hot flashes can be reduced with the concomitant use of the antidepressant venlafaxine, a selective serotonin–norepinephrine reuptake inhibitor.[32] Other antidepressants are effective in managing hot flashes but are more likely to interact with tamoxifen.

More severe adverse effects of SERMs tend to be seen in postmenopausal women, and include increased risk of endometrial proliferation and adenocarcinoma.[33] While baseline assessment and screening of the endometrium isn't indicated, postmenopausal women who experience irregular menstrual bleeding during treatment should be assessed either with endometrial biopsy or transvaginal ultrasound, as indicated.[34]

Women who are on SERMs also have slightly elevated risks of venous thromboembolism (about 1%), pulmonary embolism (less than 1%), and stroke (less than 1%).[30] Patients experiencing new-onset dyspnea, swelling of the extremities, or other symptoms consistent with emboli or stroke should be immediately evaluated. Patients for whom surgery is planned should confer with their oncology team to determine whether temporarily stopping these agents is necessary.

Drug interactions. Significantly more drug–drug interactions arise with SERMs than with aromatase inhibitors. For drugs in this class, the most well-known interactions occur between tamoxifen and CYP2D6 inhibitors such as paroxetine (Paxil and others). Strong CYP2D6 inhibitors have been found to decrease the plasma concentration of tamoxifen by 23% to 71%, thereby decreasing the drug's efficacy and increasing the risk of disease recurrence or progression.[35,36]

Furthermore, cross-resistance is possible with SERMs; that is, patients who have been on one SERM in the past have a significantly lower likelihood of response to treatment with another SERM.[37,38] And because raloxifene is also used to treat osteoporosis, there is a greater risk of inadvertent therapeutic duplication.[39]

One interaction has been reported to occur only with raloxifene. In one case study involving a patient with hypothyroidism, raloxifene was found to interfere with the absorption of the thyroid hormone replacement drug levothyroxine (Synthroid).[40] Patients taking both agents should be advised to separate ingestion by 12 hours to mitigate the risk of interaction.[40] Every effort should be made to avoid these drug combinations. For more on drugs with SERM interactions, see Table 2.[41]

Table 2. Commonly Prescribed Agents with SERM Interactions[41, a]

• bupropion (Wellbutrin and others)
• cinacalcet (Sensipar)
• citalopram (Celexa)
• fluoxetine (Prozac, Sarafem)
• paroxetine (Paxil and others)
• ritonavir (Norvir)
• thioridazine

SERM = selective estrogen receptor modulator.
[a]This list is not all-inclusive. Possible drug–drug interactions should be checked on a case-by-case basis.

ANTINEOPLASTIC AGENTS

Drugs in this class include capecitabine (Xeloda).

Indications. Capecitabine is the only oral chemotherapeutic agent approved by the FDA for breast cancer treatment, and it is only indicated in patients with metastatic disease.[42] It works by inhibiting DNA

synthesis and causing apoptosis, and is taken until disease progresses or adverse effects become intolerable.

Common adverse effects and management. The most common adverse effects experienced by patients on capecitabine include diarrhea (12% to 67%) and the dermatologic condition known as hand–foot syndrome (11% to 63%).[43,44] Diarrhea is managed with the traditional low-fiber, bland diet, incorporating foods such as bananas, rice, applesauce, and toast and eliminating potential irritants such as strong spices and dairy products. Increased fluid intake is recommended. Patients usually experience uncomplicated diarrhea that is well controlled with diet modifications and early initiation of loperamide (Imodium). Patients with complicated diarrhea should be assessed for infections such as *Clostridium difficile* and may require more aggressive management with antibiotics.[45]

Hand–foot syndrome involves excessive dryness and reddening or darkening of the palms of the hands, the soles of the feet, or both.[46] Patients can use topical creams, emollients, and cool compresses or soaks to alleviate symptoms, and should avoid constrictive clothing, ill-fitting footwear, and prolonged exposure to temperature extremes.[46-48] Patients may also benefit from the use of topical antihistamines.[46] In more severe cases, hand–foot syndrome may progress to painful edema and blistering or cracking of the skin. In such cases treatment interruption, dose reduction, or discontinuation of therapy may be required.[46]

Drug interactions. Capecitabine should not be given concurrently with the anticoagulant warfarin (Coumadin). When taken together, increases in the international normalized ratio and exaggerated anticoagulant activity can occur.[44] Capecitabine also interacts with the antiepileptic agent phenytoin (Dilantin, Phenytek), causing increased serum concentrations of phenytoin that can lead to toxicity.[44]

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

Mammalian target of rapamycin (mTOR) is a protein that regulates cell growth and proliferation; mTOR inhibitors interfere with its action. Drugs in this class include everolimus (Afinitor).

Indications. In breast cancer patients, everolimus is approved for use in combination with exemestane for the treatment of metastatic ER/PR-positive disease. This combination works by creating a dual blockade in the cell growth process: first exemestane interferes with estrogen production, and then everolimus blocks the mTOR pathway.[49]

Common adverse effects and management. The adverse effects of everolimus are unique compared with those of other oral treatment agents. Oral mucositis and rash are the most common, with incidences of 50% to 80% and 36% to 50%, respectively.[50] Onset occurs shortly after treatment initiation, and dose interruption may be necessary, although toxicity tends to plateau after seven to eight weeks of therapy.[51] Oral mucositis manifests as aphthous lesions that have grayish centers and red borders. Treated early, these respond well to topical steroids such as dexamethasone rinses and clobetasol creams.[52,53] Rash presents primarily on the trunk and face, and is acneiform or maculopapular.[50] Preventative measures include washing the skin with mild soaps and using topical moisturizers.[54] It's important to note that this rash is not a sign of hypersensitivity, and treatment is focused on symptom palliation.

Less common but more severe adverse effects include noninfectious pneumonitis (19%), treatment-induced hyperglycemia (11% to 16%), and severely elevated liver function test results (4%).[49-51,55] Nononcology providers can help patients to optimize glycemic and lipid control before the initiation of oral treatment for breast cancer. It's also important for nononcology providers to be aware that some symptoms of breast cancer treatment–related adverse effects can mimic nononcologic issues. For example, a patient presenting with everolimus-induced hyperglycemia might be mistakenly diagnosed with type 2 diabetes and may not receive appropriate treatment for this adverse effect. Drug toxicity must always be included in the differential diagnosis, and collaboration with the oncology team is essential in the event that treatment interruption or discontinuation is required.

To lower the risk of adverse events, it's essential that nononcology providers be aware of which anticancer drugs their patients are taking.

For patients experiencing everolimus-induced hyperglycemia, metformin (Glucophage and others) is the preferred first-line treatment because it doesn't cause hypoglycemia and most other antidiabetic medications are ineffective.[56] That said, other treatments may be needed for optimal control. When everolimus is discontinued, the patient's dosage of any concurrent antidiabetics should be carefully tapered so as to avoid hypoglycemia. For those with everolimus-induced

hyperlipidemia, lifestyle modifications should be paired with lipid-lowering medications. Continual monitoring should ensure that triglyceride levels don't rise such that the patient is at risk for pancreatitis.[57]

Drug interactions. As everolimus is metabolized primarily in the liver by CYP3A4, there is heightened risk of interactions with other drugs metabolized by the same enzyme.[55] Coadministration with a CYP3A4 inhibitor has been shown to increase serum levels of everolimus, which can result in significant toxicity.[58] Coadministration with a CYP3A4 inducer increases the clearance of everolimus, reducing serum levels and potentially decreasing the drug's efficacy.

KINASE INHIBITORS

Protein kinases are enzymes that modify numerous proteins and control cell growth. Drugs in this class include lapatinib (Tykerb) and palbociclib.

Indications. Lapatinib is approved for metastatic, human epidermal growth factor receptor 2–positive (HER2-positive) breast cancer. It's used in conjunction with either capecitabine or letrozole to block HER2 receptors in cancer cells.[59] Palbociclib, which is also approved for use in conjunction with letrozole or fulvestrant (Faslodex),[60] received accelerated FDA approval in February 2015 for patients with ER/PR-positive, HER2-negative, metastatic breast cancer.[61]

Common adverse effects and management. Although lapatinib and palbociclib are both kinase inhibitors, their adverse effect profiles differ because they have somewhat different mechanisms of action.

The adverse effects of lapatinib reflect its impact on human epidermal growth factor, which is found in various cells, including the dermal layers of the gastrointestinal tract and skin. As a result, the most common adverse effects are diarrhea (60% to 65%) and an acne-like rash of pustules (3% to 44%) primarily localized to the face and trunk.[59,62] The incidence of diarrhea increases when lapatinib is coadministered with capecitabine. Mild nausea (31% to 44%) and loss of

Table 3. Common Vaccine Safety for Immunocompromised Breast Cancer Patients and Their Close Contacts[70-72]

Vaccine	Inactivated: Safe During Treatment	Live: Contraindicated During Treatment	Safe for Close Contact	Transmission from Close Contact May Occur
Adenovirus[a]		X		X
Diphtheria, tetanus, and pertussis (DTaP or TDaP)	X		X	
Hepatitis A	X		X	
Hepatitis B	X		X	
Herpes zoster (shingles)[b]		X		X
HPV	X		X	
Influenza (ID or IM)	X		X	
Influenza (intranasal)		X		X
MMR		X	X	
MMRV		X	X	
Meningococcal	X		X	
Pneumococcal	X		X	
Polio[c] (IM or SC only)	X		X	
Rotavirus[d]		X		X
Varicella		X		X
Vaccinia (smallpox)		X		X
Yellow fever		X	X	

HPV = human papillomavirus; ID = intradermal; IM = intramuscular; MMR = measles, mumps, rubella; MMRV = measles, mumps, rubella, varicella; SC = subcutaneous.
[a]Used in military populations; following vaccination, there is risk of viral transmission via stool for 28 days.[73]
[b]The virus can be transmitted from those vaccinated to their close contacts (time frame unspecified).[74]
[c]The oral polio vaccine is no longer administered in the United States but is still used internationally. It is not safe for immunocompromised patients or their close contacts.
[d]The virus can be shed in the stool for up to 15 days after vaccination; whether transmission can occur is unclear.[75]

appetite (11%) may occur but rarely impact normal activities.[59] Diarrhea management follows the same principles discussed for capecitabine and requires diligent monitoring to avoid dehydration and electrolyte imbalances.[45, 52]

Proper management of rash is important to avoid secondary topical skin infections. Patients should be advised to wash with mild soap, protect their skin from sun exposure, and use alcohol- and fragrance-free moisturizers.[63] Beyond these measures, treatment choices must be made cautiously so as not to risk altering the drug's efficacy. Studies have shown that rash severity can be a direct indicator of treatment efficacy with drugs in this class, and systemic measures to reduce the rash may affect drug efficacy.[64] If the patient is asymptomatic (no pruritus or signs of secondary infection), then topical corticosteroids may be considered.[64] If the patient is symptomatic, then topical corticosteroids should be given in conjunction with an oral antibiotic such as doxycycline.[63]

Palbociclib affects cell division and DNA replication. Its adverse effects, which are primarily hematologic, include anemia (3% to 35%), thrombocytopenia (17% to 20%), and neutropenia (12% to 75%); bowel disturbances such as diarrhea (17% to 21%) and nausea (23% to 25%) can also occur.[65-67] Unique to palbociclib is a 4% risk of pulmonary embolism.[66, 67] Toxicity management isn't specific to the agent; bleeding precautions, infection prevention behaviors, and close monitoring of laboratory results are all essential. As with patients on tamoxifen, those presenting with new-onset dyspnea should be assessed to rule out pulmonary embolism.

Drug interactions. As with the other oral agents discussed, potential interactions are a concern. Because both lapatinib and palbociclib are metabolized by the enzyme CYP3A4, the manufacturers caution against the concomitant use of CYP3A4 inducers, which could increase the drugs' metabolism and decrease their effect. CYP3A4 inhibitors (such as grapefruit juice) should also be avoided because of potential alterations to serum drug levels and, in the case of lapatinib, heightened risk of QTc interval prolongation.[59, 67]

It's important to note that patients taking palbociclib are at higher risk for neutropenia and therefore for infection.[65, 66] Because of these risks, the concomitant administration of the antipsychotic agent clozapine (Clozaril and others) should be avoided, as it increases the risk of severe neutropenia, and patients must have certain minimum white blood cell and absolute neutrophil counts before beginning treatment.[68]

SPECIAL CONSIDERATION: VACCINES

Oral agents that affect the immune system, such as capecitabine and palbociclib, put patients at increased risk for infection. Standard infection prevention protocols must be adhered to, and patient education should be continually reinforced. With regard to vaccination, the literature emphasizes the importance of collaboration between specialists and nononcology providers in order to protect immunocompromised patients from receiving vaccines that could increase their risk of infection.[69] In general, live attenuated vaccines should not be administered to these patients because the virus may still replicate, thus raising the possibility of infection. These patients should also limit their exposure to others who have recently received a live vaccine, because of the risk of transmitted infection. Table 3[70-75] lists common vaccines and specific recommendations regarding immunocompromised patients and their close contacts.

CASES REVISITED

It's extremely important that the NP treating Ms. Panko be aware of her breast cancer history. If Ms. Panko is currently being treated with tamoxifen, then a raloxifene prescription for osteoporosis management would result in SERM duplication. And if she was treated with tamoxifen in the past, there's an increased likelihood of cross-resistance to raloxifene now. Thorough review of Ms. Panko's medical history, including oncology treatment, will ensure the safe, effective management of her osteoporosis.

Ms. Whalen's employee wellness nurse recognizes that palbociclib is an oral treatment for breast cancer, and decides to double-check before recommending the shingles vaccine. She soon verifies that because palbociclib increases the risk of neutropenia and thus of infection, live virus vaccines such as the shingles vaccine should be avoided. The nurse's astuteness in assessing this patient's medications may have saved Ms. Whalen from harm.

CONCLUSIONS

Many breast cancer patients and survivors seek care in nononcology settings, whether for acute symptoms and complaints related to their cancer diagnosis or treatment or for unrelated concerns. Yet many nononcology providers are unfamiliar with the various oral agents used to treat breast cancer, and their possible adverse effects and drug interactions. It's imperative that all providers be aware of these agents and know when a patient is currently taking or has taken them. Nononcology nurses are usually the first to assess a patient's symptoms and obtain the medical history, and they play a role in medication reconciliation. As such, nurses' awareness and knowledge of these oral agents can have a major impact on the continuity and safety of patient care.

It's also imperative that nononcology providers collaborate with the oncology team in addressing a patient's health concerns. The collaborative approach offers clear benefits that extend beyond symptom management. Nononcology providers will be better able to reassure patients about ongoing care, assess

family function and caregiver burden, and provide "realistic hope" and advice regarding treatment or symptom relief.[6, 10, 76] ▼

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