Endocrine Therapy for Breast Cancer
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Abstract
Endocrine therapy is the primary treatment for the most common types of breast cancer. Endocrine agents work by inhibiting the tumor-stimulating effects of estrogen in hormone-sensitive tumors. A new class of targeted drugs synergize with endocrine agents to improve survival for patients with metastatic disease. Endocrine therapy is continued for years, and long-term survival is common, although toxicities often occur due to the alteration of the physiologic effects of estrogen. It is important, therefore, that primary care providers remain knowledgeable about patient needs during and after treatment.

Introduction
As of 2018, chemotherapy is no longer recommended for many patients diagnosed with early-stage hormone receptor–positive (HR+) disease, the most common form of breast cancer. In HR+ breast cancers, estrogen stimulates tumor growth. For these patients, endocrine therapy used as the primary treatment after the cancer has been removed by surgery (with or without radiation) reduces recurrence and mortality. Endocrine therapy is also used for metastatic HR+ breast cancer where the primary goal of therapy is prolongation of survival and palliation. Endocrine therapy typically continues for at least 5 years.

The goal of this article is to provide a review of endocrine therapies commonly used in the treatment of HR+ breast cancer in the United States. Given the prevalence of breast cancer, improvements in survival, and duration of endocrine therapy, primary care providers may likely encounter many patients receiving endocrine therapies; therefore, it is essential that they be knowledgeable about their use. We do not cover other types of drug treatment here, and this article is specific to women, although male patients are also treated with endocrine therapy for breast cancer.

Background
In 2019, approximately 4 million women in the United States were living with a history of breast cancer; and in 2020, more than 250,000 women will be newly diagnosed. Breast cancer does occur in men, although rarely; in males, the majority of tumors are HR+. Studies including men are limited, and thus treatment options have typically been extrapolated from studies of women.

More than 90% of breast cancer in women is nonmetastatic at diagnosis. Although Black women are slightly less likely than White women to be diagnosed with breast cancer, their associated death rate is higher due to factors including subtype of breast cancer, socioeconomic issues, and access to care. Addressing these disparities is an active area of research.

The strongest risk factors for all races are increasing age and female gender, but other risk factors include body weight, dose and duration of hormone therapy in menopause, exercise, alcohol ingestion, and reproductive history.

Treatment options for breast cancer include local/regional strategies (i.e., surgery with or without radiation) and pharmacologic approaches including endocrine therapy. The choice of therapy depends on many factors, including stage of disease, comorbidities, menopausal status, and molecular subtype. Molecular tumor markers currently guiding treatment are estrogen or progesterone receptors (ER or PR) and human epidermal growth factor receptor 2 (HER2). Tumors positive for ER and/or PR are considered HR+: the majority of HR+ tumors are ER+. For early-stage HR+ breast cancer, analysis of a set of genes can help estimate the risk of cancer recurrence and guide whether patients need chemotherapy in addition to endocrine therapy. Tumors overexpressing HER2 are categorized as HER2+, and those negative for all 3 markers are categorized as triple-negative breast cancer. The latter group carries the worst prognosis.

Approximately 70–80% of breast cancers will be HR+ (including a minority that are also HER2+). Endocrine therapy, including the aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs) or downregulators (SERDs), provides the pharmacological backbone for the treatment of HR+ breast cancer.
Endocrine Treatment

Figure 1 outlines endocrine therapy typically used for the frontline treatment of HR+ breast cancer.8 Endocrine therapy is typically begun following completion of initial radiation and/or chemotherapy. For nonmetastatic disease, duration of endocrine therapy may be up to 10 years depending on factors such as menopausal status, patient and clinician preference, and drug(s) used.18 Endocrine therapy for 5 years in this setting reduces the rate of recurrence (most recurrences will be distant) by approximately half, the development of a second breast cancer by approximately one-third, and breast cancer mortality by approximately 30%.6,11,12 The 5-year survival rates for nonmetastatic HR+ breast cancer are approximately 80–100% depending on stage, with most recurrences occurring within the first 5 years.13

More than 150,000 women in the United States are living with metastatic breast cancer.24 Approximately 75% of current metastatic breast cancer cases are due to a recurrence of earlier stage disease, highlighting the importance of effective treatment for earlier stages.14 Endocrine therapy for metastatic breast cancer continues until disease progression, with multiple regimens usually tried,9,15 and thus may continue for years.16 Overall, the median survival for metastatic HR+ breast cancer from time of diagnosis of metastases is estimated at approximately 4–5 years.14 Cyclin-dependent kinase (CDK)4/6 inhibitors, designed to arrest tumor cell replication and synergize with endocrine therapy for metastatic breast cancer, have recently been shown to extend survival.16,17

Mechanisms of Action of Endocrine Therapies

Endogenous estrogens are made primarily in the ovaries but also in peripheral tissues (the main postmenopausal source) via an enzyme called aromatase, which converts androgens to estrogens.18 In general, sex hormones exert their actions by binding to intracellular receptors, leading to altered gene transcription. This results in changes in protein synthesis with various biological effects.18 ER distribution is broad and accounts for an array of effects (eg, endometrial, metabolic, bone, cardiovascular, coagulant, and others). When ER are present on breast cancers, endogenous estrogen can stimulate tumor growth and antiestrogen endocrine therapies can be used successfully to inhibit tumor growth.18

SERMs selectively act as mixed agonists-antagonists at ERs depending on location, and their side effect profiles differ accordingly.18 For example, tamoxifen has partial agonist effects in the endometrium and bone but antagonist effects in breast tissue. Raloxifene has agonist effects in bone and lipids but antagonist effects in breast tissue and the endometrium. Thus tamoxifen increases the risk of endometrial cancer whereas raloxifene does not.18 Tamoxifen is used in pre- and postmenopausal women for all stages of breast cancer.6,10,12

The SERD fulvestrant is a pure ER antagonist; however, when it binds ER in breast cancer cells, the receptors are downregulated.18 Fulvestrant is injected intramuscularly, and its use is limited to advanced or metastatic disease.19

Ovarian suppression or ablation may be combined with endocrine therapy in premenopausal or perimenopausal women to further reduce estrogen.18 Ovarian ablation can be accomplished surgically via oophorectomy or pharmacologically with a gonadotropin-releasing hormone ( GnRH) agonist (eg, leuprolide).13,25 Continuous GnRH agonist administration works through negative feedback, resulting in reduced luteinizing and follicle- stimulating hormones, which leads to suppression of ovarian estrogen production.13 Survival improvements have been reported for premenopausal women who take tamoxifen along with ovarian suppression/ablation, but as the combination increases adverse effects, its use is generally limited.20

Als (eg, anastrozole, letrozole, and exemestane) work by inhibiting the aromatase enzyme responsible for estrogen synthesis. They are administered orally and used for all stages of postmenopausal (including induced menopause) breast cancer in women.20,21

The SERMs tamoxifen and raloxifene and the AIs anastrozole and exemestane are also administered for a duration of 5 years to prevent HR+ breast cancer in women considered to be at high risk.6,13,20 Metastatic breast cancer eventually develops resistance to endocrine therapy, and CDK4/6 inhibitors are effective in mitigating resistance.16,22 Cancer is a disease of uncontrolled cell division and growth. Proteins CDK4 and 6 tightly control the cell cycle (which guides cell division); the CDK4/6 pathway is known to be overactive in HR+ breast cancer via activation of the ER.22 CDK4/6 inhibitors (eg, palbociclib) stop cell cycle progression and inhibit
tumor growth. These drugs increase survival for women with HR+ metastatic breast cancer when used in combination with AIs or SERDs.

Safety Considerations

Endocrine treatment duration in breast cancer can continue for years, emphasizing the importance of effective communication among the patient, primary care provider, and cancer specialist. Although cancer specialists manage most cancer treatment side effects, primary care providers may be the first to assess them. Primary care providers must be knowledgeable about (1) how to identify side effects, (2) strategies for maintaining treatment adherence, and (3) when to refer patients to a specialist. Note that nonadherence has been reported for tamoxifen and the AIs.

See Table for side effects related to drugs that inhibit the effects of estrogen and for highlights of management strategies that can be implemented in collaboration with the cancer specialist. Our discussion focuses on notable side effects related to estrogen inhibition and on comparing and contrasting differences between classes of drugs. Current prescribing information should be consulted for a comprehensive list. Side effects generally span multiple systems (notably cardiovascular, endocrine, dermatologic, gastrointestinal, central nervous system, and musculoskeletal).

AIs are generally preferred over tamoxifen for postmenopausal patients; however, choice of therapy is guided by safety concerns. For example, if hot flashes become problematic for the patient on tamoxifen, the oncologist may switch to an AI. Conversely, patients who develop intolerable arthralgias may be switched to tamoxifen.

Tamoxifen is associated with endometrial cancer, hot flashes, and thromboembolism (notably deep vein thrombosis and pulmonary embolism). Note that cancer also increases the risk for thromboembolic disease. Additional side effects include irregular menstruation, mood changes, increased triglycerides, ocular changes including cataracts, and hepatic abnormalities.

The majority of patients on endocrine therapy experience side effects, and more than 12% prematurely discontinue treatment primarily due to adverse events. Musculoskeletal symptoms are a particularly common reason for nonadherence with AIs. Compared with tamoxifen, AIs have a higher risk of bone density loss and associated osteoporosis-related fractures and of sexual dysfunction.

Estrogens are considered cardioprotective via a variety of mechanisms, including regulation of lipids and substances known to produce vasodilation. Tamoxifen acts as an estrogen agonist within the cardiovascular system and is considered cardioprotective. In contrast, AIs may have a slightly higher incidence of hypertension and hypercholesterolemia compared to tamoxifen, although without an increase in cardiovascular ischemic events; however, there is an increased incidence of ischemic events in women with preexisting ischemic heart disease who take anastrozole.

The side effects associated with fulvestrant are similar to those reported with AIs, with the exception of injection site pain and a higher rate of elevated liver enzymes associated with fulvestrant. Ovarian ablation or pharmacologic suppression induces menopause, and the subsequent side effects associated with decreased estrogen may be enhanced with the addition of a SERM, SERD, or AI. Menopausal symptoms from inducing this state may be worse than from natural menopause due to the abrupt reduction in hormones.

The most common side effects associated with CDK 4/6 inhibitors (used with endocrine therapy) include nausea, diarrhea, fatigue, transaminase elevation, and myelosuppression (particularly neutropenia). The neutropenia is reversible upon discontinuation. Interstitial lung disease/pneumonitis has been reported with all CDK 4/6 inhibitors and can be fatal. Patients will be monitored for signs/symptoms of TE.

AIs — aromatase inhibitors; DVT — deep vein thrombosis; PE — pulmonary embolism; SERM — selective estrogen receptor modulator; TE — thrombotic event.

Table Notable Side Effects Related to Estrogen Inhibition

<table>
<thead>
<tr>
<th>Class/Agent(s)</th>
<th>Side Effect</th>
<th>Incidence</th>
<th>Management Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERM/tamoxifen</td>
<td>Hot flashes</td>
<td>40–80%</td>
<td>Lifestyle changes</td>
</tr>
<tr>
<td>Endometrial (uterine) cancer</td>
<td>2- to 3-fold increase over baseline</td>
<td>Consider pharmacologic</td>
<td></td>
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<tr>
<td>Thromboembolic events</td>
<td>2- to 3-fold increase for DVTs and PEs versus baseline or AI</td>
<td>Regular gynecologic assessment</td>
<td></td>
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<tr>
<td>Embryo-fetal toxicity</td>
<td></td>
<td>Monitor for signs/symptoms of TE</td>
<td></td>
</tr>
<tr>
<td>AIs/anastrozole, letrozole, exemestane</td>
<td>Hot flashes</td>
<td>~40%</td>
<td>Effective nonhormonal contraception</td>
</tr>
<tr>
<td>Musculoskeletal (eg, arthralgias, joint stiffness, tendonitis)</td>
<td>35–50%</td>
<td>Avoid lactation</td>
<td></td>
</tr>
<tr>
<td>Reduction in bone mineral density, increased risk of osteoporotic fracture</td>
<td>5-year fracture risk: 8.2%</td>
<td>Life-style changes</td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction (eg, vaginal dryness, cystitis, decreased libido)</td>
<td>10–20%</td>
<td>Consider pharmacologic treatment</td>
<td></td>
</tr>
<tr>
<td>Hypertension, ischemic heart events, and hypercholesterolemia</td>
<td></td>
<td>Routine symptom assessment</td>
<td></td>
</tr>
<tr>
<td>Embryo-fetal toxicity</td>
<td></td>
<td>Exercise, analgesics, acupuncture, physical therapy</td>
<td></td>
</tr>
</tbody>
</table>

See Runowicz et al, Survivorship Care Guidelines, for details. See prescribing information for complete toxicities and warnings.

* Bolded text indicates warnings for > 1 medications within the class. See prescribing information for complete toxicities and warnings.

** Percent of patients who experience effect, unless otherwise noted.

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Note that cancer also increases the risk for thromboembolic disease. Additional side effects include irregular menstruation, mood changes, increased triglycerides, ocular changes including cataracts, and hepatic abnormalities. The majority of patients on endocrine therapy experience side effects, and more than 12% prematurely discontinue treatment primarily due to adverse events.

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An increased incidence of venous thromboembolism has been
Drug Interactions, Pregnancy, and Lactation

Concomitant medications may increase the toxicity or reduce the efficacy of exemestane, tamoxifen, and the CDK4/6 inhibitors due to drug–drug interactions. These drugs are metabolized by hepatic cytochrome P450 enzymes; some CDK4/6 inhibitors also block activity of CYP450 enzymes, leading to interactions. For example, the CYP450 enzyme CYP3A plays a major role in the metabolism of exemestane; if exemestane is administered with a drug that induces CYP3A, exomestane metabolism to inactive metabolites may increase, resulting in reduced effectiveness.34

Tamoxifen provides another interesting example of a potential drug interaction. Tamoxifen is a prodrug with minimal activity and is metabolized to the active metabolite endoxifen via the enzyme CYP2D6, as well as other CYP450 enzymes (see Figure 2).18,52 Inhibitors of CYP2D6 may reduce formation of endoxifen, thereby reducing the efficacy of tamoxifen. For instance, hot flashes associated with tamoxifen treatment can be treated with selective serotonin reuptake inhibitors (SSRIs), but certain SSRIs inhibit CYP2D6 and may interact with tamoxifen.10 Of note, foods (eg, grapefruit juice), supplements and herbal medications may also interact with endocrine inhibitor drugs.

All the medications discussed can cause fetal harm when administered during pregnancy. Women of reproductive potential must be advised to use effective nonhormonal contraception and to avoid lactation while on these drugs and sometimes for a period after discontinuation.29-35

Summary and Conclusions

Endocrine therapy is commonly prescribed for a majority of breast cancer patients. A recent review emphasized the need for primary care providers to be educated about its use and about the importance of collaboration with cancer specialists.10 Oncology professional associations have provided recommendations for primary care providers addressing breast cancer survivorship care that cover the period during which HR+ patients will be receiving endocrine therapy; highlights from these guidelines are incorporates into the Table.25 For example, hot flashes are common with SERM or AI drugs and may affect adherence. Lifestyle and environmental modifications (eg, reducing alcohol, wearing layers) may be helpful.25 Several pharmacologic options (eg, venlafaxine, gabapentin) have evidence to support effectiveness; however, their use is not approved by the US Food and Drug Administration.25

When considering pharmacologic options, care should be taken to check for drug interactions.

Many of the side effects of endocrine therapy commonly occur with aging due to age-related loss of estrogen (eg, reduced bone mineral density, sexual dysfunction, hypertension). These events may be accelerated or intensified by antiestrogen therapies to prevent or treat HR+ breast cancer, and they should be closely monitored. Other drug-specific side effects, such as the increased risk of endometrial cancer with tamoxifen, must also be kept in mind. Although surveillance and management for these effects often follow standard guidelines, adjustment of the cancer treatment (eg, change from tamoxifen to an AI) may be warranted. In addition, the median age at diagnosis of breast cancer is 62, meaning the presence of comorbid conditions is likely, further complicating follow-up care.3 Primary care clinicians should coordinate care with the cancer specialist when possible, both during and after active treatment, and ideally via the use of a survivorship care plan (provided by the cancer specialist).25

Professional guidelines recommend counseling patients at each visit to maintain adherence and thus maximize the benefits of endocrine treatment and to reduce the likelihood of recurrence.25 In addition to side effects, reasons for or predictors of nonadherence to medications generally include cost, presence of comorbid conditions, lengthy treatment, history of nonadherence, skepticism about treatment benefits, lack of social support, mental illness, and poor communication between patient and provider.23-25 Identifying these issues can help the clinician to individualize counseling.

Survivorship guidelines also address long-term effects of nonendocrine treatments, surveillance for recurrence or development of new cancers, adoption of a healthy lifestyle, and coordination of care.25

In conclusion, endocrine therapy is important across all stages of HR+ breast cancer and will likely remain the backbone of treatment for the foreseeable future. The advent of CDK4/6 inhibitors potentially extends the duration of effectiveness of endocrine treatments and prolongs survival in women with metastatic disease.

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References


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