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Endocrine therapy for breast cancer in the primary care setting

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ABSTRACT

The treatment of hormone-positive breast cancer (BCa) is a rapidly evolving field. Improvement in the understanding of the mechanisms of action and resistance to anti-hormonal therapy has translated, in the past decade, into multiple practice-changing clinical trials, with the end result of increased survivorship for patients with all stages of hormone-positive cancer. The primary care physician will thus play an increasing role in the routine care, surveillance, and treatment of issues associated with anti-hormonal therapy. The aim of the present review was to provide a focused description of the issues relevant to primary care, while briefly highlighting recent advances in the field of anti-hormonal therapy.

Key Points

- Hormone-positive BCa is the most prevalent form of BCa and, compared with the other subtypes, is usually associated with better survival.
- Survivorship has significantly increased for all stages of hormone-positive BCa, making the primary care physician a key player in the care of affected patients.
- The two most common classes of anti-hormonal agents used in these patients are selective estrogen receptor modulators and aromatase inhibitors. Each class of medication is associated with signature side effects.
- Within the past decade, multiple novel estrogen receptor blockers (for example, fulvestrant) and agents aimed at circumventing resistance to endocrine therapy [inhibitors of cyclin-dependent kinase 4/6 and of mTOR (the mechanistic target of rapamycin)] have gained clinical ground. Understanding their side effects will be increasingly relevant to primary care physicians.
- Multidisciplinary care is always encouraged in the care of cancer patients receiving anti-hormonal therapy.

Key Words Breast cancer, endocrine therapy, primary care, survivorship

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INTRODUCTION

Breast cancer (BCa) affects 1 in 8 women during their lifetime[1]. Approximately 3 in 4 of those cancers are positive for either the estrogen or the progesterone receptor, where estrogen and progesterone are the key drivers of carcinogenesis[2]. Endocrine therapy, which lowers estrogen levels and inhibits the growth of the cancer, remains the mainstay systemic treatment for hormone receptor–positive BCa in the adjuvant, metastatic, and (occasionally) neoadjuvant settings. Given increased survivorship and the long duration of treatment exposure in these patients (often 5–10 years), there is an increased need for primary care involvement and collaboration between general practitioners and oncologists[3]. In the present review, we summarize the latest evidence for the use of endocrine therapy in the adjuvant and metastatic settings, and we provide practical tips for managing the adverse effects of that therapy.

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ADJUVANT ENDOCRINE THERAPY FOR BCa

Adjuvant therapy is often decided by the oncologist based on clinical, pathologic, and genetic scoring parameters. Several meta-analyses have demonstrated a consistent benefit for a patient's survival with the addition of endocrine therapy in hormone receptor–positive nonmetastatic BCa. The three classes of agents used are the selective estrogen receptor modulators (such as tamoxifen), the aromatase inhibitors (AIs), and ovarian suppression. Figure 1 summarizes the sequencing strategies for those agents, and notes key definitions (for example, the definition of menopause, and low-risk vs. high-risk patients).

Premenopausal Patients

For premenopausal women at high risk of recurrence, the choice is between tamoxifen and an AI, plus ovarian suppression in high risk cases, based on a discussion with the patient about the benefits and risks.

In the high-risk subgroup (defined as <35 years of age at diagnosis or a need for adjuvant chemotherapy after surgery), the addition of ovarian suppression (whether chemical or surgical) to tamoxifen or exemestane is associated with a 4.5%–7.7% absolute reduction in BCa recurrence at 5 years[4]. For all other premenopausal patients at standard risk, tamoxifen remains the treatment of choice. Tamoxifen is administered once daily as a 20 mg pill for a minimum of 5 years. Compared with placebo, its use is associated with a significant absolute reduction in BCa mortality to 23.9% from 33.1% at 15 years (an improvement of 9.2% ± 1.0%), preventing 1 BCa death for every 11 patients treated[5,6]. Notably, AIs should not be used as monotherapy in premenopausal women, because they might induce ovarian reactivation and estrogen production, but they can be used in combination therapy with ovarian suppression in high-risk patients. Any patient on AI therapy who experiences a recurrence of their menstrual periods should be promptly evaluated, with measurement of serum estradiol and a referral back to the oncologist.

Postmenopausal Patients

In the postmenopausal setting, the 3 most commonly used AIs (which are equally effective) are anastrozole (1 mg daily), letrozole (2.5 mg daily), and exemestane (25 mg daily) administered for 5 years. Compared with tamoxifen, the AIs are associated with a reduction in BCa recurrence, particularly during years 0–1 [relative risk (RR): 0.64; 95% confidence interval (CI): 0.52 to 0.78] and years 2–4 (RR: 0.80; 95% CI: 0.68 to 0.93)[6]. In a patient approaching, but not yet having reached a menopausal state, consideration might be given to starting tamoxifen for the first 2–3 years and switching to an AI afterward. Compared with a 5-year course of tamoxifen, the switch strategy is associated with a reduction in BCa recurrence during years 2–4 (RR: 0.56; 95% CI: 0.46 to 0.67) and with fewer deaths from BCa (RR: 0.84; 95% CI: 0.72 to 0.96). No further benefit for recurrence is observed beyond the treatment period[7].

Duration of Therapy

After 5 years of tamoxifen, either continuation of tamoxifen or a switch to an AI for an additional 5 years is effective in reducing the odds of distant recurrence and of new primary BCas, with some evidence suggesting improved BCa-free and overall survival[8,9]. Some, but not all, data suggest that, for women completing 5 years on an AI, an additional 5 years of AI also improves recurrence-free survival, without

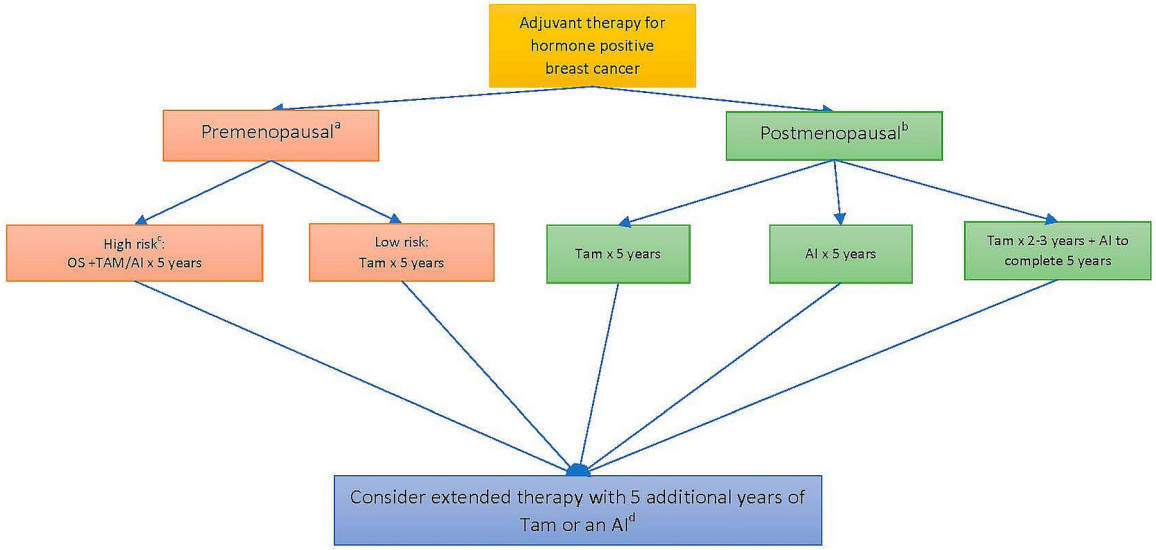

FIGURE 1 Algorithm for choice of endocrine therapy in the adjuvant setting. [a]Menopause: Defined as any patient less than 60 years of age who previously underwent bilateral oophorectomy *or* who has not had any menstrual periods for 12 months or more in the absence of tamoxifen, chemotherapy, or ovarian suppression, *and* whose serum estradiol is in the postmenopausal range *or* who is amenorrheic on tamoxifen, with follicle-stimulating hormone and serum estradiol in the postmenopausal range. [b]Any patient 60 years of age or older. [c]Any patient less than 35 years of age or any premenopausal patient who has received chemotherapy in the adjuvant setting. [d]Additional treatments to be decided in conjunction with an oncologist, on a case-by-case basis. OS = ovarian suppression; Tam = tamoxifen; AI = aromatase inhibitor (letrozole, anastrozole, exemestane).

improvement in overall survival[10,11]. The absolute benefit of extended therapy is small and must be weighed against the potential side effects of venous thrombosis and endometrial cancer with tamoxifen and of osteoporotic fractures with the AIs. A decision for extended treatment should be made in consultation with an experienced oncologist.

SIDE EFFECTS AND HEALTH-RELATED ISSUES WITH ENDOCRINE THERAPY

Each class of anti-endocrine agent has its signature-specific side effects (summarized in Table I).

Up to 94% of patients experience side effects while taking endocrine therapy, and as many as 18% discontinue treatment[12]. Although most side effects will be managed by the oncologist, an increasing number of patients will present to their primary care physician with the initial complaint. It's therefore crucial for the general practitioner to be able to identify, target, and institute the multidisciplinary interventions appropriate for the successful treatment of the side effects. Successful treatment will, in turn, maintain patient adherence with their therapy and prevent rare life-threatening complications.

Managing the Side Effects of AIs

AI-Induced Bone Loss

Estrogen deficiency has long been recognized as a risk factor for osteoporosis by increasing bone resorption through osteoclastogenesis. In a meta-analysis of seven trials comparing AIs with tamoxifen in postmenopausal women with early-stage BCa, use of AIs significantly increased the risk of bone fractures (odds ratio: 1.47; 95% CI: 1.34 to 1.61)[13]. The U.S. National Comprehensive Cancer Network recommends an evaluation with baseline bone mineral density testing and follow-up every 2 years for women with BCa undergoing therapy that lowers sex steroids[14]. Given osteoclastogenesis from estrogen deficiency, the use of osteoclast inhibitors such as bisphosphonates not only prevents bone loss, but, in postmenopausal women, is associated with a reduction in BCa recurrence (RR: 0.86; 95% CI: 0.78 to 0.94) and BCa mortality (RR: 0.82; 95% CI: 0.73 to 0.93)[15]. The latest guidelines from Cancer Care Ontario and the American Society of Clinical Oncology therefore indicate that postmenopausal women and patients on ovarian suppression receiving adjuvant systemic treatment should be considered for intravenous zoledronic acid (4 mg every 6 months) or oral clodronate (1600 mg daily) for 3–5 years[16]. Supplementation with 1200 mg elemental calcium (total diet plus supplement) and 800 IU vitamin D daily is recommended for all patients[14].

AI-Induced Musculoskeletal Symptoms

The use of AIs has been associated with an increased risk of arthralgias, significantly increased tendon thickness, and carpal tunnel syndrome[17–19]. Most of the carpal tunnel syndrome cases were mild-to-moderate in severity and did not require treatment.

The arthralgia or musculoskeletal syndrome induced by AIs is variously defined in the literature, but is usually symmetrical, affecting hands and wrists with morning stiffness[20]. Given the lack of a standard definition, prevalence varies in the clinical trials, but is estimated to be 45%–50%. Severity also varies, with the intensity of the symptoms attenuating after prolonged exposure to AIs[21]. However, the symptoms can at times also be debilitating, and this side effect is one of the most common causes of therapy discontinuation. No clear treatment has yet been established, but exercise, massage therapy, acupuncture, and nonsteroidal anti-inflammatory drugs have all been shown to lessen the burden of symptoms to varying degrees[22]. Switching the AI can result in better tolerance and compliance, with 72% of patients continuing letrozole at 6 months after anastrozole was stopped because of musculoskeletal symptoms[23].

AI-Induced Sexual Dysfunction

The diminishment of estrogen synthesis during AI therapy is similar to that seen with aging. The consequences often include vaginal dryness and atrophy, which can in turn result in cystitis, vaginitis, painful intercourse (dyspareunia), and decreased libido[24]. Because those effects are often underreported, and because they result in significant physical and emotional distress for patients and their partners alike, sexual dysfunction should be actively discussed with patients[25]. The complexity of female sexual dysfunction necessitates a biopsychosocial approach to assessment and management. Potential interventions range from education and lifestyle changes to sexual counselling, sexual aids (for example, lubricants and lidocaine preparations), medications (non-hormonal), and dietary supplements. All of the foregoing approaches have been shown to be helpful to varying degrees[26]. For refractory cases, low-dose vaginal estrogen could be considered in collaboration with an oncologist[25].

AI-Induced Cardiovascular Disease

Estrogen has a cardioprotective role in women, and compared with tamoxifen therapy, AI therapy has been associated with higher rates of hyperlipidemia and hypertension[27]. However, rates of severe cardiovascular disease such as myocardial infarction and stroke in patients treated with AIs are similar to those in the non-cancer population[28]. Patients taking AIs should be routinely screened for hypertension, hyperlipidemia, and metabolic syndrome.

Managing the Side Effects of Tamoxifen

Hot Flashes

Hot flashes are one of the most common and bothersome side effects of tamoxifen, being reported in up to 80% of patients undergoing therapy[29]. They also occur to a much lesser extent in patients taking AIs. Drugs that inhibit the activity of CYP2D6, such as the selective serotonin reuptake inhibitors, reduce the occurrence of tamoxifen-related hot flashes by decreasing the conversion of tamoxifen to its most active metabolite, endoxifen[30]. However, strong CYP2D6 inhibitors could adversely affect drug efficacy. Therefore, moderate CYP2D6 inhibitors (such as sertraline and duloxetine) are preferred over strong inhibitors (such as paroxetine and fluoxetine) for the treatment of hot flashes.

Venous Thromboembolism

The relative risk of venous thromboembolism is increased by a factor of 2–3 in older women receiving tamoxifen[31,32]. The risk seems to be further pronounced when therapy is extended to 10 years from 5 in the adjuvant setting[8]. Risk factors for tamoxifen-induced venous thromboembolism include prior surgery, fracture, immobilization, and heterozygous factor v Leiden carrier status[33]. However, the risk of fatal pulmonary embolism does not seem to increase with tamoxifen use extended to 10 years (0.2%), especially for women less than 54 years of age[6,8].

TABLE I Endocrine therapy in the adjuvant setting: benefits and adverse effects and their management

Therapeutic agent	Benefit	Adverse effects		
		Type	Prevalence	Management
Tamoxifen				
	When used for 5–10 years in the adjuvant setting, is associated with a 9.2%±1% absolute reduction in breast cancer mortality over 15 years			
		Hot flashes	40%–80%	■ Lifestyle changes in dressing, bedding ■ For severe symptoms try SSRI, SNRI (venlafaxine, citalopram, escitalopram, sertraline) ■ Avoid paroxetine, fluoxetine
		Venous thromboembolism (VTE)	Relative increase in VTE by a factor of 2–3 Pulmonary embolism: 0.2% over 5 years	■ Use caution in patients with factor V Leiden hetero- or homozygosity, recent fracture, recent surgery, immobilization, prior history of VTE ■ Treat VTE per guidelines
		Endometrial cancer	Relative increase by a factor of 2.7 (1.2/1000 patient–years)	■ No routine surveillance for standard-risk patients ■ Premenopausal patients: any irregular vaginal bleeding to be investigated with endometrial biopsy ■ Postmenopausal patients: all vaginal bleeding to be investigated with endometrial biopsy; otherwise, only normal routine gynecologic exam per standard guidelines.
		Ocular pathologies	Cataract: 3.7% of patients	■ Consider yearly eye examination
		Fatty liver disease	Up to 33% of patients	■ No routine screening recommended ■ If fatty liver documented, obtain liver enzymes every 3–6 months ■ Stop tamoxifen if liver enzymes exceed twice the upper limit of normal
Aromatase inhibitors				
	When used for 5–10 years in the adjuvant setting, are associated, compared with tamoxifen, with a reduction in the relative risk for breast cancer recurrence of 36%±13% in year 1 and 20%±12% in years 2–4			
		Osteoporosis and fractures	Relative increase in fractures of 47%±13%; absolute increase of 2%	■ Bone mineral density baseline and every 2 years ■ Vitamin D: 800 IU daily ■ Total calcium (diet + supplement): 1200 mg daily ■ Postmenopausal patients (includes premenopausal patients on ovarian suppression): consider intravenous zoledronic acid 4 mg every 6 months or oral clodronate 1600 mg daily
		Arthralgias, musculoskeletal symptoms	45%–50%	■ Switch the aromatase inhibitor ■ Consider exercise, massage, acupuncture, NSAIDs
		Sexual dysfunction	Varies with symptoms but loss of libido, vaginal dryness, and dyspareunia each reported in the range of 10%–20%	■ Biopsychosocial approach ■ Education, counselling ■ Sexual aids (lubricants, lidocaine preparations)
		Cardiovascular disease (CVD)	Similar rate of serious CVD; increased risk of hypertension and hypercholesterolemia	■ Routine screening for hypertension, hypercholesterolemia, and metabolic syndrome

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs.

Endometrial Cancer

Tamoxifen has been associated with a risk for both endometrial cancer and uterine sarcoma that is increased by a factor of 2.7; however, the absolute annual risk of endometrial cancer remains low at 1.2 per 1000 patient–years[34,35]. The elevated risk of cancer persists as long as the patient takes tamoxifen and declines after treatment discontinuation[36]. The following recommendations are in place for surveillance of uterine cancer in women taking tamoxifen[37]:

- In premenopausal women, any irregular bleeding should be investigated by hysteroscopy or endometrial biopsy (or both). The same recommendation applies to postmenopausal women experiencing new-onset vaginal bleeding.
- In postmenopausal women without vaginal bleeding, routine age-appropriate screening is recommended.

Tamoxifen-Induced Ocular Pathologies

Exposure to tamoxifen is associated with an increased risk of cataracts (3.7%) and, less commonly, with reversible corneal pigmentation and irreversible retinal deposits in association with macular edema and vision loss[38]. Although these issues are less common, a routine annual eye exam is recommended for all patients.

Tamoxifen-Induced Fatty Liver Disease

Overall, tamoxifen has a favourable effect on lipid profile[39]. However, it has recently been reported that, based on ultrasonography, fatty liver is incidentally found in one third of patients taking tamoxifen[40]. Clinically relevant steatohepatitis is nevertheless very uncommon, and no routine screening is therefore required. Tamoxifen can be continued unless liver function tests reach twice the upper limit of normal. For patients with documented fatty liver disease, liver function tests every 3–6 months are recommended.

METASTATIC BCa

Inhibitors of Cyclin-Dependent Kinase 4/6

Endocrine therapy remains the mainstay treatment for patients with metastatic hormone receptor–positive, HER2-negative BCa not presenting in visceral crisis. However, the advent of inhibitors of cyclin-dependent kinase 4/6 (CDK4/6), such as palbociclib, ribociclib, and abemaciclib, in combination with endocrine therapy to overcome endocrine resistance, has been a breakthrough for the first-line treatment of postmenopausal women with hormone-positive metastatic disease. The addition of a CDK4/6 inhibitor to letrozole or anastrozole has been shown to increase progression-free survival to 24–25 months compared with 14–15 months with letrozole or anastrozole alone, with overall survival data currently being immature[41–43]. These newer agents are associated with significant rates of neutropenia and lymphopenia (affecting up to 92% of patients on therapy) and, less commonly, with anemia and thrombocytopenia[41–43].

Unlike traditional chemotherapy, which causes neutropenia through bone marrow cell apoptosis, CDK4/6 inhibitors cause cell-cycle arrest without depleting the bone marrow of precursor white cells. As a result, the occurrence of febrile neutropenia is rare (1%–2%), and neutropenia is rapidly reversed within 48 hours of therapy cessation, without the need for stimulating factors. It is therefore very common for patients followed in primary care to have their blood results flagged for abnormal counts while receiving these therapies. Inhibitors of CDK4/6 should be discontinued only if the patient has clinical signs of an infection. Dose adjustments for severe cases will be performed by the oncologist who actively follows the patient.

In summary, the CDK4/6 inhibitors require monitoring for the initial 2 weeks and then with monthly clinic visits, a complete blood count, and liver enzymes[41–43]. For ribociclib, baseline electrocardiography should be obtained, with a follow-up in 2 weeks, and then monthly monitoring for prolongation of QTc.

Fulvestrant

Given intramuscularly, fulvestrant is another novel endocrine agent that works by selectively degrading the estrogen receptor. Currently, fulvestrant is used only in the metastatic setting, either in the first line for patients presenting with *de novo* metastatic hormone-positive disease, or in later lines in combination with the CDK4/6 inhibitor palbociclib[44,45]. Like the AIs, fulvestrant is associated with arthralgias and hot flashes, but it is associated with higher rates of liver enzyme elevation and local injection site reactions[44,45].

Everolimus

Everolimus, an inhibitor of MTOR (the mechanistic target of rapamycin), has been added to endocrine therapy with exemestane to overcome resistance to endocrine therapy. Currently, the use of everolimus in combination with exemestane is limited to postmenopausal patients who have progressed on prior endocrine therapy. The addition of everolimus increases progression-free survival by 4.1 months, but is also associated with increased risks for stomatitis, pneumonitis (3%), anemia, hyperglycemia, and fatigue[46].

SUMMARY

The treatment of hormone receptor–positive BCa is a constantly evolving field. Newer agents that aim to circumvent resistance, combination therapies, and the duration of therapy are often the subjects of large practice-changing clinical trials. As therapies improve, so does the survivorship of affected patients with cancer at all stages. As in many other chronic diseases, such as hypertension and diabetes, the primary care physician will have to be aware of the specific issues affecting the increasingly prevalent BCa population and of the screening and interventions required to adequately manage the consequences of anti-hormonal therapy. A multidisciplinary approach and consultation with oncology specialists are always recommended.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AA has received advisory fees from Novartis for their drug ribociclib. KE has no conflicts of interest to declare.

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