

Endocrine Therapy in Older Women with Early-Stage Hormone Sensitive Breast Cancer

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Abstract

Breast cancer is the most common cancer affecting women worldwide, with the highest risk in those aged 70 and over. Most older women (80% to 85%) have hormone receptor positive breast cancer and thus the use of endocrine therapy is common in this population. Typically, women receive endocrine therapy for at least 5 years to reduce the risk of cancer recurrence and decrease breast-cancer mortality. However, adherence to hormonal therapy may be an issue, particularly in older women, as side effects may lead to early discontinuation and/or non-adherence. Older women on endocrine therapy are often cared for by primary care physicians and geriatricians and therefore, an understanding of oral endocrine therapy, as well as its potential side effects, is essential for treating physicians. This review describes the benefits of endocrine therapy in patients with resected breast cancer, compare different hormonal therapies with regards to side-effects and discuss management strategies with a particular focus on the concerns of older breast cancer patients on endocrine therapy. Mrs. Smith is a 75-year-old woman whose family doctor noted a 3 cm to 4 cm lump in her left breast during a routine physical exam. She has no palpable lymph nodes. Her family doctor sends her for a mammogram which reveals a 2.6 cm spiculated mass in the left upper outer quadrant. Biopsy reveals an invasive ductal carcinoma.

Keywords: Breast cancer; Endocrine therapy; Sensitive; Early stage

Introduction

Breast cancer is the most common cancer affecting women worldwide with an estimated 1.6 million cases diagnosed in 2012 [1]. In the United States, 1 in 8 women will develop breast cancer in their lifetime with women age 65 and over accounting for 41% of all newly diagnosed breast cancer and almost 60% of all breast cancer deaths [2]. The risk of developing breast cancer increases with age, with the highest risk in those age 70 and over [3].

Older women are more likely to have more advanced disease at diagnosis [4-6]. However, tumors in older women are more likely to have more favourable biology, including higher rates of hormone receptor positivity, lower rates of HER-2 positivity, lower rates of proliferation, and a lower frequency of p53 accumulation [4,5,7-10]. Despite more favourable tumor biology, increasing age is associated with a higher risk of death from breast cancer [4], potentially due to under-treatment which is more common with increasing age [11,12].

Many older women receive adjuvant endocrine therapy due to the high proportion of hormone receptor positivity (80% to 85%) [4], more favourable toxicity profile, and limited evidence supporting chemotherapy use in women age 70 and over due to their under-representation in clinical studies [13]. With the increasing prevalence of breast cancer combined with 5-year survival rates of close to 90% [2], primary care physicians and geriatricians are increasingly relied upon to see and manage patients receiving these therapies [14]. This is particularly true in patients age 80 and over [15]. Thus, a better understanding of the potential risks and benefits are necessary.

Mrs. Smith is referred to a surgeon. The surgeon notes that she has a history of hypertension, Type II diabetes mellitus, and osteoarthritis. Her medications include hydrochlorothiazide, metformin, and vitamin D. She is independent in her activities of daily living, as well as her instrumental activities of daily living. Her ECOG PS is 0. She lives at home with her husband who has Alzheimer's disease, and for whom she is the primary caregiver. They live in a two-story home, and rely on their daughter who lives nearby for support.

The surgeon discusses the option of lumpectomy with radiation or mastectomy. She is hesitant to have surgery because she is concerned

about who would care for her husband while she is recovering. The surgeon requests receptor status to be done and she is found to be ER/PR positive, HER-2/neu negative.

Treatment of Early-Stage Breast Cancer

Standard treatment for localized breast cancer involves definitive surgical excision, either with mastectomy or with breast-conserving therapy and radiation. Older women, however, are less likely to have surgery than younger women with breast cancer [6,16]. For women with hormone sensitive disease, primary treatment with endocrine therapy alone is an option. One study suggests that up to 42% of women, age 70 and over, are treated with endocrine therapy alone. A Cochrane review of women, 70 years of age and over, with operable breast cancer found that although there was no difference in overall survival in those treated with surgery vs. primary endocrine therapy, that surgery provided better local control with less risk of local complications [17].

Primary endocrine therapy can provide disease control for 2 years to 3 years, so is an option for patients with hormone sensitive breast cancer with a life expectancy of <2 years, who are unfit, or who refuse definitive surgical resection [17,18]. Generally, however, most women with localized breast cancer should be offered surgical resection for localized breast cancer irrespective of age.

Mrs. Smith meets with the medical oncologist. Reviewing her function and comorbid conditions, the oncologist discusses that she has an estimated average life expectancy of 12 years. The oncologist suggests that Mrs. Smith should have surgery because this would decrease the

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likelihood of local complications in the future. Her daughter offers to move in with her parents to help during the post-operative period.

Mrs. Smith proceeds with a mastectomy and sentinel lymph node biopsy. She recovers well with no complications. Pathology reveals a 2.2 cm grade 2 ER/PR positive, HER-2/neu negative invasive ductal carcinoma. There is cancer in two of two lymph nodes. Margins were negative.

She returns to meet with the medical oncologist to discuss the need for further treatment.

Adjuvant Endocrine Therapy

Following definitive local therapy, additional systemic therapy may be indicated to decrease the risk of breast cancer recurrence and potentially breast cancer related death. The benefit of adjuvant systemic treatment depends on the risk of recurrence, which is based on the characteristics of the breast cancer (size, lymph node involvement, hormone receptor and HER-2 status) and the patient's risk of non-cancer related mortality. A thorough and accurate assessment of the patient's health and overall life expectancy is important in this decision-making process, a skill set geriatricians are adept at.

In the general breast cancer population, adjuvant endocrine therapy is recommended in most patients with early stage hormone sensitive breast cancer [18,19]. In patients with tumors smaller than 0.5 cm and no lymph node involvement, or those who have significant comorbidity, adjuvant endocrine therapy may potentially be omitted as the magnitude of benefit in this population is small [8,10,19].

The benefit of adjuvant endocrine therapy was demonstrated in a large meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which demonstrated a 39% decrease in breast cancer recurrence, 40% decrease in contralateral breast cancer, and a 30% decrease in breast cancer mortality, with the use of tamoxifen for 5-years compared to surgery alone [20]. A benefit was observed both in younger and older women. Recent studies suggest an additional benefit of continuing tamoxifen for 10 years [21]. However, relatively few women ages 70 and over (9%) were included [21].

Aromatase inhibitors (AI), a newer class of endocrine agents, have been shown to decrease the risk of breast cancer recurrence by a further 15%, and contralateral breast cancer by 40% [22-25]. In women, age 70 and over, who have completed 5-years of tamoxifen, an additional 5-years of an AI demonstrated a further decrease in breast cancer recurrence compared to placebo with no differences in QOL and toxicity compared to their younger counterparts [26]. The current recommendation is that all women receive an AI as a component of their adjuvant endocrine therapy, either upfront for 5-years, in sequence after 2 years to 3 years of tamoxifen for up to 5-years, or in sequence after 5-years of tamoxifen for another 5-years of therapy [19] (Table 1). The choice of upfront AI versus a switch strategy is often determined by the overall risk of breast cancer recurrence, as well as toxicity profile of the drug. Recent studies suggest that ten years of aromatase inhibitors may decrease local breast cancer recurrences [27] with one study demonstrating a decreased risk of distant metastases [28]. Other studies however have been negative [29,30] and no studies have yet to show an improvement in overall survival with 10 years of AI treatment. Ten years of AI can be considered in selected women with high risk of breast cancer recurrence with a reasonable life expectancy who are tolerating AI well. In women who cannot receive or decline to receive an AI, 5-years and potentially 10-years of tamoxifen is an acceptable alternative.

No contraindications to aromatase inhibitors
Tamoxifen × 2 years to 3 years → Aromatase inhibitor to complete 5 years
Aromatase inhibitor × 2 years to 3 years → Tamoxifen to complete 5 years
Aromatase inhibitor × 5 years
Tamoxifen × 5 years → aromatase inhibitor × 5 years
Aromatase inhibitors × 10 years
Contraindication to aromatase inhibitor or patient refusal
Tamoxifen × 5 years. May consider tamoxifen for up to 10 years

Table 1: Acceptable endocrine therapy strategies in older women.

Considerations in Older Women

Increased age alone should not preclude adjuvant systemic therapy. This is important as older women, particularly those >70 years of age, are at high risk of under-treatment, which can result in increased rate of recurrence (HR 1.21) and breast cancer mortality [31]. Although increasing age is associated with a higher risk of death from non-cancer causes (HR 4.13) [31] and thus proportionally less deaths related to breast cancer, the absolute proportion of breast cancer related deaths, even in those 85 and older, is still significant (29%) [32].

Advanced age is associated with an increased burden of comorbid conditions, with 40% patients 80 years and older having one or more comorbid conditions [33]. Increasing burden of comorbid conditions is strongly associated with a higher risk of death from non-cancer related causes with those women who have 3 or more comorbidities (using the Satariano score) at a 20 fold increased risk of death from non-cancer related causes [16]. Similarly, patients with functional impairment in at least one domain, more commonly observed in older adults, have been found to have an increased risk of overall mortality and death from non-breast cancer related causes [34]. Although there is a higher prevalence of comorbid conditions with increasing age, endocrine therapy use is similar in older and younger women [32].

Drug Metabolism and Drug-Drug Interactions

Tamoxifen is a selective estrogen receptor modulator (SERM), which competitively inhibits the estrogen receptor in the breast. Tamoxifen is a pro-drug that undergoes metabolism by the hepatic cytochrome P450 system, specifically CYP2D6 and CYP3A4/5, to produce endoxifen, the primary active metabolite [35].

Almost 100 variants of CYP2D6 have been reported [36]. Patients with CYP2D6 polymorphisms associated with poor/intermediate activity, metabolize tamoxifen less effectively resulting in reduced levels of endoxifen [37]. Some retrospective studies have suggested that these patients have a higher risk of breast cancer recurrence and an increased risk of breast cancer mortality, while others found no difference in breast cancer outcomes or overall survival [38-41]. Increased age is associated with increased plasma levels of endoxifen and other tamoxifen metabolites [42,43]. The clinical significance of this is unknown, however, and there is currently no evidence to suggest that older women should receive lower doses of tamoxifen, or that lower doses of tamoxifen are as effective as standard doses in preventing breast cancer recurrences. Currently CYP2D6 genotype testing is not routinely recommended in breast cancer patients initiating tamoxifen [44].

Many drugs inhibit CYP2D6 function. Polypharmacy is common in older adults with cancer who take an average of six prescription medications [45]. It is unclear whether concomitant use of CYP2D6 inhibitors with tamoxifen affects breast cancer outcomes. Some studies suggest that co-prescription of CYP2D6 inhibitors increases the risk of breast cancer recurrence and associated death [46,47], while other studies have not noted this association [48]. Nevertheless, it

CYP 2D6	
Moderate-potent inhibitors	Weak-moderate inhibitors
Paroxetine	Amitryptilline
Fluoxetine	Nortryptilline
Bupropion	Haldol
Thioridazine	Verapamil
Perphenazine	Nifedipine
Pimozide	Cimetidine
Quinidine	Sertraline
Ticlopidine	
Terbinafine	

Table 2: Common inhibitors of CYP2D6.

is recommended that moderately-potent inhibitors of CYP2D6 be avoided if possible in women on tamoxifen [48] (Table 2). While there is no clear recommendation regarding weak to moderate inhibitors of CYP2D6, an alternative option should be considered when possible [48].

Drug interactions may also occur between tamoxifen and warfarin. Several case reports indicate that tamoxifen may increase the risk of bleeding complications while on warfarin [49,50] and as such it is advisable to closely monitor the INR in patients receiving warfarin and adjust the dose if required [51].

Aromatase inhibitors (AI) are another class of oral endocrine agents. Peripheral conversion of circulating androgens to estrogen by the enzyme aromatase forms the primary source of estrogen in post-menopausal women [52]. AI inhibit aromatase, thus reducing circulating levels of estrogen and inhibiting cell growth. Despite metabolism by P450 enzymes, there is no significant drug-drug interaction with commonly prescribed drugs that requires monitoring or caution [53].

Side Effects

Although AI are associated with a slight decrease in the risk of breast cancer recurrence compared with tamoxifen, the choice of endocrine agents is often influenced by differences in their side effect profiles. Both tamoxifen and AI are associated with side effects related to estrogen derivation including vasomotor symptoms such as hot flashes. The prevalence of hot flashes in tamoxifen users ranges from 40% to 70% [54-57], while AI may be associated with fewer hot flashes (36% to 38%) [25,58]. Genitourinary side effects that are common include vulvovaginitis, vaginal dryness or non-infectious discharge, and urinary incontinence [58,59].

Other more significant side-effects stemming from tamoxifen's estrogen agonist effect on the uterus includes an increased incidence of endometrial cancers in post-menopausal women (from 0.2% to 0.8%) [58]. Though the frequency of endometrial cancer remains low after 5 years of tamoxifen use, it nearly doubles (3.1%) when use is prolonged to 10 years [21].

There is a significant increase in the relative risk of thromboembolic events such as pulmonary embolism and strokes during tamoxifen use [60]. Data from adjuvant trials using tamoxifen confirm increased rates of venous-thromboembolic events (1.9% to 4.5%) [54,58]. Nevertheless, tamoxifen may have a protective effect with respect to some cardiac risk factors, as it is noted to reduce levels of low-density lipoprotein (LDL) [61]. Unlike tamoxifen, AI have no pro-estrogenic effects and as a result have a lower incidence endometrial cancer (0.2% vs. 0.8%) and venous thromboembolic events (2.4% to 2.8% vs. 4.1% to 4.9%) [25,58].

The most of troublesome side effects of AI is the presence of

musculoskeletal symptoms, including arthralgias, myalgias, and bone pain. Clinical trials indicate that about one third of women experience arthralgias [25,58]. In clinical practice, however, up to 60% of women taking AI report arthralgias or bone pain, with 30% characterizing their symptoms as severe and 20% discontinuing AI as a result [62]. AI-induced arthralgias (AIA) can be associated with morning stiffness and myalgias and typically start a median of 1.6 month after starting treatment (range weeks to >1 year), peaking at 6 months [63]. The risk of AIA is higher in patients who are obese, have baseline osteoarthritis or arthralgias, have received chemotherapy or have used hormone replacement therapy in the past [64,65].

AI are also associated with an increased incidence of osteoporosis (~33%) and fractures (~10%) compared to tamoxifen [25,58,66]. However, this risk appears to abate after discontinuation of AI [67]. Exemestane may be associated with a slightly lower incidence of osteoporosis compared to anastrozole [66]. Tamoxifen has an agonist effect on the bone resulting in a noted reduction in osteoporotic fractures during its use [68].

Given the involvement of multiple lymph nodes and Mrs. Smith's good functional status, the medical oncologist recommends that Mrs. Smith receive further treatment with endocrine agents. They discuss the option of tamoxifen vs. aromatase inhibitors. Mrs. Smith is concerned about developing arthralgias from an aromatase inhibitor given her pre-existing issues with osteoarthritis. Mrs. Smith agrees to a trial of tamoxifen.

Mrs. Smith makes an appointment to see her family doctor after being on tamoxifen for six months. She complains of significant hot flashes that are preventing her from sleeping. She is complaining of moderate fatigue that is impacting her ability to concentrate and she admits to skipping her medications at times.

Management of Side Effects of Tamoxifen and AI

Vasomotor symptoms

Vasomotor side effects are common with the use of oral endocrine agents. Non-pharmacological strategies such wearing lighter clothes, decreasing the room temperature, avoidance of noted triggers or changing the timing of medication use may help ameliorate some symptoms. Relaxation training and cognitive behavioural therapy has been found to reduce the incidence and severity of hot flashes in some studies [69,70]. Other non-pharmacologic interventions, such as exercise, have not been shown to improve vasomotor symptoms [70,71].

Hormone Replacement Therapy (HRT) has long been used to help ameliorate menopausal symptoms in women, though this practice has dropped dramatically since the reporting of the results of the women's health initiative. However, in women with hormone receptor positive breast cancer receiving endocrine therapy, there is naturally a concern about the association of HRT with an increased risk of breast cancer [72]. For this reason, non-hormonal pharmacologic agents are generally preferred (Table 3).

SSRI=serotonin selective reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor

**Potent inhibitor of CYP2D6–consider avoiding in patients on tamoxifen

Multiple studies and two systematic reviews found that selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and citalopram, and serotonin norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, decrease vasomotor symptoms in patients with

Class	Effective Dose
SSRI/SNRIs	Initial dose 37.5 mg/d – titrate to 75 mg/d after
Venlafaxine	1 week if needed
Paroxetine**	10 mg/d
Citalopram	10-20 mg/d
Gabapentin Pre-gabalin	≥900 mg/d 75 mg BID
Clonidine	0.1 mg/d

Table 3: Non-hormonal pharmacologic options for management of vasomotor symptoms.

breast cancer compared to placebo [73-75]. In patients on tamoxifen, however, avoidance of moderately-potent inhibitors of CYP2D6 such as paroxetine and fluoxetine (Table 2), which may decrease the efficacy of tamoxifen, should be avoided if possible. Gabapentin, pregabalin, and clonidine also decrease the frequency and severity of hot flashes compared to placebo [73,74,76-78] and are also reasonable options.

Comparing non-hormonal agents, one systematic review concluded that venlafaxine and paroxetine appeared to be most effective of the SSRIs/SNRIs [74]. In head-to-head studies, venlafaxine, gabapentin, and clonidine appear to reduce hot flash scores to a similar degree (33% to 66%) [74,79,80]. Patient comorbidity and drug side effect profiles may dictate selection of agents, though one study found that 2/3 of patients preferred venlafaxine over gabapentin [79].

Lastly, switching from one hormonal agent to another (i.e., from tamoxifen to an AI, or between AI) may help alleviate vasomotor symptoms in some women and is an option if the above strategies are ineffective.

Vulvovaginal symptoms

Vulvovaginal symptoms, such as dryness, are common in women on endocrine therapy affecting almost 50% of women on endocrine therapy, particularly those on AI [81]. Potential vaginal irritants such as scented toilet paper, soaps and fabric softeners, as well as synthetic garments should be avoided [59,82]. Regular sexual activity may help promote blood flow to the area improving vaginal atrophy [83]. Localized treatment with vaginal moisturizers, such as Vagisil and Replens, as well as the use of lubricants during intercourse may help alleviate symptoms [59,84].

Vaginally delivered low dose estrogen therapy improves symptoms of vulvovaginal atrophy and can result in an improvement in quality of life [85,86]. However, it is absorbed systemically to some extent and has been shown to increase serum estradiol levels to variable degrees [86,87]. This raises some concerns about the safety of vaginal estrogens in patients with breast cancer, particularly in patients on AI though the clinical implications of this increase in estrogen on breast cancer outcomes is unclear [82,86]. No increased risk of breast cancer recurrence was observed in a small cohort study (n=69) of women with breast cancer receiving topical vaginal estrogen [88]. Some suggest that vaginal estrogen therapy can be considered after a discussion of risks and benefits with the patient, particularly as vaginal symptoms that are not well controlled can potentially result in non-compliance or early discontinuation [59]. If utilized, consideration of vaginal estrogens with lower levels of systemic estrogen uptake should be considered [87]. Tamoxifen is associated with less vulvovaginal atrophy and dryness due to its weak pro-agonistic effect on the vagina and changing from an AI to tamoxifen is also a reasonable alternative strategy.

Endometrial cancer

Although tamoxifen is associated with a higher risk of endometrial cancer, there is currently no indication for routine screening of patients

with either transvaginal ultrasound or endometrial biopsies [89,90]. However, it is important to counsel patients to report any vaginal bleeding [90]. The American College of Obstetricians and Gynecologists recommends that post-menopausal women be thoroughly investigated when presenting with vaginal bleeding, and that tamoxifen be reassessed upon development of atypical hyperplasia [91].

Bone loss

Bone loss associated with AI use can have significant implications for older women as consequent fractures may lead to hospitalization, disability and institutionalization [92]. Patients receiving AI therapy should have baseline bone mineral density testing and this should be repeated regularly [19,93,94]. Patients should be counseled on established strategies to prevent bone loss including regular exercise, calcium and vitamin D supplementation, and smoking cessation, as well as recommendations to prevent falls including regular strength and balance training and reduce the use of psychotropic medications [95]. Bisphosphonates are indicated as dictated by current osteoporosis management guidelines [93]. The utilization of a switch strategy using tamoxifen initially may help mitigate the effects of subsequent use of AI [94].

Arthralgias

Educating patients about AI associated musculoskeletal side-effects before treatment initiation and assessing their baseline pain level due to pre-existing conditions is essential to optimally assess for the onset of AI-induced arthralgias (AIA) [96]. Initial management for AIA includes lifestyle modification such as weight loss, exercise, massage therapy, and physiotherapy [97,98]. Randomized studies of an exercise intervention and another using acupuncture have shown a reduction in the severity of pain from AIA [99,100]. While these studies are promising, further validation of these strategies are required.

If AIA are refractory to conservative management, pharmacologic intervention such as acetaminophen should be considered. Although non-steroidal anti-inflammatory drugs (NSAIDs) are an option [97,101], they should be used cautiously in older adults. If symptoms persist tramadol, low dose narcotics or intra-articular injections may be considered [97,102,103]. Co-analgesics, such as tricyclic antidepressants and gabapentin, can also be considered in conjunction with analgesia [97].

If AIA do not improve with non-pharmacologic interventions or analgesics switching to a different AI or to tamoxifen may be helpful. While comparisons of AI have demonstrated similar rates of arthralgia [66,104], some evidence suggests that some patients may benefit from a switch to another AI [105]. Switching to tamoxifen, which is associated with a lower rate of arthralgias (29.4% vs. 35.6%) [58], is also an option.

Adherence with Adjuvant Endocrine Therapy

As with any oral medication, efficacy of the treatment depends on patient adherence to the prescribed medication. This is a particularly relevant issue in older adults, who are often on multiple medications due to the presence of comorbid conditions and are at higher risk of cognitive impairments [106-108].

In patients prescribed endocrine therapy in the adjuvant setting, studies indicate that 13% to 42% do not start treatment [15,109-111], with higher values reported in studies which checked prescription refills, rather than by self-report [15,107,108]. One study found that women who were older at diagnosis (age 80 or older) were less likely to initiate therapy while another found that older women were more

likely to fill the initial prescription [15,108]. Another study found women who were frail or pre-frail were more likely to not initiate recommended endocrine therapy [15,111]. This may be because women who are frailer have a higher risk of non-cancer related death with prior studies showing that women with a Satariano comorbidity index of 2+ have a 4.2x to 20x increased risk of death without recurrence [10,112]. Increased age alone, however, should not be a reason not to initiate or continue adjuvant endocrine therapy as older women, particularly those 80 and over, are at high risk of under-treatment, which has been shown to result in increased breast cancer mortality [10-12].

Of women who initiate adjuvant endocrine therapy, early discontinuation of treatment prior to the completion of 5-years is common, ranging from 25% to 73% [15,109,111,113-118]. Even in those patients who continue with endocrine therapy, only 60% to 81% of women are considered adherent (defined as having medication for at least 80% of the days) [109,110,114,116,119,120]. The rate of early discontinuation is highest in the first year (15-32%) with a rate of discontinuation of about 10% annually in subsequent years [9,109,118].

Older women may be at a particularly high risk of early discontinuation and non-adherence. Increasing age, especially age greater than 75 years or 85 years old, has been associated with both early discontinuation and non-adherence [15,108,109,111]. Furthermore, multi-morbidity and polypharmacy (>15 medications), which are common in this population, are also associated with an increased risk [109,115-117,120]. One study found that an increase in comorbid conditions (HR 1.52) or cardiopulmonary comorbidities (HR 1.75) 3-years after breast cancer diagnosis, compared to at the time of breast cancer diagnosis, was predictive of early discontinuation of endocrine therapy, potentially indicating a decision by patients or physicians to stop treatment due to an increased risk of non-cancer mortality [117]. This was suggested in another study in which adjuvant endocrine therapy was discontinued more commonly by physicians in women age 80 and over, compared to women age 60-79, due to serious medical reasons not related to breast cancer (17% vs. 4.7%, $p=0.003$) [15]. Interestingly, being frail at diagnosis was not found to be predictive of early discontinuation [111].

Women who do not receive chemotherapy [109,113] or radiation [109], more commonly seen with increasing age, are also at higher risk of non-adherence. Early discontinuation and non-adherence can be especially concerning in women who have had breast conserving therapy but have not received any breast irradiation [117]. Omission of radiation is an acceptable strategy in some women >70 years old with small node-negative hormone sensitive tumors receiving endocrine therapy, as studies suggest no survival disadvantage, though there is a higher risk of local recurrence [121,122]. This, however, is in the context of endocrine therapy and thus adherence with endocrine therapy is particularly important in this subset of women. In fact, it has been shown that mortality is higher in women who discontinue hormonal therapy early (HR 1.49; 10-year survival 73.6% vs. 80.7%, $p<0.001$), as well as in those who are non-adherent with endocrine therapy (HR 1.25; 10-year survival 77.8% vs. 81.7%, $p<0.001$) [113].

Discontinuations within 12 months of initiation are more often due to the presence of intolerable adverse effects compared to late discontinuations (43% vs. 24%) [15,117]. Thus, addressing side effects such as hot flashes and arthralgias (as discussed above) and/or considering a switch from one agent to another (i.e., tamoxifen to aromatase inhibitor or vice versa), may help improve compliance. Financial factors, such as amount of copayment and household income may also influence non-adherence and premature discontinuation of

endocrine therapy [109,116,118,120]. Prescription of generic forms of endocrine therapy may be one method to help improve patient compliance [116].

Mrs. Smith's doctor reviews the rationale for tamoxifen and emphasizes the importance of taking it on a regular basis. They discuss non-pharmacological methods to manage her hot flashes. Mrs. Smith says that she is already wearing light clothing and using a fan at night. They discuss the possibility of starting her on venlafaxine to help her symptoms and she is amenable to trying it.

Mrs. Smith starts on a low dose of venlafaxine. On follow-up with her family doctor 6 weeks later she notes a slight improvement in her hot flashes. Her family increases the dose of venlafaxine. On subsequent follow-up Mrs. Smith reports a marked improvement in her hot flashes. She reports no difficulty with taking her medication and states she is taking all her medication on a daily basis.

Conclusion

In summary, breast cancer is common in older women and most have hormone sensitive disease. Surgical resection should be offered as a standard to most women with localized disease regardless of age unless their estimated life expectancy is <2 years or they are unfit or refuse surgery. Adjuvant endocrine therapy significantly decreases the risk of recurrent breast cancer, contralateral breast cancer, and breast-cancer related mortality in both younger and older women. Assessment of the overall health of older women is important to determine the likelihood of cancer vs. non-cancer death. Early discontinuation and non-adherence is prevalent and may be associated with higher rates of mortality. Monitoring and addressing side effects from adjuvant endocrine therapy is important to help decrease early discontinuation of treatment.

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