Adjuvant Endocrine Therapy in Premenopausal Women With Breast Cancer

Kunal C. Kadakia, MD, and N. Lynn Henry, MD, PhD

The authors are affiliated with the University of Michigan Comprehensive Cancer Center. Dr Kadakia is a hematology/oncology fellow and Dr Henry is an associate professor in the breast oncology program.

Corresponding author:
Norah Lynn Henry, MD, PhD
University of Michigan Comprehensive Cancer Center
1500 East Medical Center Drive
Med Inn Building C450
Ann Arbor, MI 48109-5843
Tel: (734) 936-4991
Fax: (734) 936-4940
E-mail: norahh@med.umich.edu

Abstract: Breast cancer remains the leading cause of cancer-related mortality in premenopausal women. Multiple advances in local and systemic therapies have dramatically improved outcomes in women with hormone receptor–positive early-stage breast cancer. Despite these advances, early and late relapses occur. Therefore, multiple adjuvant endocrine therapy trials have been conducted with the goal of decreasing breast cancer recurrence and mortality. Recently, large international trials evaluating extended endocrine therapy and ovarian suppression with and without tamoxifen or exemestane have been reported. These studies add to the large body of existing data on adjuvant endocrine therapy in premenopausal women with breast cancer and provide additional therapeutic options in those at high risk of disease recurrence. This review will synthesize the most recent data and promote an evidence-based approach, highlighting quality-of-life concerns, to considering adjuvant endocrine therapies in premenopausal women.

Keywords
Adjuvant therapy, endocrine therapy, ovarian ablation, ovarian suppression, quality of life, tamoxifen

Introduction

In the United States, breast cancer remains the most common cancer in women, with more than 230,000 new cases and 40,000 deaths per year.[1] The vast majority of new cases represent early-stage disease (ie, stage I or II), and approximately 25% of cases are diagnosed in premenopausal women. Hormone receptor (HR)–positive breast cancer is the most common subtype,[2] and decades of clinical trials optimizing adjuvant endocrine therapies have led to significantly improved outcomes.[3] Most recently, large international trials have shown decreased breast cancer recurrence rates with extended endocrine therapy[4] and adjuvant ovarian suppression.[5,6] Despite these advances, the optimal strategy for endocrine therapy in premenopausal early-stage HR-positive breast cancer remains challenging given the good prognosis of many patients, the inherent risk of overtreatment, and the short- and long-term toxicities associated with such therapies.

This review focuses on the current state of evidence related to adjuvant endocrine therapy for HR-positive breast cancer in premenopausal women, primarily the most recent data related to extended endocrine therapy and the role of ovarian suppression. Additionally, these data will be reviewed in the context of quality-of-life (QOL) and survivorship concerns as they relate to premenopausal women.

Endocrine Therapies

Adjuvant endocrine options for premenopausal women in the contemporary era include tamoxifen with or without ovarian suppression (OS)/ovarian ablation (OA), an aromatase inhibitor (AI) with OS/OA, or OS/OA alone. Treatment with endocrine therapy is indicated only for breast cancers that have estrogen receptor (ER) expression measured by clinically validated techniques.[7]

Tamoxifen is a selective ER modulator that can be used to treat both pre- and postmenopausal women with breast cancer. When administered for 5 years, tamoxifen reduces the risk of disease recurrence in early-stage breast cancer by approximately 40% and the risk of breast cancer death by approximately 30%.[8] The therapeutic effect is independent of plasma estradiol levels.

The goal of therapy is to reduce ER signaling. Because the ovaries produce the vast majority of estrogen in premenopausal women, an alternative to tamoxifen monotherapy is OA or OS, either alone or in combination with tamoxifen. OA is the most effective modality to suppress circulating estrogen and is achieved either via bilateral oophorectomy or radiation, both of which lead to permanent cessation of menses. Alternatively, ovarian function can be suppressed temporarily with the use of luteinizing hormone-releasing hormone (LHRH) agonists such as triptorelin, goserelin (Zoladex, AstraZeneca), or leuprolide (Lupron, Abbvie). Consideration should be given to administering these intramuscular or subcutaneous depot agents every 28 days (rather than every 84 days) because most clinical trials used monthly administration and the efficacy of the medication could wane before the end of the dosing period.[9] However, owing to lack of efficacy data, using OS/OA as the sole therapy for breast cancer treatment is not recommended unless a patient is unable or unwilling to receive treatment with another appropriate systemic therapy.[9]

Another alternative to tamoxifen is an AI. In postmenopausal women with early-stage breast cancer, the AIs—including the nonsteroidal agents anastrozole and letrozole and the steroidal agent exemestane—appear to be equally effective[10] and consistently are more effective than tamoxifen in postmenopausal women.[11] However, AI medications alone are not useful in premenopausal women because these drugs act peripherally by blocking the conversion of androgens to estrogens and have no impact in high-estrogen states.[12] As such, it is imperative to: (1) determine menopausal status prior to considering endocrine therapy in any patient with HR-positive breast cancer and (2) combine therapy with OS/OA if AI treatment is given to a woman who is not definitely postmenopausal.

Thus, for a premenopausal woman, endocrine therapy options include tamoxifen alone, OA/OS alone, or OA/OS in combination with either tamoxifen or an AI. As described later in this review, determining which premenopausal women should receive endocrine therapy in combination with OS/OA is complex because of efficacy and tolerability issues.

Menopausal Status and Chemotherapy-Induced Ovarian Failure

Menopause has been broadly defined as age greater than 60 years, having undergone bilateral oophorectomy, or having amenorrhea for at least 12 months in the absence of factors potentially influencing menstruation (eg, chemotherapy, tamoxifen, or OS).[13] Confirming menopausal status can be a challenge in women who have undergone hysterectomy without bilateral oophorectomy or who develop chemotherapy-induced ovarian failure (CIOF). Women younger than 60 years with HR-positive breast cancer who have undergone hysterectomy without bilateral oophorectomy and who will be receiving chemotherapy should have ovarian function assessed prior to chemotherapy initiation in order to determine prechemotherapy menopausal status. This information helps to inform the choice of endocrine therapy and the potential need for monitoring of ovarian function.

Women with CIOF can experience reactivation of ovarian function during AI therapy despite having estradiol concentrations in the postmenopausal range at the time of AI initiation.[14,15] Estradiol levels also can increase even if menses do not resume. Notably, younger age at the time of chemotherapy is independently associated with a higher chance of ovarian function recovery following AI therapy, and no upper age limit has been identified.[15]

One small study of 58 women with CIOF who had a mean age of 48 years demonstrated a lower disease-free survival (DFS) rate in the cohort that experienced ovarian function recovery (based on resumption of menses or elevated estradiol levels).[14,15] By contrast, 2 other studies identified no difference in breast cancer outcomes with AI therapy. Subgroup analyses of the Breast International Group (BIG) 1-98 trial including 105 patients with CIOF compared letrozole vs tamoxifen as frontline therapy in postmenopausal women. In the second study, subgroup analyses of the MA.17 trial included women

who were premenopausal at the time of tamoxifen initiation and compared letrozole vs placebo after 5 years of tamoxifen.[16,17] The reason for the discrepancy between these findings is uncertain, and may be due to differences in patient populations.

In the absence of meeting the age criteria (>60 years) or having undergone bilateral oophorectomy, consensus guidelines suggest possibly testing plasma follicle-stimulating hormone levels and estradiol levels to confirm postmenopausal state.[13] However, a recommended monitoring interval has not been established, and the available estradiol assays in most laboratories are not sensitive enough to detect very low concentrations of estradiol.[18-20] Ultrasensitive estradiol assays utilizing mass spectroscopy are commercially available and can be considered for women at risk for recovery of ovarian function. Women with CIOF who are younger than 50 years of age are at high risk of ovarian function recovery. In addition, providers should not assume that all women older than 50 years of age who become postmenopausal from chemotherapy will remain postmenopausal during AI therapy. Either tamoxifen or OS/OA plus either tamoxifen or AI therapy should be used, or ovarian function should be closely monitored using ultrasensitive estradiol assays.

Efficacy of 5 Years of Adjuvant Tamoxifen

Initially convened in 1985, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) utilizes individual patient-level data to conduct meta-analyses on multiple aspects of early breast cancer therapy. Until recently, the standard adjuvant endocrine therapy for patients with HR-positive premenopausal breast cancer was 5 years of tamoxifen.[21] This recommendation was largely based on the 2011 EBCTCG analysis comparing tamoxifen vs no tamoxifen in patients with ER-positive early-stage breast cancer (n=10,645).[8] For the entire ER-positive cohort, 5 years of tamoxifen treatment reduced the risk of breast cancer recurrence by nearly one-half through 10 years (recurrence rate ratio [RR], 0.53 during years 0-4; recurrence RR, 0.68 during years 6-9; both $P<.00001$) with a stable recurrence rate observed during years 10 to 14 (recurrence RR, 0.97). Breast cancer mortality was reduced by nearly one-third through 15 years (death RR, 0.71 during years 0-4; death RR, 0.66 during years 5-9; death RR, 0.68 during years 10-14; all $P<.0001$). Most strikingly, the absolute mortality difference with 5 years of tamoxifen compared with no therapy was 3 times higher at year 15 (24% vs 33%) compared with year 5 (9% vs 12%), suggesting an ongoing benefit despite discontinuation of tamoxifen (ie, a carryover effect). All findings were independent of progesterone receptor status, use of chemotherapy, and nodal status. Young, presumably premenopausal women (age <45 years) had similar reductions in recurrence, breast cancer death, and all-cause mortality compared with those 55 to 69 years of age.

Even comparing patients with low-level vs high-level ER-positive expression, no statistically significant difference in efficacy was observed. In the EBCTCG meta-analysis, determination of ER overexpression was based on historical ligand-binding assays and utilized a cutoff of 10 femtomoles of receptor protein per mg cytosol protein. Although modern assessment of ER status is based on immunohistochemistry (percentage of tumor cells stained by an antibody against ER), concordance with historical ligand-binding assays is good.[22] Current guidelines recommend that a breast cancer with least 1% of tumor cells positive for ER be considered ER-positive and treated accordingly in order to avoid omitting a potentially beneficial therapy from the patient's treatment regimen.[13]

Risk of Late Relapse in HR-Positive Breast Cancer

The risk of relapse in breast cancer varies over time and is dependent on a number of prognostic features including stage, histopathology, and HR status. Unlike HR-negative breast cancer, which typically has the highest relapse rates early after diagnosis, HR-positive breast cancer has a unique predilection for late relapses.[23] Based on Surveillance, Epidemiology, and End Results (SEER) data,[24] HR-positive breast cancer has an estimated annual hazard rate for relapse of approximately 1% to 2% that plateaus and persists through years 10 to 15.

Extended Tamoxifen Therapy (10 Years vs 5 Years)

Despite the carryover effect of 5 years of tamoxifen therapy, late relapses occur. Therefore, multiple trials have examined prolonged endocrine therapy to determine whether continued treatment beyond 5 years will improve breast cancer outcomes. National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-14, the largest historical trial, only included patients who were lymph node (LN)–negative, and surprisingly observed an advantage for those who discontinued tamoxifen at 5 years compared with those who received extended therapy (DFS, 82% vs 78%, respectively; $P=.03$).[25]

In contrast to the above data, 2 recently reported large trials demonstrated improvements in breast cancer outcomes with extended tamoxifen therapy. The ATLAS (Adjuvant Tamoxifen: Longer Against Shorter)[4] trial randomly assigned women with ER-positive or ER-unknown early-stage breast cancer who had completed 5 years of tamoxifen to receive 5 additional years or to observation.

Table 1. Adjuvant Tamoxifen Trials Testing Treatment Beyond 5 Years

Study	Number of Patients (%)	Study Arm	Recurrence Rate, N (%)	*P* Value	Breast Cancer Mortality, N (%)	*P* Value	Overall Mortality, N (%)	*P* Value
ATLAS,[4] total	12,894 total, 6846 ER-positive	Tam Control	617 (21) 711 (25)	0.002	331 (12) 397 (15)	0.01	679 (10.5) 691 (10.7)	0.84
ER-positive, premenopausal	326 (10) 304 (9)	Tam Control	64 (20) 73 (24)	0.79	NR	NR	NR	NR
ER-positive, postmenopausal	3035 (89) 3044 (89)	Tam Control	553 (18) 638 (20)					
aTTom[26]	6953 total, 2755 ER-positive	10 y tam 5 y tam	580 (28) 672 (32)	0.003	392 (NR) 443 (NR)	0.05	849 (NR) 910 (NR)	0.10
2013 meta-analysis[27]	29,138 total, 15,739 ER-positive	Tam Control	828 (11) 1018 (13)	0.01	454 (10) 563 (12)	0.0003	823 (11) 911 (12)	0.03

ATLAS, Adjuvant Tamoxifen: Longer Against Shorter; aTTom, Adjuvant Tamoxifen-To Offer More?; ER, estrogen receptor; tam, tamoxifen; NR, not reported; y, year.

The aTTom (Adjuvant Tamoxifen-To Offer More?)[26] trial randomly assigned women with ER-positive or ER-unknown early-stage breast cancer to 5 or 10 years of tamoxifen. Ten years following randomization, the ATLAS trial identified an absolute reduction in breast cancer recurrence of approximately 4% in ER-positive patients (21.4% with continued tamoxifen vs 25.1% on observation; *P*=.002). A very modest absolute reduction in breast cancer mortality and a nonsignificant difference in overall mortality also were observed in the entire cohort (Table 1). As was observed in the 2011 EBCTCG meta-analysis, the effect of extended tamoxifen was time-dependent, with a relatively minor decrease in recurrence rates during years 5 through 9 (relative risk, 0.90; 95% CI, 0.79-1.02; *P*=.10) and a nearly 25% reduction after year 10 (relative risk, 0.75; 95% CI, 0.62-0.90; *P*=.002). These findings were independent of age, stage, or menopausal status.

Mirroring the ATLAS data, at 15 years after diagnosis the aTTom trial demonstrated a similar absolute reduction in breast cancer recurrence of approximately 4% (28% for 10 years of tamoxifen vs 32% for 5 years of tamoxifen; relative risk, 0.85; 95% CI, 0.76-0.95; *P*=.003) with a modest reduction in breast cancer mortality and no difference in overall mortality. However, combined analyses of both trials showed that after year 10, extended tamoxifen significantly reduced breast cancer mortality (relative risk, 0.75; 95% CI, 0.65-0.86; *P*=.002) and overall survival (relative risk, 0.84; 95% CI, 0.77-0.93; *P*=.005).[26] A recent meta-analysis combining these data along with prior extended tamoxifen trials have confirmed these findings.[27]

How Might Extended Therapy Be Applied to Premenopausal Women?

As shown in Table 1, fewer than 10% of patients in ATLAS were premenopausal at the time of randomization, which limits generalizations. However, there is a suggestion of a greater absolute reduction in recurrence rate with extended tamoxifen therapy in premenopausal women as compared with postmenopausal women (4.4% vs 2.7%, chi-square *P*=.79).[4] In the NSABP B-14 study described above, analysis conducted by age (≤49 vs ≥50 years) failed to demonstrate a difference in DFS between groups.[25]

At present, no validated assays are available to estimate the benefit gained from extended endocrine therapy. Recent data suggest that the Breast Cancer Index, an 11-gene assay that combines the Molecular Grade Index (assessing tumor grade and proliferation), the HOXB13:IL17BR index, and 4 reference genes, may be helpful for predicting risk of late recurrence, but this tool is not yet recommended for routine clinical use.[28] Development of such a tool could optimize treatment decision-making by identifying patients with increased risk of delayed recurrence who would benefit from extended treatment vs patients with minimal risk who could avoid extra treatment and the associated toxicity.

Current guidelines recommend that patients who remain premenopausal or perimenopausal following 5 years of adjuvant tamoxifen should be offered extended therapy for up to 10 years.[13,21,29]

Historical Data Supporting Ovarian Suppression or Ovarian Ablation

Multiple historical trials comparing a variety of adjuvant chemotherapy combinations with OS/OA have been conducted.[30] In 2007, ER-positive premenopausal women (n=11,906) were included in the LHRH-Agonists in Early Breast Cancer Overview meta-analysis.[31] When used alone, LHRH agonists did not significantly reduce recurrence or breast cancer mortality. However, the addition of LHRH agonists to tamoxifen, chemotherapy, or

Table 2. Clinical Trials Evaluating Ovarian Suppression in Combination or Sequential Therapy for Premenopausal ER-Positive Breast Cancer

Trial	Patients	Median Follow-up	Treatment	Disease-Free Survival			Overall Survival		
				%	HR (95% CI)	*P* Value	%	HR (95% CI)	*P* Value
INT-0142[49]	N=345 100% LN- 0% chemo	9.9 y	Tam + OFS	89.7	1.17 (0.64-2.12)	.62	97.6	1.19 (0.53-2.65)	.67
			Tam	87.9			95.2		
ABCSG-12[33]	N=1803 70% LN- 5% chemo	62 mo	Anas + OFS	89.3	1.08 (0.81-1.44)	.59	94.9	1.75 (1.08-2.83)	.02
			Tam + OFS	90.2			97		
SOFT/TEXT,[6] joint analysis	N=4690 58% LN- 57% chemo	68 mo	Exem + OFS	91.1	0.72 (0.6-0.85)	<.001	95.9	1.14 (0.86-1.51)	.37
			Tam + OFS	87.3			96.9		
SOFT,[5] entire cohort	N=3066 65% LN- 53% chemo	67 mo	Exem + OFS	90.9	0.64 (0.49-0.83)	NR	NR		
			Tam + OFS	88.4	0.81 (0.63-1.03)	.09	96.7	0.74 (0.51-1.09)	.13
			Tam	86.4			95.1		
SOFT, prior chemo	N=1628 100% chemo		Exem+ OFS	83.8	0.7 (0.53-0.92)	NR	92.3	0.87 (0.59-1.27)	NR
			Tam + OFS	80.7	0.82 (0.64-1.07)	.96	94.5	0.64 (0.42-0.96)	.03
			Tam	77.1			90.9		
SOFT, <35 y	N=233 94% chemo		Exem + OFS	83.4	NR		NR		
			Tam + OFS	78.9	NR		NR		
			Tam	67.7	NR		NR		

ABCSG, Austrian Breast and Colorectal Study Group; Anas, anastrozole; CI, confidence interval; Exem, exemestane; HR, hazard ratio; LN-, lymph node negative; mo, months; NR, not reported; OFS, ovarian function suppression; SOFT, Suppression of Ovarian Function Trial; Tam, tamoxifen; TEXT, Tamoxifen and Exemestane Trial; y, years.

both reduced breast cancer recurrence by 13% (95% CI, 2.4-21.9; *P*=.02) and breast cancer mortality by 15% (95% CI, 1.80-26.7; *P*=.03). LHRH agonists alone showed similar efficacy to chemotherapy alone.

Notably, this meta-analysis observed a differential benefit in younger patients (age <40 years). The authors hypothesized that younger women were more likely to recover ovarian function following chemotherapy, and therefore, most likely to benefit from OS/OA. Despite these findings, a number of unanswered issues remain. The analyzed trials were largely conducted prior to the contemporary use of anthracyclines and taxanes (which are associated with lower rates of CIOF) and the standard use of tamoxifen and AIs.

Contemporary Trials of Ovarian Suppression

Studies have shown consistent but relatively small improvements in breast cancer recurrence with AIs vs tamoxifen in the postmenopausal setting[11]; however, it was still unclear whether premenopausal women who undergo OS/OA would benefit from concurrent AI therapy compared with tamoxifen. Three large contemporary trials have reported the role of OS/OA in combination with tamoxifen or an AI in premenopausal women. The main outcomes of the Austrian Breast and Colorectal Study Group (ABCSG)-12 trial,[32,33] Suppression of Ovarian Function Trial (SOFT),[5] and Tamoxifen and Exemestane Trial (TEXT)/SOFT joint analysis[6] are shown in Table 2.

The ABCSG-12 trial randomly assigned 1803 HR-positive premenopausal women with early-stage breast cancer to receive goserelin plus tamoxifen or goserelin plus anastrozole with or without zoledronic acid. Most patients did not receive chemotherapy. At 62 months, there was no difference in DFS between those who received anastrozole vs tamoxifen (HR, 1.08; 95% CI, 0.81-1.44; *P*=.591). Surprisingly, overall survival appeared worse in

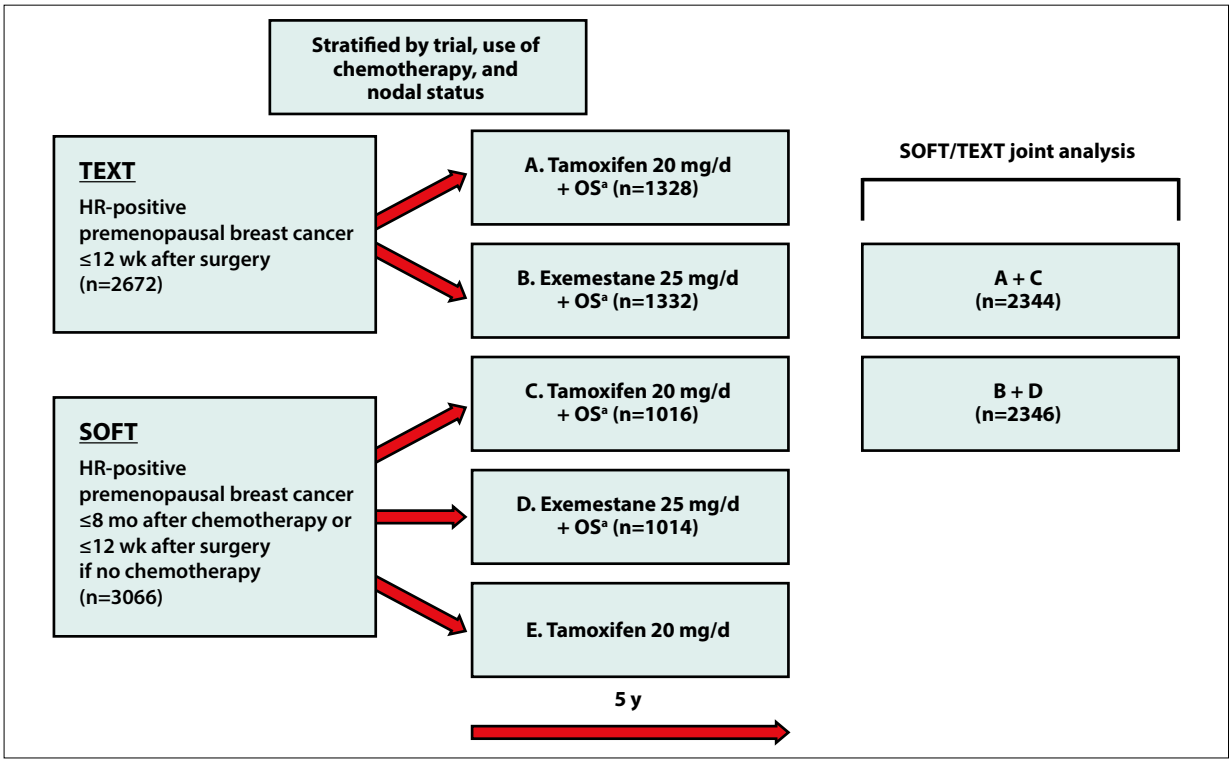

Figure 1. Design and treatment allocation for SOFT, TEXT, and the joint analysis.

d, days; HR, hormone receptor; mo, months; OS, ovarian suppression; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial; wk, weeks; y, years.

[a]TEXT, triptorelin 3.75 mg intramuscularly every 28 days for 6 months, then optional bilateral oophorectomy or irradiation; SOFT, choice of OS method (triptorelin, bilateral oophorectomy, or radiation).

those randomly assigned to receive anastrozole compared with tamoxifen (46 vs 27 deaths, respectively; HR, 1.75; 95% CI, 1.08-2.83; *P*=.02). This finding initially suggested a possible distinct synergism between tamoxifen and the LHRH agonist compared with anastrozole. However, an unplanned subgroup analysis appeared to show that obesity was associated with a 3-fold increase in risk of death in women receiving anastrozole vs tamoxifen (HR, 3.03; 95% CI, 1.35-6.82; *P*=.004), possibly because of inadequate ovarian suppression by LHRH agonists in obese patients.[34]

The specific design and treatment allocations for the SOFT and TEXT trials, as well as the joint analysis, are shown in Figure 1. In TEXT, all women received OS and were randomly assigned 1:1 to receive tamoxifen or exemestane. By contrast, SOFT consisted of 3 arms, and patients were randomly assigned 1:1:1 to receive tamoxifen alone or OS/OA with either tamoxifen or exemestane. Owing to lower-than-expected event rates, a joint analysis of SOFT and TEXT was performed.[6] As shown in Table 2, there was a 3.8% absolute improvement in DFS (the primary endpoint in both trials and the joint analysis) in women receiving exemestane plus OS (E/OS) compared with tamoxifen plus OS (T/OS). The primary goal of adjuvant therapy is to prevent distant recurrence (and thereby death); therefore, it is notable that the difference in recurrence at a distant site, though significant, was only 1.8% (E/OS: 93.8% vs T/OS: 92%; HR, 0.78; 95% CI, 0.62-0.97; *P*<.02), and no significant difference was found in overall survival (E/OS: 95.9% vs T/OS: 96.9%).

Subgroup analyses appeared to show that women who received chemotherapy were most likely to benefit from E/OS. Of the 57.4% that received chemotherapy, the distant recurrence-free survival was better with E/OS compared with T/OS in TEXT (91.8% vs 89.2%; HR, 0.77; 95% CI, 0.56-1.06) and SOFT (88% vs 84.6%; HR, 0.81; 95% CI, 0.58-1.13). Similarly, those with LN-positive disease differentially benefited from E/OS compared with T/OS.

The primary analysis of DFS between T/OS or E/OS compared with tamoxifen alone in the SOFT trial was reported separately. As shown in Table 2, no significant difference in DFS or overall survival was observed between groups. However, 2 distinct subgroups appeared to derive benefit from OS, including those who received chemotherapy and those younger than 35 years. The preplanned subgroup analysis of women younger than 35 years revealed that OS plus tamoxifen yielded an approximately 11% absolute increase in DFS compared with

tamoxifen alone. Exemestane plus OS was associated with an even greater absolute improvement in DFS (approximately 16%) compared with tamoxifen alone.

Overall, the SOFT and TEXT data provide compelling evidence that an AI or tamoxifen plus OS can significantly reduce the risk of recurrence compared with tamoxifen alone in premenopausal women at the highest risk for relapse (ie, age <35 years and those who maintain premenopausal status following chemotherapy).

Overall Survival and the Role of SOFT/TEXT in the Contemporary Era

In the SOFT and TEXT trials, no improvement in overall survival was seen with the addition of OS. However, given the few events observed in this cohort, the overall excellent prognosis (5-year survival, 96%-97%), and the long natural history of HR-positive breast cancer, the absence of an overall survival difference is likely due to insufficient follow-up. Long-term results (10-15 years) are eagerly awaited. The worse overall survival seen with AI plus OS in the ABCSG-12 trial has not yet been replicated in SOFT/TEXT; follow-up is ongoing.

Symptom Burden and Quality of Life During Endocrine Therapy

In order to appreciate the relative toxicities observed in SOFT/TEXT, it is important to consider the safety profiles of single-agent tamoxifen and AIs. Common adverse effects of endocrine therapies can be divided into: (1) symptoms that are bothersome and impact QOL and adherence and (2) serious toxicities that can impact morbidity and mortality but do not necessarily cause symptoms. Bothersome symptoms must be recognized and treated because early discontinuation of these medications is common, is often attributed to adverse effects, and likely leads to worse outcomes.[35-37]

Tamoxifen

Subjectively, adverse events for tamoxifen treatment most often include vasomotor dysfunction (eg, hot flashes and night sweats), sexual dysfunction, and menstrual irregularities. Vasomotor symptoms occur in more than 75% of women and are considered severe in up to 30%.[38,39] Multiple pharmacologic agents (eg, venlafaxine, citalopram, and gabapentin) have been tested in randomized placebo-controlled trials and confirmed to significantly improve symptoms; therefore, these drugs should be considered first-line treatment in women with burdensome hot flashes.[40]

Tamoxifen is also associated with a rare but serious risk of venous thromboembolism (VTE) and uterine cancer. The risk of uterine cancer is increased with obesity and prior use of estrogen replacement therapy.[4,26,41] Risk factors for VTE while on tamoxifen include older age, concurrent tobacco use, personal or family history of VTE, and the presence of the factor V Leiden mutation.[42]

Importantly, although the incidence of uterine cancer was higher in tamoxifen-treated patients, no significant difference was observed in women younger than 45 years (15-year incidence, 0.4% vs 0.3%; *P*=.97). Similarly, thromboembolism was observed in greater frequency in tamoxifen-treated patients vs control, all of which occurred in women aged 55 to 69 years. Taken together, these data support that young women (<45 years of age) treated with tamoxifen have the least risk for uterine cancer and thromboembolic disease, and have a similar benefit as older patients.

Treatment with tamoxifen for 10 years (compared with 5 years) is associated with a further increase in uterine cancer and thromboembolic disease. In ATLAS, an increased cumulative risk of uterine cancer during years 5 to 14 was observed (incidence, 3.1% vs 1.6%; recurrence RR, 1.74; 95% CI, 1.30-2.34; *P*=.0002). This resulted in an absolute mortality increase of 0.2% in the extended therapy group. The incidence of pulmonary embolism was also increased (recurrence RR, 1.87; 95% CI, 1.13-3.07; *P*=.01). However, there was no increased risk of stroke, and tamoxifen appeared to have a protective effect on ischemic heart disease. A similar increase in uterine cancer was observed in aTTom, with a slightly higher associated death rate (1.1% vs 0.6%; *P*=.02). These analyses were not separated by menopausal status or age, so whether the risks are increased in premenopausal women is unknown.

Aromatase Inhibitors

AI therapy in postmenopausal women is associated with more pronounced vulvovaginal symptoms (vaginal dryness and dyspareunia) and can lead to greater sexual dysfunction compared with tamoxifen treatment.[43] Unique to this class of medications, the AI-associated musculoskeletal symptoms can be a significant cause of morbidity in as many as 25% of patients and can lead to early discontinuation.[44] These symptoms can manifest in a variety of ways, including generalized arthralgias, carpal tunnel syndrome, tendonitis, and myalgias. Greater bone loss (osteoporosis), more fractures, and increased cardiovascular morbidity also have been observed with AIs compared with tamoxifen. In a meta-analysis of 7 trials comparing AIs vs tamoxifen in postmenopausal women, AIs significantly increased the risk of fractures (odds ratio [OR], 1.47; 95% CI, 1.34-1.61) and cardiovascular disease (OR, 1.26; 95% CI, 1.10-1.43).[45] AI-associated bone loss is more pronounced in premenopausal women.[6,33]

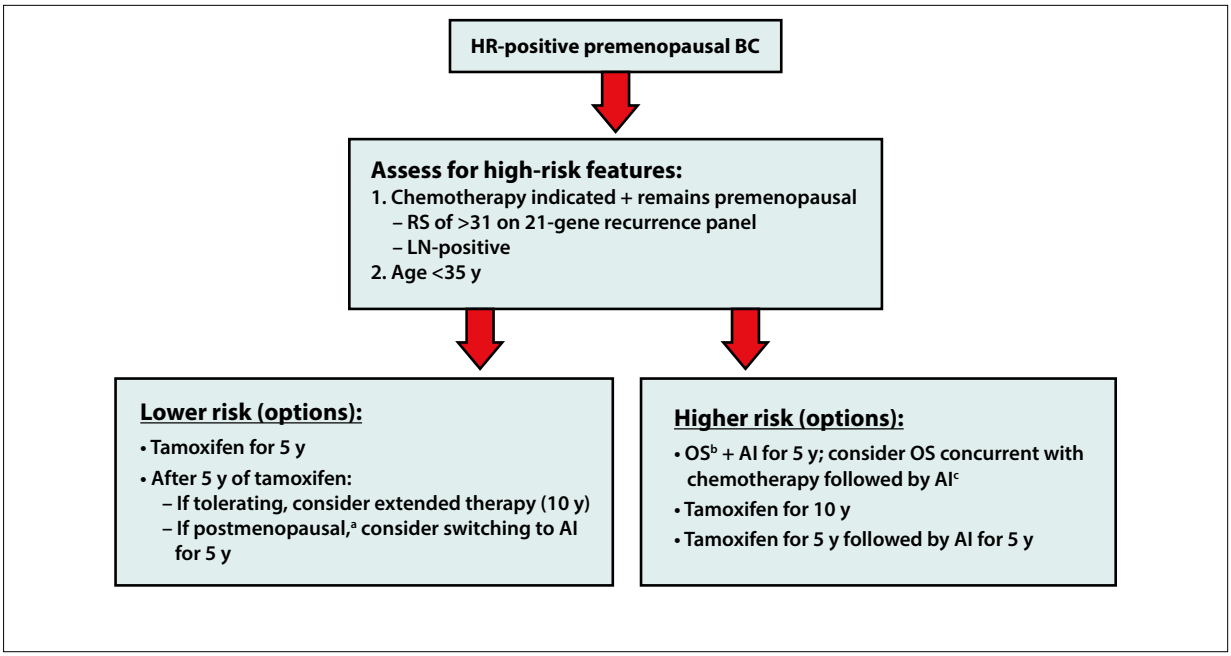

Figure 2. Adjuvant endocrine options for HR-positive premenopausal breast cancer.

AI, aromatase inhibitor; BC, breast cancer; HR, hormone receptor; LN, lymph node; OS, ovarian suppression; RS, recurrence score; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial; y, years.

[a]To confirm postmenopausal state, use follicle-stimulating hormone and plasma estradiol level to confirm postmenopausal levels. If uncertain whether definitely permanently postmenopausal at time of switch to AI, continue to monitor for breakthrough ovarian function.

[b]Unless clear indication for permanent menopause (eg, *BRCA* carrier), consider temporary ovarian suppression. Should confirm suppression of ovarian function biochemically.

[c]Concurrent OS was utilized in TEXT, which appeared to have slightly improved distant recurrence-free survival compared with SOFT.

Strategies to minimize AI-associated bone loss involve promoting regular weight-bearing exercise, limiting bone-offending medications (eg, corticosteroids) or behaviors (eg, tobacco use), and maintaining adequate vitamin D and calcium intake. Use of bisphosphonates or denosumab (Prolia, Amgen) is indicated for pre- and postmenopausal women who develop osteoporosis based on a bone density scan (DEXA; T-score of -2.5 or lower) or who are at high risk for fracture based on the World Health Organization Fracture Risk Assessment Tool (FRAX).[46]

Tamoxifen or AI Plus Ovarian Suppression

In the SOFT/TEXT joint analysis,[6] significant toxicities were observed with both E/OS and T/OS, leading to high rates of hot flashes (91.7% vs 93.3%), musculoskeletal symptoms (88.7% vs 76%), fatigue (61.3% vs 62.9%), insomnia (58.2% vs 58.5%), depression (50.3% vs 50.1%), and dyspareunia (30.5% vs 25.8%). These symptoms can lead to psychological distress, depression, worse self-image, and poor emotional, physical, and functional well-being.[47] Acknowledging the limitations of cross-trial comparisons, patients treated in SOFT/TEXT had increased toxicity compared with the older postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. Compared with the observed toxicity in SOFT/TEXT, anastrozole or tamoxifen alone in the ATAC trial led to lower reported rates of hot flashes (30%-32% with AI or tamoxifen alone in ATAC vs 91%-93% in SOFT/TEXT), fatigue (16%-20% vs 61%-62%, respectively), and dyspareunia (7%-17% vs 25%-30%, respectively). This increase in toxicity is most likely due to the ovarian suppression rather than the endocrine therapy medications themselves.

Changes in global QOL were similar between groups, although the individual symptoms differed between study cohorts. As expected, the E/OS group reported more vaginal dryness, greater loss of sexual interest, and more bone/joint pain whereas the T/OS group reported more hot flashes. More women on E/OS discontinued therapy compared with T/OS (16% vs 11%). This finding is especially troubling because it is well established that rates of early discontinuation are far higher outside of clinical trials.[48]

In the SOFT analysis, as expected, T/OS was less well tolerated than tamoxifen alone, with higher rates of grade 3 or 4 adverse events (31.3% vs 23.7%).[5] Consistent with this finding, INT 0142, a phase 3 study of T/OS compared with tamoxifen alone conducted in the United

States, also observed significantly increased toxicity with combination therapy (Table 2). Despite an early closure that precluded sufficient power to detect a difference in DFS, the patient-reported outcomes data for this secondary analysis met its accrual goal, confirming the findings of more menopausal symptoms, lower sexual activity, and inferior QOL in the subset randomly assigned to T/OS.[49] Based on the lack of disease outcomes benefit and the increased adverse effects in SOFT, tamoxifen alone should remain the standard of care for low-risk HR-positive premenopausal women.

Conclusions

More than 30 years of well-designed randomized controlled trials in early-stage breast cancer have led to markedly improved breast cancer outcomes. The recent reports of extended endocrine therapy and OS/OA further this progress and provide new therapeutic options for high-risk HR-positive premenopausal early-stage breast cancer.

How might we translate these findings to the clinic? Figure 2 provides an algorithm for considering adjuvant endocrine therapy in HR-positive premenopausal women and is consistent with the 2015 St Gallen International Expert Consensus.[29] For high-risk patients (ie, age <35 years) or those with sufficient risk to warrant treatment with chemotherapy who remain premenopausal following treatment, AI plus OS is associated with a significant improvement in DFS over tamoxifen plus OS or tamoxifen alone. Given the increased mortality with surgical menopause at an early age,[50] temporary OS with an LHRH agonist should be considered for very young women unless there is a strong indication for permanent OA (eg, *BRCA* carrier). If OS is planned, a LHRH agonist can be given concurrently with or following chemotherapy as was done in TEXT and SOFT, respectively. Prior to initiating concurrent AI therapy, suppression of ovarian function should be confirmed biochemically using an ultrasensitive estradiol assay. It will be important to aggressively manage toxicity in order to maximize compliance with therapy, or to consider switching to an alternative therapy, such as tamoxifen monotherapy, if the combination regimen is detrimental to QOL.

Following 5 years of such combination therapy, the role of extended-duration endocrine therapy with or without OS/OA remains unknown. Potential short- and long-term toxicities cannot be understated, and physical, sexual, and psychological symptoms should be aggressively treated or referred to appropriate services (psychiatry, counseling, etc). Long-term follow-up will also be needed to clarify for whom the potentially increased cardiovascular and bone risks outweigh the improvements in breast cancer outcomes.

For lower-risk HR-positive premenopausal women, tamoxifen for 5 to 10 years or switch therapy is reasonable. Notably, less than one-fifth of participants in ATLAS had low-risk (LN-negative or <2 cm) HR-positive breast cancers, which limits our ability to estimate the benefit of extended therapy in such patients. Based on the SOFT data, treatment with OS plus AI or tamoxifen may not be necessary in low-risk patients; however, long-term follow-up will be necessary to confirm these negative results.

Overall, the data from these recently reported trials highlight the excellent prognosis for many premenopausal women with breast cancer. For those with higher-risk disease, it is now evident that there are numerous effective treatment options. However, determining exactly which patients have a high enough risk of recurrence to be offered ovarian suppression is still challenging. In addition, optimization of therapy will require a continued dialogue between providers and patients in order to maximize benefit while minimizing the negative impact on QOL for younger breast cancer survivors.

Acknowledgements

Dr Henry is a Damon Runyon-Lilly Clinical Investigator supported (in part) by the Damon Runyon Cancer Research Foundation (CI C53-10). Dr Henry was supported in part by an NCI Clinical Cancer Investigator Team Leadership Award (supplement to 3-P30-CA045692, PI M Wicha).

Disclosures

The authors have disclosed no relevant financial conflicts of interest.

References

1. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin*. 2014;64(1):52-62.
2. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J Natl Cancer Inst*. 2015;107(6):djv048.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-1717.
4. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381(9869):805-816.
5. Francis PA, Regan MM, Fleming GF, et al; SOFT Investigators; International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372(5):436-446.
6. Pagani O, Regan MM, Walley BA, et al; TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371(2):107-118.
7. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784-2795.
8. Davies C, Godwin J, Gray R, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771-784.

9. Griggs JJ, Somerfield MR, Anderson H, et al. American Society of Clinical Oncology endorsement of the cancer care Ontario practice guideline on adjuvant ovarian ablation in the treatment of premenopausal women with early-stage invasive breast cancer. *J Clin Oncol*. 2011;29(29):3939-3942.
10. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27—a randomized controlled phase III trial. *J Clin Oncol*. 2013;31(11):1398-1404.
11. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28(3):509-518.
12. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. *J Clin Oncol*. 2006;24(16):2444-2447.
13. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast cancer version 2.2015. *J Natl Compr Canc Netw*. 2015;13(4):448-475.
14. Guerrero A, Gavilá J, Folkerd E, et al. Incidence and predictors of ovarian function recovery (OFR) in breast cancer (BC) patients with chemotherapy-induced amenorrhea (CIA) who switched from tamoxifen to exemestane. *Ann Oncol*. 2013;24(3):674-679.
15. Henry NL, Xia R, Banerjee M, et al. Predictors of recovery of ovarian function during aromatase inhibitor therapy. *Ann Oncol*. 2013;24(8):2011-2016.
16. Chirgwin J, Sun Z, Smith I, et al; BIG 1-98 Collaborative and International Breast Cancer Study Groups. The advantage of letrozole over tamoxifen in the BIG 1-98 trial is consistent in younger postmenopausal women and in those with chemotherapy-induced menopause. *Breast Cancer Res Treat*. 2012;131(1):295-306.
17. Goss PE, Ingle JN, Martino S, et al. Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. *Ann Oncol*. 2013;24(2):355-361.
18. Pan K, Chlebowski RT. Adjuvant endocrine therapy of perimenopausal and recently postmenopausal women with hormone receptor-positive breast cancer. *Clin Breast Cancer*. 2014;14(3):147-153.
19. Miller WG, Eckfeldt JH, Passarelli J, Rosner W, Young IS. Harmonization of test results: what are the challenges; how can we make it better? *Clin Chem*. 2014;60(7):923-927.
20. Stanczyk FZ, Lee JS, Santen RJ. Standardization of steroid hormone assays: why, how, and when? *Cancer Epidemiol Biomarkers Prev*. 2007;16(9):1713-1719.
21. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2014;32(21):2255-2269.
22. Khoshnoud MR, Löfdahl B, Fohlin H, et al. Immunohistochemistry compared to cytosol assays for determination of estrogen receptor and prediction of the long-term effect of adjuvant tamoxifen. *Breast Cancer Res Treat*. 2011;126(2):421-430.
23. Esserman LJ, Moore DH, Tsing PJ, et al. Biologic markers determine both the risk and the timing of recurrence in breast cancer. *Breast Cancer Res Treat*. 2011;129(2):607-616.
24. Overmoyer B. Treatment with adjuvant endocrine therapy for early-stage breast cancer: is it forever? *J Clin Oncol*. 2015;33(8):823-828.
25. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. 2001;93(9):684-690.
26. Gray RG, Rea D, Handley K, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [ASCO abstract 5]. *J Clin Oncol* 2013;31(15)(suppl).
27. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Lonati V, Barni S. Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. *Breast Cancer Res Treat*. 2013;140(2):233-240.
28. Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol*. 2013;14(11):1067-1076.
29. Coates AS, Winer EP, Goldhirsch A, et al; Panel Members. Tailoring therapies - improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;mdv221.
30. Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. *Cochrane Database Syst Rev*. 2009;(4):CD004562.
31. Cuzick J, Ambroisine L, Davidson N, et al; LHRH-agonists in Early Breast Cancer Overview group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet*. 2007;369(9574):1711-1723.
32. Gnant M, Mlineritsch B, Schippinger W, et al; ABCSG-12 Trial Investigators. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009;360(7):679-691.
33. Gnant M, Mlineritsch B, Stoeger H, et al; Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol*. 2011;12(7):631-641.
34. Pfeiler G, Königsberg R, Fesl C, et al. Impact of body mass index on the efficacy of endocrine therapy in premenopausal patients with breast cancer: an analysis of the prospective ABCSG-12 trial. *J Clin Oncol*. 2011;29(19):2653-2659.
35. Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Educ Couns*. 2005;59(1):97-102.
36. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol*. 2010;28(27):4120-4128.
37. Makubate B, Donnan PT, Dewar JA, Thompson AM, McCowan C. Cohort study of adherence to adjuvant endocrine therapy, breast cancer recurrence and mortality. *Br J Cancer*. 2013;108(7):1515-1524.
38. Stearns V, Ullmer L, López JF, Smith Y, Isaacs C, Hayes D. Hot flushes. *Lancet*. 2002;360(9348):1851-1861.
39. Oberguggenberger A, Goebel G, Beer B, et al. Getting the whole picture: adding patient-reported outcomes to adjuvant endocrine treatment evaluation in premenopausal breast cancer patients. *Breast J*. 2014;20(5):555-557.
40. Loprinzi CL, Barton DL, Sloan JA, et al. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. *Menopause*. 2008;15(4 pt 1):655-660.
41. Bernstein L, Deapen D, Cerhan JR, et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. *J Natl Cancer Inst*. 1999;91(19):1654-1662.
42. Khorana AA. Cancer and thrombosis: implications of published guidelines for clinical practice. *Ann Oncol*. 2009;20(10):1619-1630.
43. Baumgart J, Nilsson K, Evers AS, Kallak TK, Poromaa IS. Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. *Menopause*. 2013;20(2):162-168.
44. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol*. 2012;30(9):936-942.
45. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103(17):1299-1309.
46. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: bone health in cancer care. *J Natl Compr Canc Netw*. 2013;11:S1-S50(suppl 3).
47. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol*. 2003;21(22):4184-4193.
48. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat*. 2012;134(2):459-478.
49. Tevaarwerk AJ, Wang M, Zhao F, et al. Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2014;32(35):3948-3958.
50. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. *Maturitas*. 2010;65(2):161-166.