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CLINICAL TRIALS (S HURVITZ, SECTION EDITOR)

Adjuvant Endocrine Therapy for Hormone Receptor-Positive Early Breast Cancer in Premenopausal Patient: Understanding the Data

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Abstract Breast cancer diagnosed at a young age is associated with a poor prognosis. It is possible that inadequate endocrine therapy for the youngest women contributes to their poorer prognosis. Data on optimal endocrine therapy selection as well as duration for premenopausal women are crucial. Recently published clinical trials including Australian Breast and Colorectal Cancer Study Group-12 (ABCSG-12), E-3193, and Suppression of Ovarian Function Trial (SOFT)/ Tamoxifen and Exemestane Trial (TEXT) have shed light on the role of ovarian function suppression and aromatase inhibitors in premenopausal women. Additionally, optimal duration of endocrine therapy has been addressed in the recent Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and Adjuvant Tamoxifen—To Offer More? (aTTom) trials.

Keywords Premenopausal · Hormone receptor positive · Breast cancer · Ovarian function suppression

Introduction

Breast cancer in women less than 50 years of age makes up about 25 % of all breast cancer in the USA, and an estimated 14,000 women under the age of 40 are diagnosed with breast cancer annually [1]. Several studies have shown that young age (variably defined as less than 35–40 years of age) at diagnosis is associated with a poor prognosis [2–4]. This is partly, but not entirely, explained by an increased incidence of poor prognostic factors in young women, including high-grade, poor prognosis gene signatures and estrogen receptor (ER)-negative disease [5]. Although ER-negative disease is more common in younger women, most premenopausal patients will have ER-positive disease, and at least 60 % of breast cancer patients under age 35 have ER-positive disease [6]. However, solid data on optimal endocrine therapy selection and duration for premenopausal women have been elusive, and it is possible that inadequate endocrine therapy for the youngest women contributes to their poorer prognosis. Recently published trials have given us new information regarding both the optimal duration of tamoxifen therapy and the benefits of ovarian function suppression (OFS).

This article is part of the Topical Collection on *Clinical Trials*

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Tamoxifen

Until recently, single agent tamoxifen has been the adjuvant endocrine therapy of choice for premenopausal breast cancer patients with ER-positive disease in the USA. Despite initial concerns regarding the very high estrogen levels that can be seen in premenopausal women receiving tamoxifen [7], the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis showed that 5 years of tamoxifen resulted in a significant reduction in the risk of both recurrence (relative risk [RR] 0.61, 95 % confidence interval (CI) 0.57–0.65) and mortality (RR 0.70, 95 % CI 0.64–0.75) at 15 years independent of patient age, menopausal status, or use of chemotherapy [8]. Tamoxifen also clearly adds benefit to OFS alone as demonstrated by the E5188/INT-0101 randomized trial in which premenopausal women with node-positive receptor-positive breast cancer had a 9-year disease-free survival

(DFS) of 60 % for chemotherapy plus goserelin versus 68 % for chemotherapy plus goserelin plus tamoxifen (hazard ratio (HR) 0.74, $p<0.01$, Table 1) [9].

It should be remembered that although some women will become amenorrheic on tamoxifen therapy, it does not induce menopause. When trying to determine menopausal status in a woman on tamoxifen, FSH and LH are not reliable, as they may be suppressed by the tamoxifen therapy; estradiol levels should be measured [10].

Duration of Tamoxifen Therapy

It is well known that the risk of recurrence for women with ER-positive breast cancer extends over a very long period, with over half of recurrences occurring more than 5 years after diagnosis [11]. However, the value of extending hormonal therapy for longer than 5 years has been uncertain. Indeed, in 1995, the US National Cancer Institute issued a Clinical Announcement recommending against the use of more than 5 years of tamoxifen therapy. This was based on data from NSABP-14 (1166 patients) and the Scottish Tamoxifen Trial (661 patients), both of which included premenopausal women, indicating no advantage (and, indeed, numerically worse outcomes) with continuing tamoxifen for 10 years rather than stopping at 5 years [12, 13].

However, two much larger trials have recently reported a modest benefit to prolonging tamoxifen therapy in both pre and postmenopausal women.

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial included 12,894 women, 6848 of whom had ER+ disease. Patients who had already received tamoxifen for 5 years (hence, starting on trial at "year 5") were randomized to continue for another 5 years or to stop endocrine therapy. Among women with ER+ disease, those receiving ten total years of tamoxifen had a 21.4 % cumulative risk of recurrence during years 5–14 versus a 25.1 % risk of recurrence for those stopping therapy after 5 years. The effect was independent of age and menopausal status (fewer than 10 % of patients were premenopausal at time of study enrollment) [14•].

Breast cancer-specific survival was similarly improved with extended tamoxifen treatment in the Adjuvant Tamoxifen—To Offer More? (aTTom) trial, which included 6934 women and found a decrease in breast cancer mortality from 443 to 392 [15•]. Both studies also showed improved mortality with prolonged therapy [14•, 15•]. Based on data from these two large trials, it is clear that extended tamoxifen beyond 5 years is a reasonable approach for premenopausal women. However, the benefit of an additional 5 years of tamoxifen seems smaller than that seen with switching from tamoxifen to an aromatase inhibitor in women who were premenopausal at time of diagnosis but become clearly postmenopausal after 5 years of tamoxifen. Additionally, in order to

Table 1 Results from recently published key OFS trials in premenopausal women with hormone-positive early breast cancer

Study	Patient characteristics	Median follow-up	Tamoxifen alone	Tamoxifen + OFS	AI + OFS	OFS alone	Comments
ABCSG-12 Gnant [27]	ER+ stages 1–2; 70 % node negative; 5 % chemotherapy. (N=1803)	62 months	N/A	89 events 27 deaths	97 events 46 deaths	N/A	AI + OFS vs Tam + OFS: Events: HR 1.08; 95 % CI, 0.81 to 1.44, p=0.591 Deaths HR 1.75; 95 % CI, 1.08 to 2.83; p=0.02
INT 0101 Davidson [9]	Premenopausal, node positive; 100 % received chemotherapy (N=1503)	9.6 years	N/A	9 years DFS, 68 % 9 years OS, 76 %	N/A	9 years DFS, 60 % 9 years OS, 73 %	Tam + OFS vs OFS: DFS: HR 0.74; 95 % CI 0.60 to 0.91; p<0.01 OS: HR 0.91; 95 % CI 0.72 to 1.16; p=0.23
E-3193 Tevaarwerk [38•]	Premenopausal node negative. No chemotherapy permitted (N=345)	9.9 years	5 years DFS, 87.9 % 5 years OS, 95.2 %	5 years DFS, 89.7 % 5 years OS, 97.6 %	N/A	N/A	Tam vs Tam + OFS DFS: HR 1.17; 95 % CI, 0.64–2.12; p=0.62 OS: HR 1.19; 95 % CI, 0.53 to 2.65; p=0.67
SOFT + TEXT joint analysis Pagani; Francis [29•, 30•]	58 % node negative; 57 % chemotherapy treated (N=4690)	68 months	DFS, 84.7 % OS, 95.1 % (SOFT only)	DFS, 87.3 % OS, 96.9 % (Joint analysis SOFT/TEXT)	DFS, 91.1 % OS, 95.9 % (Joint analysis SOFT/TEXT)	N/A	AI + OFS vs Tam + OFS (Joint analysis SOFT/TEXT): DFS: HR 0.72, 95 % CI, 0.60 to 0.85; p<0.001 OS: HR 1.14; 95 % CI, 0.86 to 1.51; p=0.37 Tam + OFS vs Tam (SOFT only) DFS 86.6 % (Tam + OFS) vs 84.7 % (Tam); HR 0.83; 95 % CI, 0.66 to 1.04; p=10 OS 96.7 % (Tam + OFS) vs 95.1 % (Tam); HR 0.74; 95 % CI, 0.51 to 1.09; p=0.13

benefit from prolonged tamoxifen therapy, the patient must survive to 5 years without recurrence; highest risk women should consider more aggressive hormonal treatment earlier. The magnitude of benefit in low-risk patients will be quite small. For lower-risk women who are experiencing side effects from tamoxifen, stopping at 5 years remains appropriate.

Side Effects of Longer Therapy

Adverse effects with extended duration of tamoxifen therapy were reported in both the aTTom and ATLAS trials. No new types of adverse events were seen. The cumulative risk of endometrial cancer was higher in the extended tamoxifen group at 3.1 versus 1.6 % for controls in ATLAS and 2.9 versus 1.3 % in aTTom [14•, 15•]. Neither study reported on quality of life outcomes. Given known issues with compliance to prolonged oral therapy, it will be important to implement strategies to improve adherence for those higher-risk patients for whom extended therapy is thought to be beneficial.

It is important to note that the frequency of the most worrisome toxicities associated with tamoxifen use, venous thromboembolism and endometrial cancer, is lower in younger women. For example, in the NSABP P1 breast cancer prevention trial, the risk of developing endometrial cancer was not significantly increased in women under 50 (RR= 1.42, 95 % CI=0.55 to 3.81), but there was a statistically significant increase in risk in women 50 or older (RR=5.33, 95 % CI=2.47 to 13.17). For vascular events, the increase in HR for younger and older women (the rate of pulmonary embolus (PE) approximately doubled) was similar, but because the events are less common in younger women at baseline, the absolute number of events in young women on tamoxifen remains small. The annual rates of deep venous thrombosis (DVT)/PE were increased from 0.76/0.13 per 1000 women under 50 on placebo to 1.01/0.25 per 1000 women under 50 on tamoxifen. For women ≥50, the corresponding increases were from 0.89/0.44 per 1000 women on placebo to 1.33/0.96 per 1000 women on tamoxifen [16].

Aromatase Inhibitors

At the doses approved, aromatase inhibitors (AIs) are ineffective in premenopausal women as monotherapy.

Several large clinical trials in postmenopausal women with ER+ breast cancer have shown that AIs outperform tamoxifen in the metastatic, neoadjuvant, and adjuvant settings [17–21]. Moreover, an AI administered after 5 years of tamoxifen is of significant benefit. The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.17/Breast International Group (BIG) 1–97 trial reported that 5 years of letrozole treatment in postmenopausal women with ER+ tumors who had received 5 years of tamoxifen improved DFS significantly with a trend to benefit in overall survival [22]. A further analysis reported that the subset of women who were premenopausal at initial breast cancer diagnosis (n=877) and became definitively postmenopausal by the time of randomization after 5 years of adjuvant tamoxifen derived significantly more benefit in terms of DFS from the extended AI therapy (HR 0.25, 95 % CI: 0.12–0.51) than women who were postmenopausal at initial diagnosis (DFS HR 0.69, 95 % CI 0.52–0.91, p=0.02 for interaction) [23].

AIs must be used with caution in young women who have had chemotherapy-induced amenorrhea because they can be associated with return of ovarian function even in patients with prolonged absence of menses and laboratory studies showing an apparently postmenopausal state [24]. This is also important to consider in the setting of premenopausal women in whom a GnRH agonist is being used for OFS because GnRH agonists may not achieve complete OFS in some patients and pregnancy has occasionally been reported. Some experts advise only using monthly (rather than every 3 months) GnRH analog administration and checking estradiol levels every 6 months to make sure that OFS is maintained [25].

Several trials have compared AIs to tamoxifen in women who were premenopausal at the time of diagnosis but have had ovarian function suppressed with use of GnRH analogs.

Study of Tamoxifen or Arimidex, Combined with Goserelin Acetate to Compare Efficacy and Safety

A small randomized trial of 24 weeks of neoadjuvant endocrine therapy in premenopausal women [Study of Tamoxifen or Arimidex, combined with Goserelin Acetate to compare Efficacy and safety (STAGE)] found that complete or partial response was significantly higher in the anastrozole group (70.4 vs 50.5 %, p=0.004) [26].

Australian Breast and Colorectal Cancer Study Group-12

The Australian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial compared 3 years of tamoxifen plus goserelin with 3 years of anastrozole plus goserelin with or without zoledronic acid (4 mg every 6 months) in 1803 premenopausal women with hormone-responsive breast cancer with favorable prognosis (75 % T1, G1–2 tumors, 30 % node positive). At 62-month median follow-up, zoledronic acid reduced the risk of DFS events by 32 % (HR=0.68, 95 % CI= 0.51–0.91, p=009). There was no difference in DFS between patients who received tamoxifen + goserelin and anastrozole + goserelin (HR=1.11 [0.84, 1.50]; p=0.44). However, patients who received anastrozole had a significantly increased risk of death compared with those treated with tamoxifen (46 vs 27 deaths; HR=1.75, 95 % CI 1.08 to 2.83; p=0.02) possibly due to the higher rate of death after recurrence in the anastrozole

group [27]. It was also hypothesized that differences in body mass index might cause relative differences in efficacy of tamoxifen versus anastrazole [27]. Of note, the percentage of patients with a BMI ≥25 was only 17.3 % in the STAGE trial versus 33 % in the ABCSG-12 study [26, 28].

In the ABCSG-12 study, only 5 % of patients received chemotherapy (only neoadjuvant chemotherapy was allowed). At 62-month median follow-up, 88 % of the patients who received endocrine therapy alone were free of disease and 95 % were alive [27], adding to the evidence that subgroups of premenopausal breast cancer patients with hormone receptor-positive early breast cancer can be spared cytotoxic chemotherapy and have excellent outcomes with hormonal therapy alone.

Suppression of Ovarian Function Trial/Tamoxifen and Exemestane Trial

The International Breast Cancer Study Group (IBCSG)-led Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) also compared OFS (mostly with the GnRH agonist, triptorelin) plus an AI (exemestane) to OFS plus tamoxifen as adjuvant therapy for premenopausal women with hormone receptor-positive disease. The SOFT trial had a third arm of tamoxifen alone. In TEXT, there were only two arms, and OFS started simultaneously with chemotherapy if the physician chose to administer chemotherapy. In SOFT, if chemotherapy was administered, patients had to have a premenopausal estradiol level documented within 8 months after chemotherapy completion. Both trials continued the endocrine therapy for 5 years (versus the three prescribed in the ABCSG study). Bisphosphonates were not permitted unless indicated for reduced bone density (T score, −1.5 or lower) unless the patient was participating in a randomized trial of adjuvant bisphosphonate therapy. A prespecified joint analysis of the 4690 patients on the OFS arms of the two studies was performed at a median follow-up of 68 months. Exemestane plus OFS significantly improved DFS relative to tamoxifen plus OFS (91.1 vs 87.3 % with HR 0.72, 95 % CI 0.60–0.85, $p<0.001$), 5-year breast cancer-free interval (92.8 vs 88.8 %, HR 0.66, 95 % CI 0.55–0.80, $p<0.001$), and rate of freedom from distant recurrence (93.8 vs 92.0 % HR 0.78, 95 % CI 0.62–0.97, $p=0.02$) in premenopausal women with hormone-positive breast cancer. No significant difference in overall survival was seen although, given the long natural history of ER-positive breast cancer, survival data are obviously premature [29•, 30•]. However, as the trials did not specify what was to happen after 5 years (further, endocrine therapy was not forbidden) and as the ATLAS trial results (supporting prolonged tamoxifen therapy) became available during the period of trial recruitment, analyses at later time points may be complicated.

Use of aromatase inhibitor therapy for premenopausal patients with hormone receptor-positive breast cancer relies on adequate OFS. The SOFT-EST trial is a small prospective substudy of the SOFT trial which aims to describe estradiol, estrone, and estrone sulfate levels during monthly triptorelin + exemestane ($n=90$) or triptorelin + tamoxifen ($n=30$) and to assess if there is a group of women with suboptimal estrogen suppression. Preliminary results of this substudy were presented at ASCO in 2014 and suggest that while most patients on triptorelin plus exemestane reached estradiol levels below the defined threshold of 2.72 pg/mL (10 pmol/L), 27 of 79 patients had estradiol levels above this threshold at least once. Two had vaginal bleeding more than 3 months after starting triptorelin, one in the setting of suboptimal estrogen suppression. The clinical relevance of this data will need to be further explored; an optimal estradiol cutoff level for potential clinical monitoring is not well established at this time [31].

Detailed patient-reported outcomes were collected on both SOFT and TEXT and showed more hot flushes and sweats with tamoxifen plus OFS and more vaginal dryness and loss of sexual interest in patients on exemestane plus OFS. Changes in global quality of life scales were similar between the two treatments [32]. At the median follow-up of 68 months in TEXT trial, 16.1 % of patients in the exemestane-ovarian suppression group and 11.2 % of those in the tamoxifen-ovarian suppression group had discontinued treatment early [29•].

The difference between the results of the ABCSG-12 trial and the results of the TEXT and SOFT trials may relate to greater statistical power in the combined analysis of TEXT and SOFT (with three times the number of events of disease recurrence, second invasive cancer, or death in TEXT and SOFT as in the ABCSG-12 trial), to different treatment durations, or to both [33]. The 3-year duration of AI therapy in the ABCSG-12 trial may have been insufficient as compared with 3 years of tamoxifen, which is known to exert a carryover effect after the cessation of treatment [8].

Ovarian Function Suppression

OFS can be achieved by various methods including surgery, radiation, chemotherapy, and GnRH agonists. There is no available evidence favoring a specific form of OFS. OFS itself clearly has benefit in the adjuvant therapy of premenopausal women with estrogen receptor (ER)-positive breast cancer. The EBCTCG meta-analysis of nearly 8000 women under the age of 50 with ER-positive or ER-unknown breast cancer who were randomly assigned to OFS or no further treatment showed an approximately 25 % relative reduction in risks of recurrence and mortality at 15-year follow-up with OFS. There was a trend toward greater benefit with ovarian ablation in subset of women with ER+ tumors. The impact on outcomes for women who also received chemotherapy was

smaller with OFS producing non-statistically significant lower RRs for recurrence and mortality of 10 and 8 %, respectively. The smaller effect of OFS in patients receiving chemotherapy is likely a consequence of the fact that chemotherapy itself can induce OFS [34].

Chemotherapy-Induced Amenorrhea

The impact of adding OFS to adjuvant chemotherapy was studied in the ECOG-led Intergroup 0101 trial where 1503 premenopausal hormone receptor-positive, node-positive early breast cancer patients were randomized to six cycles of cyclophosphamide, adriamycin, and 5-fluorouracil (CAF), CAF followed by 5 years of monthly goserelin (GnRH agonist), or CAF followed by 5 years of monthly goserelin and daily tamoxifen. The study showed that the addition of the combination of tamoxifen plus goserelin improved DFS when compared to chemotherapy alone, but no significant effect on DFS was shown with the addition of goserelin alone. However, a trend to DFS benefit from addition of goserelin to chemotherapy was demonstrated in an unplanned retrospective analysis of women <40 years, possibly because they were the least likely to become menopausal with chemotherapy [9].

Amenorrhea, even if transient, has been associated with improvement in treatment outcomes in several clinical trials. In the NSABP B-30 trial of node-positive patients treated with adjuvant anthracycline- and taxane-containing regimens, premenopausal women with ER+ tumors who had amenorrhea for six or more months after completion of chemotherapy had a significantly better survival and lower disease recurrence than those with no amenorrhea. All patients received tamoxifen in this trial, supporting the hypothesis that OFS may provide benefit even in the setting of tamoxifen use [35–37].

The risk of chemotherapy-induced amenorrhea depends on multiple factors including specific chemotherapy regimen, total dose, dose-intensity, duration of treatment, and patient's age and ovarian reserve at time of treatment initiation. In women <35 years, adjuvant chemotherapy is less likely to induce permanent amenorrhea [35–37]. Additionally, more modern standard chemotherapies such as docetaxel plus cyclophosphamide (TC) are generally less associated with premature menopause than older regimens such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) [37].

Recent Results of Trials Investigating Role of OFS Added to Tamoxifen

E-3193, INT-0142

The E-3193 trial randomly assigned 345 premenopausal, lymph node-negative, hormone receptor-positive breast cancer patients (median age 45 years) to 5 years of tamoxifen versus 5 years of tamoxifen with OFS. No adjuvant chemotherapy was permitted. At a median follow-up of 9.9 years, there was no difference in DFS between tamoxifen alone and tamoxifen + OFS at 87.9 and 89.7 %, respectively. Overall survival was also similar (95.2 versus 97.6 %, $p=0.67$). Addition of OFS led to increased menopausal symptoms, lower sexual activity, and worse health-related quality of life at year 3 [38•].

Suppression of Ovarian Function Trial

The SOFT trial randomized 1021 premenopausal women with hormone receptor-positive tumors to receive 5 years of adjuvant tamoxifen alone and 1024 to receive versus tamoxifen + OFS (analysis of the third arm, exemestane + OFS, was reported with the TEXT trial as discussed above). About 47 % of the patients did not receive chemotherapy, and about 53 % had received chemotherapy and remained premenopausal as defined by estradiol levels in the premenopausal range within 8 months after chemotherapy. At a median follow-up of 67 months, the estimated DFS rate at 5 years was 86.6 % in the tamoxifen + OFS group and 84.7 % in the tamoxifen group (HR 0.83; 95 % CI; 0.66–1.04, $p=0.10$). Hot flushes, sweating, decreased libido, vaginal dryness, insomnia, depression, musculoskeletal symptoms, hypertension, and glucose intolerance were all reported more frequently in the tamoxifen + OFS group than in the tamoxifen alone group. The rate of nonadherence with OFS was 21.9 % at 4 years after randomization [30•].

Subgroups That May Benefit from Addition of OFS

It would seem that the benefit of ovarian suppression to tamoxifen overall is not large and is associated with toxicity. There is further benefit to addition of an AI to OFS, which will make the toxicities worthwhile in women with higher-risk disease. The SOFT trial was stratified by whether women were previously treated with chemotherapy or not. Premenopausal women who did not receive chemotherapy in the SOFT trial did exceedingly well with tamoxifen alone with 95.8 % remaining breast cancer free at 5 years. Women who received chemotherapy and remained premenopausal were a higher-risk group, with larger tumors, higher grade, and more positive nodes. In women who received prior chemotherapy, the 5-year breast cancer-free interval was 78.0 % in the tamoxifen group versus 82.5 % in the tamoxifen + OFS group versus 85.7 % in the exemestane + OFS group [30•]. Obviously, only some of the factors controlling choice to administer chemotherapy are likely to make addition of OFS more worthwhile; for example, adding OFS to a patient who received chemotherapy because of very low levels of ER would seem counterintuitive.

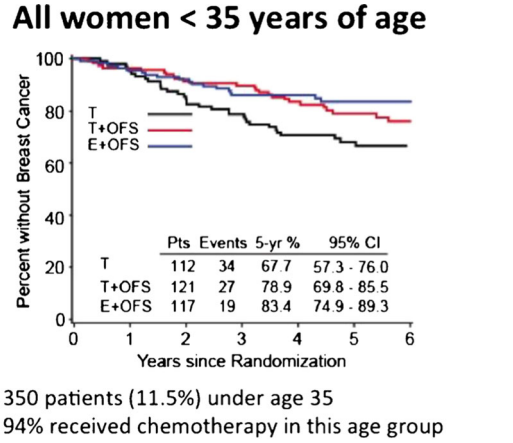

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Fig. 1 All women <35 years of age on SOFT/TEXT

A total of 350 women age less than 35 participated in SOFT. Ninety-four percent had received chemotherapy. In this group, the rate of freedom from breast cancer at 5 years was 67.7 % for patients assigned to tamoxifen alone, 78.9 % for those assigned to tamoxifen + OFS, and 83.4 % for those assigned to exemestane + OFS [30•] (Fig. 1).

Fertility

As women delay childbearing, an increasing number of breast cancer patients have not yet completed their families. Young patients with breast cancer are often concerned about treatment-induced infertility [39]. Conception after breast cancer does not seem to affect cancer outcomes per se, but hormonal therapy must be paused to allow pregnancy, and this is worrisome in young women whose cancer outcomes seem to depend so strongly on adequate endocrine therapy. The IBCSG, within the BIG–North American Breast Cancer Groups (NABCG) collaboration, has launched an observational study (Pregnancy Outcomes and Safety of Interrupting endocrine therapy for young women with endocrine responsive breast cancer who desire pregnancy (POSITIVE)) addressing interruption of endocrine therapy to allow pregnancy (NCT02308085).

Conclusions

For low-risk premenopausal women with ER-positive breast cancer, tamoxifen alone represents sufficient adjuvant endocrine therapy and, for many women, sufficient adjuvant therapy altogether. Ten rather than 5 years of therapy will offer slight increased benefits. Women who become definitively postmenopausal during chemotherapy can be cautiously switched to an aromatase inhibitor.

For higher-risk women, particularly those who are very young, adding OFS and using an aromatase inhibitor will produce better outcomes. Addition of bisphosphonate can also be considered in the setting of OFS + AI therapy. Although data on the anticancer effects of bisphosphonates are conflicting, they clearly protect bone density. Whether hormonal therapy in higher-risk women should be continued beyond 5 years and what that therapy should be (possibly, tamoxifen after 5 years of AI plus OFS or five more years of AI plus OFS) remain unknown. Ongoing trials will help estimate the benefit of prolonged AI therapy, at least in postmenopausal women, help estimate the benefit of chemotherapy in node-positive patients with lower genomic risk scores, and help estimate the risk of interrupting hormonal therapy to allow pregnancy. Strategies to mitigate toxicity and improve adherence are critical to the efficacy of all long-term hormonal therapy.

Compliance with Ethics Guidelines

Conflict of Interest Gini F Fleming reports that she is a North American co-chair for SOFT trial. Poornima Saha declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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