HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Gynecol Oncol. 2017 October ; 147(1): 153–157. doi:10.1016/j.ygyno.2017.06.023.

Current Advances in Endocrine Therapy Options for Premenopausal Women with Hormone Receptor Positive Breast Cancer

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Introduction

The American Cancer Society estimates 252,710 women will be diagnosed with breast cancer in the United States in 2017 [1]. Breast cancer accounts for 30% of all new cancers in women. The median age of diagnosis is 61 years. Although breast cancer mostly occurs among older women, in rare cases it can occur in women younger than 45 years of age. About 11% of all new breast cancers in the United States are diagnosed in women younger than 45 years of age who are still premenopausal [2].

About 70% of invasive breast cancers are hormone receptor (HR) positive. The mainstay of treatment for all women with HR positive breast cancer is endocrine therapy either after chemotherapy or as endocrine therapy alone. The decision to recommend chemotherapy in HR positive breast cancer is multifactorial. Factors such as presence of HER2/neu overexpression, lymph node involvement, and genomic tests such as Oncotype DX (Genomic Health, Redwood City, CA) play a role in decisions to recommend chemotherapy in HR positive breast cancer. Whether or not chemotherapy is recommended, all patients with HR positive breast cancer are recommended to have adjuvant endocrine therapy.

Different options for endocrine therapy have recently been reported for premenopausal women with HR positive breast cancer and include ovarian function suppression (OFS).

In this review, we focus on the different strategies related to adjuvant endocrine therapy, including length of time of treatment, type of endocrine treatment, use of ovarian suppression, and adverse effects of different types of endocrine therapy.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Adjuvant Endocrine Therapy

Adjuvant endocrine therapy is recommended for all patients with HR positive breast cancer (including estrogen receptor [ER] positive, and/or progesterone receptor [PR] positive).

Recent studies have extended the recommendation of length of time for endocrine therapy to 10 years. Additionally, the International Breast Cancer Study Group (IBCSG) randomized phase 3 trials, the Suppression of Ovarian Function Trial (SOFT), and the Tamoxifen and Exemestane Trial (TEXT) have reported on the impact of OFS in premenopausal women with HR positive breast cancer who are recommended to receive endocrine therapy [3, 4].

Current options for endocrine therapy now include tamoxifen alone, and ovarian suppression with tamoxifen or an aromatase inhibitor (AI). The decision to proceed with one particular therapy should not only factor into the risk of relapse and effectiveness of therapy, but also include presence of co-morbidities, side effects, and patient preference. Issues specific for younger patients, such as desire for future pregnancy, side effects, and quality of life, should also factor into treatment decisions regarding adjuvant endocrine therapy.

Duration of Use of Endocrine Therapy

Tamoxifen use is the standard of care for premenopausal women with HR positive breast cancer, as 5 years of therapy has been demonstrated to reduce the annual breast cancer death rate by 31% [5]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2011 meta-analysis demonstrated that 5 years of tamoxifen compared to none was associated with a 15-year risk reduction for breast cancer-specific recurrence and a mortality reduction of 39% [6].

Additionally, data from the ATLAS (*Adjuvant Tamoxifen: Longer Against Shorter*) and aTTom (*The United Kingdom adjuvant Tamoxifen—To offer more*) studies demonstrate a reduction in recurrence and mortality after 10 years of tamoxifen therapy [7, 8].

The ATLAS randomized trial included 12,894 women with early breast cancer who had completed 5 years of treatment with tamoxifen. They were randomly allocated to continue tamoxifen to 10 years or stop at 5 years. The ATLAS trial's analysis of 6846 women with ER positive disease demonstrated that allocation to continue tamoxifen reduced the risk of breast cancer recurrence (recurrence rate ratio [RR] 0.84, 95% confidence interval [CI] 0.76−0.94), reduced breast cancer mortality ($p = 0.01$), and reduced overall mortality ($p = 0.01$).

With regards to toxicity, there was a noted increased risk of endometrial cancer (RR 1.74, 95% CI 1.3−2.34) and pulmonary embolus (RR 1.87, 95% CI 1.13−3.07) after 10 years of use. It was noted that the cumulative risk of endometrial cancer during years 5–14 was 3.1% (mortality 0.4%) for women allocated to continue versus 1.6% (mortality 0.2%) for controls (absolute mortality increase 0.2%). The authors concluded that the small increase in endometrial cancer risk for women who were allocated to continue tamoxifen for 10 years was outweighed by the decrease in breast cancer mortality noted.

A similar trial, the aTTom trial, randomized 6953 women, of whom 2755 were ER positive and 4198 were untested, to 5 years or tamoxifen or extended tamoxifen (10 years) at 176 United Kingdom centers. Although 4198 tumors were untested for ER receptors, the investigators estimated that 80% of those untested would be ER positive if their statuses were known. This is consistent with the fact that the majority of breast cancers are HR positive, and, in many studies, testing for HR receptor status is not uniformly performed.

Similar to ATLAS trial, aTTom noted allocation to continue tamoxifen for 10 years significantly reduced breast cancer recurrence (580/3468 vs 672/3485, p = .003). This reduction was time dependent, with the extended longer treatment demonstrating a reduction in both breast cancer mortality (rate ratio [RR] 0.86, 95% CI 0.75−0.97) and overall mortality. An increase in endometrial cancer was also noted (RR 2.20, 95% CI 1.31−2.34, p < 0.0001). In analyzing the patient population, the ATLAS trial included premenopausal women, as 19% of patients were under 45 years of age (median age 45 years) in each of the study arms and 32% of the women were between 45–54 years of age (median age 49 years) in each study arm.

Thus, extended duration of therapy benefits seen in premenopausal women mirrors what is noted in postmenopausal women with 10 years of endocrine therapy. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA-17 study randomized postmenopausal patients who had completed 5 years of tamoxifen to 5 years of letrozole or no further treatment. At a median follow-up of 30 months, letrozole significantly improved disease-free survival (DFS) (p < 0.001), the primary end point, compared with placebo (hazard ratio for recurrence or contralateral breast cancer 0.58; 95% CI 0.45−0.76, p < 0.001) [9]. Although it is likely that the extended therapy may have greatly contributed to the benefit, the addition of an AI to tamoxifen therapy may also have played a role.

In 2014 the American Society of Clinical Oncology (ASCO) updated its clinical guidelines to recommend women with stage I−III HR positive breast cancer who are premenopausal/perimenopausal after 5 years of tamoxifen therapy continue therapy for a total duration of 10 years [10].

Aromatase Inhibitors (AIs)

The ATAC (*Arimidex, Tamoxifen, Alone or in Combination*) and BIG (*Breast International Group*) 1–98 trials found that adjuvant therapy with an AI is better than tamoxifen in HR positive postmenopausal breast cancer [11, 12]. Data from these large studies highlighting the superiority of AIs over tamoxifen contributed to the interest in adding OFS to premenopausal women with the goal of achieving a postmenopausal state that would allow use of an AI. Premenopausal women are not candidates for AIs without OFS because AIs alone can result in incomplete hormonal blockade of endogenous estrogens.

Ovarian Function Suppression Added to Endocrine Therapy

Ovarian ablation by surgical resection (oophorectomy) or radiation therapy as an adjuvant to breast cancer treatment was tested as early as the 1970s. Ovarian ablation was found to be an

effective adjuvant therapy in the absence of chemotherapy for patients with early breast cancer.

Initially, trials with ovarian ablation were small and ER tumor testing was not uniformly performed, as techniques for testing had not been well established. An early report from the EBCTCG demonstrated that ovarian ablation was associated with significant improvement in disease-free and overall survival, whether or not there was lymph node involvement [13].

A subsequent EBCTCG meta-analysis in 2005 of 8000 ER positive or ER unknown women < 50 years of age demonstrated improvement in DFS for those receiving ovarian ablation/ suppression in addition to other systemic cytotoxic breast therapies. Patients in these trials were grouped on whether their ovarian ablation was by surgery or irradiation (n = 4317), or by medical suppression by GnRH analog administration (n = 3408) [5].

OFS was not considered standard therapy based on limitations of these earlier studies that often included heterogeneous patient populations. Interest in OFS continued and focused on its use on young women with HR positive breast cancer with more high-risk factors, i.e., advanced disease (larger tumors, positive lymph nodes), who were recommended to receive chemotherapy. Concerns over the lack of endocrine effect on HR positive breast cancer by chemotherapy alone were fueled by studies that demonstrated an increased risk of relapse with failure to achieve chemotherapy-induced amenorrhea in premenopausal women. Trials such as the IBCSG 13–93 trial [14] and the NCIC CTG MA-5 trial [15] demonstrated that achievement of chemotherapy-induced amenorrhea correlated with improved DFS for ER positive breast cancer.

As a result of interest in and limited data on ovarian suppression in HR positive breast cancer, two large trials were initiated to address the question of ovarian suppression in addition to tamoxifen and exemestane.

The SOFT study randomly assigned 3066 premenopausal women, stratified according to prior receipt or non-receipt of chemotherapy, to receive 5 years of tamoxifen, tamoxifen plus OFS, or exemestane plus OFS. The investigators sought to determine whether OFS added to tamoxifen would improve DFS as compared with tamoxifen alone. The study also included a cohort of patients randomized to exemestane plus OFS.

Tamoxifen plus OFS was administered in 53.3% of patients who remained premenopausal after chemotherapy and in 46.7% who did not receive chemotherapy. With a median follow up of 67 months, the estimated DFS was 86.6% in the tamoxifen plus OFS group compared to 84.7% in the tamoxifen group (HR 0.83, 95% CI 0.66−1.04, p = 0.10). Although there was no significant difference for the entire population, multivariable analysis identified a benefit of tamoxifen plus OFS for those women who received chemotherapy and remained premenopausal.

It was noted that most recurrences in the study population occurred in the women who had received prior chemotherapy (the patients with higher-risk disease, i.e., more advanced stage, or clinical pathologic factors, such as higher grade, large tumor size and/or positive lymph nodes). For the subset of women who received chemotherapy, DFS was 82.5% in the

tamoxifen plus OFS group compared to 78.0% in the tamoxifen-alone group (HR 0.78; 95% CI 0.60−1.02). Additionally, the 5-year DFS was 85.7% in the exemestane plus OFS group compared to 78.0% in the tamoxifen-alone group (HR 0.65, 95% CI 0.49−0.87), demonstrating additional improvement with use of this combination therapy [3].

A comparison of the women who received or did not receive chemotherapy revealed significant differences. The 949 premenopausal women who did not receive chemotherapy, were predominantly older (> 40 years of age), with small, node-negative tumors of low to intermediate grade. They had few recurrences with greater than 95% DFS at 5 years. The 1084 women who remained premenopausal after chemotherapy were more likely to be younger (< 40 years of age) and had more adverse tumor features that warranted the use of chemotherapy. It was noted that in this chemotherapy group, 57.3% of women had positive lymph nodes and 47.3% had tumors > 2 cm in size. The authors concluded that adding OFS to tamoxifen is of benefit for a cohort of women who had a sufficient risk of recurrence to warrant adjuvant chemotherapy. OFS combined with an AI further reduced the risk of recurrence in this higher-risk premenopausal cohort. Because of the low number of events noted in the entire cohort, longer follow-up is necessary to determine whether the benefits in DFS will ultimately translate to an improvement in overall survival.

A sister study to the SOFT study was the TEXT study, with the main study goal to randomize premenopausal women with HR positive breast cancer to an AI and OFS or tamoxifen plus OFS. It was noted that the patients enrolled had lower-risk characteristics than had been anticipated, so the study investigators performed a combined analysis of data from TEXT and SOFT to be able to compare women who received exemestane plus OFS and tamoxifen plus OFS. Similar to the SOFT study, the women in TEXT who received chemotherapy were also more likely to have higher-risk characteristics, as did those in SOFT study compared to the women who did not receive chemotherapy.

The 5-year DFS was 91.1% (95% CI 89.7%−92.3%) for patients who received exemestane plus OFS compared to 87.3% (95% CI 85.7%−88.7%) for those receiving tamoxifen plus OFS. Among patients who received chemotherapy, the 5-year distant DFS was 2.6 percent higher for those women who received exemestane plus OFS compared to tamoxifen plus OFS in TEXT, and 3.4 percent higher than in the SOFT study. Differences between timing of therapy existed between the two trials, as women in TEXT began OFS during chemotherapy, at an average time of 1.2 months after surgery. Whether this early suppression played a significant role in outcomes probably warrants further investigation.

The combined analysis of data from TEXT and SOFT demonstrated that among premenopausal women with HR positive breast cancer, adjuvant therapy with exemestane plus OFS compared with tamoxifen plus OFS significantly improved DFS. The authors reported a 28% reduction in risk of recurrence, second invasive cancer, or death as well as a 34% reduction in the risk of breast cancer recurrence. However, no improvement in overall survival was noted [4].

It is important to note that although the difference in DFS was significant, questions remain whether this difference in DFS will ultimately translate to improvement in overall survival with longer follow-up.

Adverse Effects from OFS and Endocrine Therapy

In SOFT, OFS was achieved in 80.7% of patients with the use of gonadotropin-releasing hormone (GnRH) agonist triptorelin. Adverse grade 3 events were noted in 31.3% of the patients receiving OFS compared to 23.7% in the tamoxifen-alone group. Additionally, women who had OFS reported more vasomotor symptoms. Hypertension, diabetes, and osteoporosis were also more common.

When OFS is combined with exemestane, the effects, including the bone density adverse effects, are more frequent than with tamoxifen plus OFS. In the combined analysis of SOFT and TEXT, gynecologic cancer occurred in 7 patients assigned to exemestane plus OFS and in 9 assigned to tamoxifen plus OFS, including endometrial cancers in 2 and 5 patients, respectively.

A study on patient-reported outcomes with completed quality-of-life surveys comprising several global and symptom indicators at baseline, every 6 months for 24 months, and every year during years 3 to 6, from women enrolled in both trials receiving OFS with exemestane or tamoxifen, has recently been published. The median follow up was 5.7 years.

The investigators reported that women on tamoxifen plus OFS were more affected by hot flushes and sweats over the 5-year study period compared with women on exemestane plus OFS, although these symptoms improved. The patients on exemestane plus OFS were also more likely to report more vaginal dryness and greater loss of libido, and these symptoms persisted for the entire study period. Changes in global quality-of-life indicators from baseline were small and similar between treatments over 5 years. The authors concluded from a quality-of-life perspective that there was no strong indicator to favor tamoxifen with OFS vs AI with OFS [16].

The SOFT and TEXT studies support the use of OFS in premenopausal women with higher-risk HR positive disease. The use of exemestane plus OFS adds additional benefits over the use of tamoxifen plus OFS, but does have more overall adverse effects, including, but not limited to, vasomotor symptoms and bone density effect.

Choices for Ovarian Ablation; Is BSO an Alternative?

Many studies support BSO to reduce the risk of breast cancer among high-risk premenopausal women who have tested positive for mutations in *BRCA1* or *BRCA2* genes, and it is commonly recommended because of its additional benefit of risk reduction for ovarian cancer. A recent study by Metcalfe et al [17] reported a breast cancer mortality risk reduction of 0.38 (95% CI 0.19–0.77) in women with *BRCA1* who had an oophorectomy after diagnosis of breast cancer. This was retrospective study, where BSO was performed at a median of 6 years after diagnosis. Women with *BRCA1* mutations have higher proportion of ER negative breast cancers where hormonal manipulation and endocrine therapies are less

likely to be effective, and thus what the true effect of ovarian suppression is in this group does require further investigation. The benefits for ovarian cancer risk reduction are well established in *BRCA* carriers, and its role as OFS for HR positive breast cancer in premenopausal women is a viable option for some women who are recommended OFS.

For some premenopausal women, particularly those who have completed childbearing and who are older, the option of BSO is a good alternative to medical ovarian suppression therapy. These women can avoid monthly, costly injections as well as medical visits. The women who choose this option are usually > 40 years of age.

The risk of surgical complications from laparoscopic BSO is low, with many reports stating that it is < 2%. It is important to counsel these women of the potential complications from surgery, including the risk of conversion to laparotomy, and the risk of vascular, gastrointestinal, and urogenital tract injury. Adjuvant hysterectomy at time of BSO is not currently advocated, as it does significantly increase the risk of surgical complications. Although, the ATAC trial reported an increased risk of endometrial cancer for women on 10 years of tamoxifen therapy, many patients who start on tamoxifen will eventually change over to AIs during the duration of their therapy. For premenopausal patients, tamoxifen alone does not substantially increase the risk of endometrial cancer. In SOFT and TEXT, the incidence of endometrial cancers was small; however, questions remain regarding the endometrial effects of tamoxifen plus OFS in premenopausal women as extended therapy.

Limited data are available on comparison of BSO versus medical OFS. A study of 136 premenopausal women with metastatic breast cancer randomly assigned to GnRH agonist versus BSO did not demonstrate a difference in overall survival. The study was underpowered and closed early due to poor accrual [18].

Additionally, there is concern that medical OFS with GnRH agonists may not be complete in some premenopausal patients and may result increase in FSH and estradiol. It is not clear whether these effects are persistent in some or all patients on AIs plus OFS using GnRH agonists. Further study is necessary, as the efficacy of AIs in patients without ovarian suppression is suboptimal. In certain circumstances, oophorectomy may be considered, particularly if there is concern of incomplete medical ovarian suppression [19].

Further research on patient choice for type of ovarian ablation, as well as quality-of-life factors, and a comparison of efficacy and side effects of surgical ovarian ablation compared to medical OFS, is necessary.

Conclusions

Data are now available to help guide decisions regarding optimal endocrine therapy. Data also support the use of tamoxifen alone in premenopausal women with low-risk disease. OFS should be considered for the patient who has high-risk disease factors that would warrant recommendations for systemic chemotherapy. In addition, the St. Gallen and recent ASCO clinical guidelines advocate that in cases where OFS is considered, exemestane is a better treatment choice.

In conclusion, tailoring the choices for endocrine therapy includes selection of OFS for some premenopausal women with HR positive breast cancer with higher-risk disease. The alternative of tamoxifen therapy alone is still available for the majority of women. Further research is necessary on patient decision making regarding ovarian ablation, and on the associated medical, surgical, and quality-of-life factors.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017; 67:7–30. [PubMed: 28055103]
2. Centers for Disease Control and Prevention. www.cdc.org (Accessed May 26, 2017).
3. Francis PA, Regan MM, Fleming GF, Lang I, Ciruelos E, Bellet M, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015; 372:436–46. [PubMed: 25495490]
4. Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Lang I, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014; 371:107–18. [PubMed: 24881463]
5. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 365:1687–717. [PubMed: 15894097]
6. Early Breast Cancer Trialists' Collaborative G. Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011; 378:771–84. [PubMed: 21802721]
7. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. 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; 381:805–16. [PubMed: 23219286]
8. Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, 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. J Clin Oncol. 2013; 31 (supplement; abstract No. 5).
9. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005; 97:1262–71. [PubMed: 16145047]
10. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, 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; 32:2255–69. [PubMed: 24868023]
11. Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. J Clin Oncol. 2007; 25:486–92. [PubMed: 17200148]
12. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 2008; 9:45–53. [PubMed: 18083636]
13. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1996; 348:1189–96. [PubMed: 8898035]
14. International Breast Cancer Study G. Colleoni M, Gelber S, Simoncini E, Pagani O, Gelber RD, et al. Effects of a treatment gap during adjuvant chemotherapy in node-positive breast cancer: results of International Breast Cancer Study Group (IBCSG) Trials 13–93 and 14–93. Ann Oncol. 2007; 18:1177–84. [PubMed: 17429101]
15. Parulekar WR, Day AG, Ottaway JA, Shepherd LE, Trudeau ME, Bramwell V, et al. Incidence and prognostic impact of amenorrhea during adjuvant therapy in high-risk premenopausal breast

cancer: analysis of a National Cancer Institute of Canada Clinical Trials Group Study–NCIC CTG MA.5. J Clin Oncol. 2005; 23:6002–8. [PubMed: 16135468]

16. Bernhard J, Luo W, Ribi K, Colleoni M, Burstein HJ, Tondini C, et al. Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. Lancet Oncol. 2015; 16:848–58. [PubMed: 26092816]
17. Metcalfe K, Lynch HT, Foulkes WD, Tung N, Kim-Sing C, Olopade OI, et al. Effect of Oophorectomy on Survival After Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. JAMA Oncol. 2015; 1:306–13. [PubMed: 26181175]
18. Taylor CW, Green S, Dalton WS, Martino S, Rector D, Ingle JN, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol. 1998; 16:994–9. [PubMed: 9508182]
19. Dowsett M, Lonning PE, Davidson NE. Incomplete Estrogen Suppression With Gonadotropin-Releasing Hormone Agonists May Reduce Clinical Efficacy in Premenopausal Women With Early Breast Cancer. J Clin Oncol. 2016; 34:1580–3. [PubMed: 26729430]
20. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. 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; 26:1533–46. [PubMed: 25939896]