Commentary
Adjuvant endocrine therapy for premenopausal women with early breast cancer

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Abstract

Adjuvant endocrine therapy is a pivotal component of treatment for premenopausal women with early-stage hormone receptor-positive breast cancer. Currently, the standard endocrine therapy for premenopausal women is tamoxifen; a role for ovarian suppression or ablation has also been identified. Uncertainty remains about the optimal use of endocrine therapy in this setting. The role of ovarian suppression with tamoxifen or aromatase inhibitor, the optimal duration of adjuvant endocrine therapy and the utility of biomarkers and pharmacogenetic studies to select therapy are questions worthy of further investigation.

Endocrine therapy interrupts the estrogen-estrogen receptor alpha (ER) signaling pathway by either interfering with ER-ligand interaction through the use of selective ER modulators (SERMs) like tamoxifen or decreasing production of the ligand, estrogen, via ovarian ablation or suppression (OA/OS) or aromatase inhibition. These interventions represent some of the first targeted therapies to treat any type of cancer. They exemplify the power of understanding the role of a biological pathway by careful target identification and selective targeting of that pathway. Unfortunately for premenopausal women with endocrine-responsive breast cancer, we ignored cancer biology and treated these women with chemotherapy alone for a number of years. Only more recently have we rightly reinstated endocrine therapy as the most important part of management of premenopausal women with early-stage hormone receptor (HR)-positive breast cancer.

In 1896, Sir George Beatson successfully palliated meta-static breast cancer in young women with bilateral oophorec-tomy and established the role of endocrine therapy in the form of OA in managing women with breast cancer [1]. Fifty years later, investigators from the Christie Hospital in England conducted the first randomized controlled trial of ovarian irradiation in breast cancer patients, which, along with five succeeding randomized clinical trials, further confirmed a role

for OA in managing premenopausal women with operable breast cancer [2]. The 1970s brought the belief that endocrine therapy was less effective in premenopausal women as initial trials in unselected patients showed that chemotherapy, rather than endocrine therapy, improved the overall survival of these women. It was not until the 1990s when serial reports of the early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis reaffirmed the efficacy of OA/OS in women younger than 50 years of age by demonstrating that OA/OS reduced the incidence of breast cancer recurrence and mortality by 30% [3]. Meanwhile, researchers also postulated that the benefit of adjuvant chemotherapy might be partially derived from chemotherapy-induced OS, a common consequence of chemotherapy in premenopausal women. These findings stimulated a series of randomized controlled trials evaluating the efficacy of OA/OS versus chemotherapy or in addition to chemotherapy. Unfortunately, none of those clinical trials incorporated tamoxifen because of another false belief that tamoxifen was ineffective in premenopausal women. Indeed, it was not until 1995 that the EBCTCG overview unequivocally rejected this misconception about tamoxifen by demonstrating its efficacy in lowering the breast cancer recurrence rate and mortality in premenopausal women with HR-positive breast cancer. Currently, tamoxifen is the standard adjuvant endocrine therapy in premenopausal women, and monotherapy with OS is considered a reasonable alternative if pregnancy is planned. Some practitioners also accept a role for OS plus tamoxifen [4].

The benefits of tamoxifen in premenopausal women with HR-positive breast cancer have stood the test of time. The 2000 EBCTCG meta-analysis demonstrated that, in women with HR-positive breast cancer, five years of adjuvant tamoxifen halved the annual recurrence rate and reduced breast cancer related mortality by 31%, regardless of age, nodal status or

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EBCTCG = Breast Cancer Trialists' Collaborative Group; ER = estrogen receptor; GnRH = gonadotrophin hormone-releasing hormone; HR = hormone receptor; OA = ovarian ablation; OS = ovarian suppression.

use of chemotherapy [3]. Five years of tamoxifen was noted to be more effective than one to two years of tamoxifen [3]. Small clinical trials comparing five years to ten years of tamoxifen treatment failed to demonstrate superiority of therapy of longer duration, leading to the current practice of five years of tamoxifen [3]. Two ongoing large randomized clinical trials, Adjuvant Tamoxifen Treatment-Offer More (aTTom) and Adjuvant Tamoxifen-Longer against Shorter (ATLAS), should add to our understanding about the optimal duration of adjuvant tamoxifen use in premenopausal women.

OA/OS can be achieved by surgery, radiation, chemotherapy, or gonadotrophin hormone-releasing hormone (GnRH) agonists such as goserelin, leuprorelin and triptorelin [5]. If ovarian targeted therapy is to be used, the 2007 St Gallen panel recommended GnRH agonist as a first line agent for OS, and accepted oophorectomy as a reasonable alternative; radiation induced OA was universally rejected [4].

The efficacy of OS compared to chemotherapy or in addition to chemotherapy has been investigated in numerous clinical trials [6]. A recently published meta-analysis collected data from 16 randomized clinical trials involving 9,022 premenopausal women with early-stage HR-positive breast cancer. Use of GnRH agonist alone showed a non-significant reduction in recurrence rate and death after breast cancer but this analysis included only 338 patients and lacked statistical power. GnRH agonists showed similar efficacy to chemotherapy (largely CMF-like) in trials that enrolled 3,184 women. The meta-analysis also failed to show significant superiority of GnRH agonist plus tamoxifen over tamoxifen or chemotherapy. It did, however, show an additional benefit of GnRH agonist when used with chemotherapy with or without tamoxifen in both recurrence rate (hazard ratio 0.88, 95% confidence interval 0.77 to 0.99, $p = 0.04$) and disease-free survival (hazard ratio 0.85, 95% confidence interval 0.73 to 0.99, $p = 0.04$). This additional benefit was noted in women younger than 40 years of age, in whom chemotherapy-induced amenorrhea is less common, and was not observed in women 40 years or older who are likely to become postmenopausal as a consequence of chemotherapy. As few patients in these trials were given tamoxifen in both arms, it is not possible to evaluate whether GnRH adds to the benefit obtained from tamoxifen. The meta-analysis concluded that GnRH agonists were effective agents in treating premenopausal women with HR-positive early breast cancer [7]. Even though this analysis is the most comprehensive examination of the use of GnRH agonists in early breast cancer, it is limited by insufficient statistical power for some of the questions posed. Also, some might argue that the chemotherapy studied is not contemporary as only a minority of trials used anthracycline-based chemotherapy and none employed a taxane. Most importantly, none of the trials used tamoxifen in an optimal fashion; in particular, no study compared GnRH agonist plus tamoxifen with chemotherapy plus tamoxifen.

The role of OA by surgery has also come under scrutiny again with the advent of testing for BRCA1 and BRCA2 mutation in women in hereditary breast cancer families. It has been recognized that prophylactic oophorectomy can reduce risk of developing both breast and ovarian cancer in such women [8]. Mutation carriers are often identified at the time of breast cancer diagnosis. By extrapolation from other data sets, it seems likely that prophylactic oophorectomy that may be pursued by these women might be a useful adjuvant therapy for HR-positive breast cancer.

Failure to recognize the importance of endocrine therapy, especially tamoxifen, in the treatment of premenopausal women with breast cancer led to a lag in identifying the optimal use of endocrine therapy. Thus, several questions remain to be answered, and the role of combination endocrine therapy is one of them. The strategy of GnRH agonist plus tamoxifen has not been shown to be superior to either approach alone in early breast cancer. Also, although monotherapy with aromatase inhibitors alone is not indicated in premenopausal women, the combination therapy of OS and aromatase inhibitors is a rational and intriguing consideration. Several of these unanswered questions will be addressed in ongoing trials. The Suppression of Ovarian Function Trial (SOFT) compares the efficacy of tamoxifen versus OS plus tamoxifen versus OS plus exemestane for five years in premenopausal women with HR-positive breast cancer; this trial includes women who have received adjuvant chemotherapy and remain premenopausal thereafter. Successful completion of this trial is vital as it will identify the optimal endocrine therapy regimen for premenopausal women. Two trials are further examining the role of combined endocrine therapy. Both the Tamoxifen and Exemestane Trial (TEXT) and Austrian Breast Cancer Trial 12 are randomizing women to OS plus tamoxifen or to OS plus aromatase inhibitor. Unfortunately, both the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE) and Premenopausal Optimal Management IS Endocrine therapy (PROMISE) trials were closed early due to poor accrual. Hence, the most important question of whether premenopausal women with early-stage HR-positive breast cancer receiving combined endocrine therapy would benefit from chemotherapy will likely never be answered in a prospective fashion.

In addition, the optimal duration of endocrine therapy for premenopausal women to balance the potential benefits and side effects associated with the treatment needs to be determined. Endocrine therapy significantly affects reproductive options in premenopausal women as women are counseled not to become pregnant during the several years of adjuvant endocrine therapy. Young women may also experience menopausal symptoms, such as hot flushes, vaginal dryness and sexual dysfunction, with any of these endocrine therapies. The long term side effects of endocrine therapy on bone health, cognitive function and cardiovascular health also require further investigation.

Finally, it is clear that we are now beginning to tailor our therapy choices based on better understanding of both tumor and host biology. It took decades for us to recognize that interventions like tamoxifen and OS are most effective for cancers that express HR. The advent of genomic and proteomic assays that allow analysis of multiple variables of the tumor simultaneously will surely enhance our ability to select endocrine therapy for the individual patient more precisely. Indeed tests like the Oncotype Dx assay are but the first step in this process. Similarly, in the near future, we may also need to tailor our treatment based on the biology of the host. Currently, choice of endocrine therapy is made, in part, on the patient's menopausal status. It is likely that other measures, such as pharmacogenetic assays, will increasingly come into play. For example, early work suggests that response to tamoxifen may be influenced by single nucleotide polymorphisms in the *CYP2D6* gene, a member of the cytochrome p450 family that plays a role in converting tamoxifen to its active metabolite, endoxifene. Seven to ten percent of Caucasians have *CYP2D6* variants, and patients with homozygous *CYP2D6* variants may have decreased *CYP2D6* activity and endoxifene levels in small studies of breast cancer patients receiving tamoxifen [9]. Further study to confirm these findings, investigate the role of other *CYP2D6* variants, and determine the clinical ramifications of these variants is needed before *CYP2D6* genotype determination should become a routine test to determine tamoxifen use [10]. It is highly likely such tumor- and host-based assays will be an increasingly common part of oncology in the 21st century.

It is sobering to compare the slow pace of development of endocrine therapy in premenopausal women with HR-responsive breast cancer with the development of anti-HER-2 based therapy. The former has taken over 100 years while the first anti-HER-2 therapy went from identification of the target gene/protein to proof of survival benefit of trastuzumab in women with advanced breast cancer that over-expresses HER-2 protein in less than 20 years. This comparison reminds us of the importance of targeting therapy based on a good understanding of cancer biology and the value of well-designed and adequately powered clinical trials.

Competing interests
The authors declare that they have no competing interests.

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