editorials

Back to the Beginning: The Role of Ovarian Suppression in Management of Hormone Sensitive Breast Cancer in Premenopausal Women

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Although many consider targeted therapy a modern concept, targeted therapy in breast cancer dates back to 1889, when Schinzinger[1] first proposed oophorectomy as adjunctive therapy for breast cancer to alter the hormonal milieu of the malignancy. Beatson[2] put the proposal into practice, reporting decreases in cutaneous metastases in a premenopausal woman after oophorectomy in 1896. The mechanism underlying the response to oophorectomy remained mysterious until Jenson identified the estrogen receptor (ER) 75 years later.[3] Since that time, the ER has become the most well-studied, and arguably the most important, target for breast cancer therapy.

A randomized trial in Vietnam and China found a significant improvement in disease-free survival (DFS; 5-year DFS, 75% *v* 58%; $P = .0003$) and overall survival (OS, 78% *v* 70%; $P = .041$) with adjuvant oophorectomy and tamoxifen compared with surgery alone in the absence of chemotherapy or selection based on tumor ER expression, with benefits persisting at 10 years.[4] By the 1980s, pharmacological inhibition of estrogen signaling, first with diethylstilbestrol and then tamoxifen, had largely supplanted ovarian suppression in higher-income countries. In fact, many wondered if ovarian suppression still had a role in the era of adjuvant chemotherapy and antiestrogen therapeutics. The INT-0101 (E5188) trial did not show any benefit from the addition of ovarian suppression with an LHRH agonist to chemotherapy and tamoxifen in premenopausal women with ER-positive disease.[5] Unfortunately, E5188 failed to recognize and control for impact of chemotherapy on ovarian function, leaving the question largely unanswered.

Learning from the failures of the past, the SOFT trial enrolled approximately 3,000 women with premenopausal ER-positive breast cancer to tamoxifen alone, ovarian suppression plus tamoxifen, or ovarian suppression plus the aromatase inhibitor exemestane.[6] Adjuvant chemotherapy was allowed but had to be completed before enrollment. Critically, menses had to persist through, or resume after, chemotherapy to participate in SOFT. In contrast, TEXT assumed benefit of ovarian suppression, randomly assigning patients to tamoxifen or exemestane in conjunction with ovarian function suppression. First reported in 2015, the SOFT trial found a significant improvement in DFS with exemestane plus ovarian suppression compared with tamoxifen in premenopausal patients who had received prior chemotherapy (5-year DFS, 85.7% *v* 78.0%; hazard ratio, 0.65; 95% CI, 0.49 to 0.87).[6] A combined analysis of the SOFT and TEXT trials confirmed that adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence in premenopausal women with ER-positive breast cancer (5-year DFS, 91.1% *v* 87.3%; hazard ratio, 0.72; 95% CI, 0.60 to 0.85; $P < .001$).[7,8]

Long-term follow-up of trials in premenopausal women with ER-positive breast cancer remains critical because of both propensity for late recurrence and cumulative risk of late toxicities from early menopause. In the articles that accompany this editorial, Pagani et al[9] and Francis et al[10] report a sustained improvement in DFS at 12 years and, for the first time to our knowledge, an improvement in OS with incorporation of ovarian suppression as a component of endocrine therapy. Not surprisingly, the survival benefit was greatest in patients with a higher risk of recurrence including those with grade 3 tumors (5.5%), tumors > 2 cm (4.5%), diagnosis age < 35 years (4.0%), or prior adjuvant chemotherapy (3.3%). Despite the improvements in DFS, adoption of ovarian suppression as a standard component of adjuvant therapy has been modest. The improvements in OS reported in the SOFT trial, similar in magnitude to the benefit of adjuvant cytotoxic therapy, highlight the profound benefit of optimal hormone therapy. Unlike the novel agents we frequently highlight, ovarian suppression (or oophorectomy) is readily available and inexpensive, making this effective intervention available worldwide.[11]

Management of ER-positive breast cancer requires playing the long game, with endocrine therapy continuing for a minimum of 5, and often 10, years. Chronic toxicities are real and deserving of greater attention. Ovarian suppression plus exemestane increased treatment-related adverse events including hot flashes, musculoskeletal

ASSOCIATED CONTENT

See accompanying articles on pages 1370 and 1376

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THE TAKEAWAY

In the articles[9,10] that accompany this editorial, SOFT and TEXT investigators report a sustained improvement in long-term outcomes (disease-free survival) and for the first time an improvement in overall survival for premenopausal women with estrogen receptor–positive breast cancer through incorporation of ovarian suppression as a component of endocrine therapy. Based on these data, ovarian suppression with an aromatase inhibitor should become the preferred initial hormone therapy recommendation for all premenopausal women with high-risk (ie, grade 3, T2, and age < 35 years) estrogen receptor–positive breast cancer.

events, vaginal dryness, and reduced libido.[12] Importantly, these toxicities led to early discontinuation of oral endocrine therapy with ovarian suppression plus exemestane. International breast cancer guidelines suggest a variety of options for adjuvant endocrine therapy in premenopausal women with early-stage breast cancer.[13,14] The optimal approach must consider a variety of factors, including individual cancer recurrence risk, comorbidities and symptomatology, social and financial factors, reproductive goals, and patient preference. Shared decision making is critical to achieve optimal cancer care outcomes that are tailored to a patient's specific needs and goals.[15] In this regard, the long-term outcomes reported in this edition of *JCO* quantify the absolute benefits and toxicities of differing endocrine treatment approaches in premenopausal patients and suggest subgroups that may benefit most from this combined treatment approach.

Long-term follow-up requires persistence and patience, but the field does not remain static while we wait. Some may question the relevance of these results given the changes in adjuvant treatment landscape since SOFT and TEXT were launched. Approximately 15% of participants enrolled had human epidermal growth factor receptor 2 (HER2) overexpressing tumors with inconsistent use of HER2-targeted treatment. The use of chemotherapy has also evolved. Most patients with lymph node–positive disease (91.7% in SOFT and 79.3% in TEXT) received chemotherapy; none received a cyclin-dependent kinase inhibitor. Whether changes in HER2-targeted therapy, use of chemotherapy, or addition of a cyclin-dependent kinase inhibitor alter the proportional benefit of ovarian suppression is unknown.

Despite these uncertainties, improvements in OS cannot and should not be ignored. Ovarian suppression with an aromatase inhibitor should become the preferred initial hormone therapy recommendation for all premenopausal women with high-risk (ie, grade 3, T2, and age < 35 years) ER-positive breast cancer. We favor a stepwise approach, first initiating and evaluating toxicity with ovarian suppression alone and then adding an aromatase inhibitor. Should toxicity be intolerable, reversion to tamoxifen alone, or with continued ovarian suppression remains an option and is certainly preferable to discontinuation of all antiestrogen therapies. Ovarian suppression should not be considered a mandate for patients with lower risk disease where the long-term toxicities outweigh the benefits.

So how can we best maximize well-being in premenopausal breast cancer survivors with ER-positive disease? Cancer survivorship care is recommended by international guidelines[16,17]; however, its global implementation has been challenging, primarily because of resource and time constraints in the acute care setting. Novel shared models of care that span oncology and primary care, including nurse-led services, are likely to yield more widespread implementation of best practices.[18,19] Like the approach of individualizing treatment decision making, a tailored risk stratification and needs assessment can recommend personalized survivorship care pathways spanning supported self-management (lower risk) and expert-led supportive care (moderate/high risk).[20] Technology-based remote monitoring of symptoms, quality of life, and medication adherence[21] and the incorporation of patient-reported outcome measures can improve symptom control, physical function, quality of life, adherence to treatment, and indeed survival.[22] Routine incorporation of such tools in early-stage ER-positive breast cancer has the potential to optimally support women in the years after initiation of endocrine therapy, maximizing adherence and long-term outcomes regardless of the specific antiestrogen therapy.

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