EDITORIAL

Hormone Therapy in Premenopausal Women with Early-Stage Breast Cancer

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Breast cancer is the most frequent cancer diagnosis in women worldwide and the most common cause of death from cancer. In the United States, 21% of breast cancers are diagnosed in women younger than 50 years of age, affecting almost 49,000 women, and this disease remains a leading cause of death.[1] The most common form of breast cancer is hormone-receptor–positive disease, and the incidence of this subtype, particularly among younger women, has increased in the past decade, probably owing to changes in lifestyle factors and diet. For these reasons, improving the outcome of hormone-receptor–positive breast cancer in young women is of great importance.

In this issue of the *Journal*, Pagani and colleagues report the combined analysis of two international collaborative group trials, the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT).[2] The combined analysis showed a significant improvement in disease-free survival, without an improvement in overall survival, with 5 years of suppression of ovarian function (hereafter, ovarian suppression) and the aromatase inhibitor exemestane, as compared with 5 years of ovarian suppression and tamoxifen at a median follow-up of 5.7 years (68 months). In order to interpret and apply these data to clinical practice, it is important to put them into context.

Five years of adjuvant tamoxifen is an integral component of therapy in young women with early-stage hormone-receptor–positive breast cancer, significantly reducing recurrence and improving survival.[3] A number of studies have evaluated ovarian suppression either alone or in combination with hormone therapy in early-stage hormone-receptor–positive disease, showing improved outcomes that are similar or superior to those seen with older forms of chemotherapy.[4] To date, no trial has been reported that compares the addition of ovarian suppression to standard adjuvant hormone therapy, although a trial treating premenopausal women with metastatic breast cancer showed improved progression-free survival and overall survival with the combination of ovarian suppression and tamoxifen, as compared with either treatment alone.[5] In postmenopausal women, adjuvant aromatase inhibitors are superior to tamoxifen.[6,7] These data have created two questions regarding hormone therapy in premenopausal women with early-stage breast cancer: whether adding ovarian suppression to tamoxifen improves outcomes as compared with tamoxifen alone, and whether aromatase inhibitors are superior to tamoxifen in premenopausal women treated with ovarian suppression. SOFT was designed to answer the first question; the long-anticipated results from that comparison are expected at the end of this year. The current analysis addresses the second question, concluding that exemestane is superior to tamoxifen when combined with ovarian suppression for 5 years.

Although the primary end point of the two trials was disease-free survival, the ultimate goal of adjuvant therapy is to reduce the recurrence of breast cancer at distant sites. The difference between exemestane and tamoxifen for the time interval without distant recurrence was 1.8 percentage points for the group as a whole. In patients not receiving chemotherapy, there were few distant recurrences and no appreciable differences between the exemestane and tamoxifen groups in either SOFT (99.3% and 98.6% of patients, respectively, without distant recurrence; 3 events and 6 events, respectively) or TEXT (98.0% and 98.1% of patients; 9 events and 12

events). However, in the 57.4% of patients who received chemotherapy, a clinically relevant improvement in the time interval without distant recurrence was observed in favor of exemestane, with an absolute improvement of 2.6 percentage points for TEXT (91.8% vs. 89.2%) and an absolute improvement of 3.4 percentage points in SOFT (84.6% vs. 88.0%).

The time interval without distant recurrence among patients enrolled in SOFT and TEXT and not receiving chemotherapy is excellent, even though 14.8% of the women had node-positive disease. The benefit in chemotherapy-treated patients could be due to a differential benefit of aromatase inhibitors over tamoxifen in high-risk tumors[8] or the possibility that the ovarian suppression required to derive benefit from aromatase inhibitors is more effective after chemotherapy.

The Austrian Breast and Colorectal Cancer Study Group–12 (ABCSG-12) trial also investigated ovarian suppression plus either tamoxifen or an aromatase inhibitor, with a second randomization evaluating the use of the bisphosphonate zoledronic acid.[9] This trial showed no benefit from the aromatase inhibitor and a worse outcome in obese women, which was presumably due to inadequate ovarian suppression.[10] This apparently opposing result could be due to a number of factors; only 5% of the patients in the ABCSG-12 trial received chemotherapy, the trial enrolled a smaller number of patients than TEXT and SOFT, treatment continued for only 3 years, the use of zoledronic acid may have abrogated the effect of the aromatase inhibitor, and body weight clearly played a role in the outcomes.

Serious adverse events and measures of quality of life were relatively similar between the TEXT and SOFT cohorts in the trial by Pagani et al. However, as compared with tamoxifen, the use of the aromatase inhibitor caused more sexual dysfunction, osteoporosis, fractures, and musculoskeletal symptoms, which may be more noxious to young women than the hot flushes experienced with tamoxifen, and it is too early to detect differences in the incidence of cardiovascular events. Of note, 50% of the women in both treatment groups reported depression.

How do we apply these data to clinical practice? As with any treatment, a careful assessment of risk versus benefit individualized to each patient should be the first step. The duration of follow-up is short, with almost 50% of recurrence events still expected, and there is no significant difference in overall survival as yet. Particularly in the group of women who did not receive chemotherapy, the number of events is small and the additional benefit of ovarian suppression is unknown. This group of patients could reasonably be treated with tamoxifen with or without ovarian suppression as we await the data from SOFT. For premenopausal women with high-risk breast cancer requiring chemotherapy, ovarian suppression with exemestane for 5 years is a new treatment option with the potential to reduce risk of distant recurrence.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA Cancer J Clin 2014;64:52-62.
2. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371:107-18.
3. Early Breast Cancer Trialists' Collaborative Group. 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.
4. 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;369:1711-23.
5. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001;19:343-53.
6. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010;28:3784-96.
7. Chirgwin J, Sun Z, Smith I, et al. 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;131:295-306.
8. Viale G, Giobbie-Hurder A, Regan MM, et al. Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. J Clin Oncol 2008;26:5569-75.
9. Gnant M, Mlineritsch B, Stoeger H, et al. 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;12:631-41.
10. 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;29:2653-9.

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