A n analysis of 2 international studies has demonstrated benefit to adding ovarian function suppression (OFS) to the adjuvant hormonal therapy regimen among premenopausal women with early-stage, hormone receptor (HR)-positive breast cancer carrying a high risk of recurrence (J Clin Oncol [published online ahead of print April 4, 2016]. pii: JCO643171).

The phase 3 Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) demonstrated that 5 years of adjuvant therapy with exemestane plus OFS improves outcomes compared with tamoxifen plus OFS or tamoxifen alone in premenopausal women with early HR-positive breast cancer. Results of SOFT also indicated that tamoxifen with OFS improves outcomes compared with tamoxifen alone in women whose risk of breast cancer recurrence is high enough to justify adjuvant chemotherapy administration. The current study was performed to better define the absolute amount of clinical benefit of the regimens according to a patient’s recurrence risk level.

“This analysis was intended to refine the interpretation of the overall TEXT and SOFT trial results for decision making with individual patients and for the discussion between clinician and patient of the potential magnitude of treatment benefit versus potential side effects of the treatments,” says Meredith Regan, ScD, lead author and associate professor of medicine and researcher in the department of biostatistics and computational biology at the Dana-Farber Cancer Institute in Boston, Massachusetts.

**Study Details**

TEXT included 2672 and SOFT included 3066 premenopausal women with early-stage breast cancer. In TEXT, the women were randomized before adjuvant therapy was initiated and OFS began, regardless of whether chemotherapy was to be given. SOFT was different in that it examined 2 cohorts of women: those who remained premenopausal after chemotherapy and those in whom only endocrine therapy was determined to be necessary by the clinician. TEXT included 2 study arms: 5 years of exemestane or tamoxifen, both with OFS. SOFT included 3 study arms: exemestane plus OFS, tamoxifen plus OFS, and tamoxifen alone. OFS was achieved by oophorectomy or therapy with a gonadotropin-releasing hormone antagonist. The final analysis population for the current study included 4891 patients with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

A composite recurrence risk was calculated for each patient using a Cox model incorporating age, lymph node status, tumor size and grade, HR status, and Ki-67 expression. The endpoint was the breast cancer-free interval (BCFI), defined as the time from randomization to first recurrence of local or distant invasive breast cancer or contralateral breast cancer.
breast cancer. For the entire patient population, the 5-year BCFI was 90.8%, ranging from 77.5% for patients in the highest-risk quartile to 98.6% for patients in the lowest quartile of composite risk.

In SOFT, a clinician determined that only hormonal therapy was warranted for adjuvant therapy in a subset of patients. This patient group had the lowest composite risk and a BCFI of 96%. In this group, adding OFS to the endocrine regimen did not improve outcomes compared with the use of tamoxifen alone.

In TEXT, for the group of patients who received only hormonal therapy for adjuvant treatment as decided by the clinician, the BCFI also was 96% overall. On average, the use of exemestane plus OFS improved the BCFI by 3.6% compared with tamoxifen plus OFS. In the subpopulation with the lowest composite risk, the improvement was minimal, at an approximately 1% absolute benefit in the BCFI. In the group with the highest composite recurrence risk, the benefit of exemestane plus OFS compared with tamoxifen plus OFS was approximately 10%.

In the TEXT cohort of patients whose risk of recurrence warranted adjuvant chemotherapy, the 5-year BCFI was 89.3%, with an average 5.8% absolute improvement with the use of exemestane plus OFS versus tamoxifen plus OFS. Benefits were observed across all the risk groups, with the 5-year BCFI ranging from 5% to 15% as composite risk increased.

In the SOFT group of patients whose risk of recurrence warranted adjuvant chemotherapy, the overall 5-year BCFI was 82.5%. On average, the use of exemestane plus OFS improved the 5-year BCFI by 5.4% and 7.4%, respectively, versus tamoxifen plus OFS and tamoxifen alone. The improvement was 2% for tamoxifen plus OFS versus tamoxifen alone.

In the subpopulation with the lowest composite recurrence risk, the 5-year BCFI was greater than 90% for all 3 treatment groups. However, in the other subpopulations with increasing composite risk, the absolute benefit with exemestane plus OFS ranged from approximately 5% to 15% versus tamoxifen alone. The addition of OFS to tamoxifen also conferred an absolute benefit of approximately 5% in the subpopulation with the higher risk. The benefit diminished in the lower-risk patients.

Clinical Implications
The results of these 2 complementary trials indicate that OFS is beneficial for some premenopausal women with early HR-positive breast cancer, demonstrating that the patient’s recurrence risk must be taken into account to determine whether OFS will be beneficial. Although there will be some patients for whom it may be relatively easy to decide whether OFS is indicated (ie, those at obvious very low risk or those at obvious high recurrence risk), many women will fall in between.

“In some patients, particularly those who may have only a small benefit, treatment decisions will be more difficult. These situations require careful discussions of risks, benefits, and patient preferences so that treatment decisions can be individualized to the particular patient,” says Sharon Giordano, MD, MPH, professor of medicine and chair in the department of health services research at The University of Texas MD Anderson Cancer Center in Houston.

Dr. Regan points out that the updated guidelines for adjuvant endocrine therapy in premenopausal women (such as the guidelines provided by the American Society of Clinical Oncology, Cancer Care Ontario, and the European Society for Medical Oncology) are fairly consistent in suggesting that OFS and aromatase inhibitors should be considered rather than tamoxifen alone in high-risk patients.

“The analysis provides insight that the potential improvement in 5-year freedom from recurrence is on the order of 10 to 15 percentage points,” Dr. Regan says. “On the other hand, the guidelines and this analysis support tamoxifen alone as appropriate for some premenopausal women with HR-positive disease who are at low risk of recurrence.”

Dr. Giordano, one of the authors of the updated American Society of Clinical Oncology guidelines, agrees. “For the patients who remain premenopausal after chemotherapy, there is a substantial benefit of treatment with aromatase inhibitors plus OFS, particularly for patients with intermediate to high-risk disease. These data justify offering an aromatase inhibitor plus OFS to these patients whenever possible. However, one major limitation to this study is that overall survival data are not yet available,” she says.

“The follow-up of TEXT and SOFT trial patients continues with plans to update the results in 2017,” says Dr. Regan. “Because HR-positive early breast cancer has a persistent long-term risk of recurrence, this follow-up is essential to our understanding of benefits and side effects of these treatments.”

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