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Postmenopausal Women With Early-stage Breast Cancer and Low Recurrence Score Could Skip Adjuvant Chemotherapy

Adjuvant chemotherapy may yield improved survival outcomes for premenopausal counterparts

SAN ANTONIO – After a median follow-up of 5.1 years, among women with lymph node-positive early-stage breast cancer and a recurrence score of 25 or lower who received adjuvant endocrine therapy with or without chemotherapy, postmenopausal patients had no added benefit from chemotherapy, while premenopausal patients who received chemotherapy had improved invasive disease-free survival (IDFS) and an early indication of improved overall survival (OS), according to data from the SWOG S1007 RxPONDER clinical trial presented at the 2020 San Antonio Breast Cancer Symposium, held Dec. 8-11.

"The most common form of breast cancer is hormone receptor (HR)-positive and HER2-negative, comprising about two-thirds of all invasive breast cancers," said Kevin Kalinsky, MD, MS, director of the Glenn Family Breast Center at Winship Cancer Institute of Emory University.

RxPONDER was designed and run by SWOG Cancer Research Network with support from the National Cancer Institute. It set out to determine which patients with HR-positive, HER2-negative breast cancer and one to three positive axillary lymph nodes benefit from chemotherapy and which patients could safely avoid chemotherapy and still achieve similar outcomes with endocrine therapy alone, Kalinsky said. "Up until now, there were no data from a large randomized clinical trial to guide this decision," he added.

"At the time of this analysis, our data show that postmenopausal women with HR-positive, HER2-negative breast cancer with one to three positive nodes and a recurrence score of 25 or lower can safely avoid receiving adjuvant chemotherapy. On the other hand, premenopausal patients with HR-positive, HER2-negative breast cancer with one to three positive nodes and a recurrence score of 25 or lower should consider adjuvant chemotherapy. The invasive disease-free survival rate improved by 5 percent with chemotherapy in this group," Kalinsky said.

In this clinical trial, 5,083 patients with stage 2-3 breast cancer involving one to three axillary lymph nodes and whose tissue had a recurrence score of 25 or lower were randomly assigned (1:1) to endocrine therapy alone or endocrine therapy plus chemotherapy. Roughly two-thirds of the patients were postmenopausal. Data were stratified by recurrence score (0-13 versus 14-25), menopausal status, and axillary nodal dissection versus sentinel node biopsy.

The recurrence score, which can range from zero to 100, was determined using the Oncotype Dx test. The test provides a genome-based individualized risk assessment (by evaluating 16 cancer-related genes) for early-stage invasive breast cancer.

The study was designed to assess whether the difference in IDFS for patients treated with chemotherapy, compared with no chemotherapy, was related to the recurrence score. The investigators found no association between chemotherapy benefit and recurrence score values between 0-25 when evaluating the entire study population including both premenopausal and postmenopausal women.

However, there was a significant association between chemotherapy benefit and menopausal status, triggering further analyses of the data by menopausal status.

In postmenopausal patients with recurrence scores of 25 or lower, there was no difference in the five-year IDFS between those who received chemotherapy and those who did not (91.6 percent vs. 91.9 percent, respectively).

In premenopausal patients with recurrence scores of 25 or lower, five-year IDFS was 94.2 percent for those who received chemotherapy, versus 89 percent for those who did not receive chemotherapy. Data also showed a 53 percent OS benefit in premenopausal patients, although this result is considered early due to the limited number of events at the time of evaluation. The results were similar in premenopausal women with recurrence scores 0-13 and those with recurrence scores 14-25.

“For premenopausal patients with node-positive breast cancer, we know from other studies that the most effective adjuvant endocrine therapy is ovarian suppression combined with an aromatase inhibitor. We also know that chemotherapy induces ovarian suppression that is often permanent in premenopausal women,” explained Kalinsky.

Among the premenopausal women in this study, ovarian suppression was performed in 15.9 percent of those in the endocrine therapy alone arm, versus in 3.7 percent of those in the chemotherapy plus endocrine therapy arm. “To what extent the chemotherapy benefit observed in our trial is due to chemotherapy-induced menopause remains unknown,” Kalinsky noted.

“We are reporting these data at 53.7 percent of expected IDFS events. We will continue to report updates from this study as more follow-up data are collected,” he said.

Limitations of the study include that these data represent an interim analysis. Future studies will allow for additional subset data analyses and time for continued follow-up, Kalinsky said.

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Abstract

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First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) $\leq$ 25: SWOG S1007 (RxPONDER)

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Background: The clinical utility of the RS to determine CT benefit is well established in pts with HR+, HER2-, axillary lymph node (LN)-negative BC. Retrospective analyses from SWOG S8814 support the potential prognostic and predictive role of RS for CT benefit in postmenopausal pts with LN+ BC. SWOG S1007 is a prospective, randomized trial of endocrine therapy (ET) vs. chemoendocrine therapy (CET) in women with 1-3 +LN and a RS $\leq$ 25 (NCT01272037).

Methods: Eligibility criteria included women $\geq$ 18 years of age with HR+, HER2- BC and 1-3 +LN and no contraindications to taxane and/or anthracycline based CT. Women with a RS $\leq$ 25 were randomized to receive ET or CET in 1:1 randomization using 3 stratification factors: (1) RS (0-13 vs.14-25); (2) menopausal status; and (3) axillary nodal dissection vs. sentinel node biopsy. The primary objective was to determine the effect of CT on invasive disease-free survival (IDFS) and whether the effect depended on the RS. The primary analysis was to test for a significant interaction of the treatment arm and continuous RS using a Cox regression model for IDFS, adjusting for treatment, RS, and menopausal status. A total of 832 IDFS events were expected for the final analysis. Secondary objectives included overall survival (OS). The protocol specified that interaction between treatment and the stratification variables was to be tested and, if significant, separate analyses performed by stratum. Annual interim analyses were planned starting at 24% of events. At the third interim analysis with 410 IDFS events, the Data and Safety Monitoring Committee recommended reporting results, with a decision by the NCI's Cancer Therapy Evaluation Program, the study sponsor.

Results: Of the 9,383 women screened from 2/28/11-9/29/17, 5,083 pts (54.2%) were randomized. With a median follow-up of 5.1 years, 447 IDFS events have been observed. For the primary analysis, the interaction test for CT benefit and continuous RS was not statistically significant, p=0.30. In a model with CT, RS, and menopausal status (no interaction term), higher continuous RS was associated with worse IDFS [HR 1.06, 2-sided p<0.001, 95% Confidence Interval (CI) 1.04-1.07], and CT was associated with an improvement in IDFS (HR 0.81, p=0.026, 95% CI 0.67-0.98). In a pre-specified analysis, a significant interaction was identified between CT and menopausal status (p=0.004), necessitating separate analyses by menopausal status. In postmenopausal pts (N=3350, 67%), adjusting for continuous RS, the HR for CET vs. ET was not significant (HR=0.97, p=0.82, 95% CI 0.78-1.22; 5-year IDFS 91.6% vs. 91.9%) indicating no benefit from CT. In premenopausal pts (N=1665, 33%), the HR (0.54) was statistically significant (p=0.0004, 95% CI 0.38-0.76; 5-year IDFS 94.2% vs. 89.0%), indicating CT benefit. In premenopausal pts, ovarian suppression was performed in 15.9% vs. 3.7% (ET vs. CET), and 47.9% vs. 26.4% reported menstruation after 6 months of treatment. Although the number of events is limited, the

HR for treatment adjusted by RS for OS in premenopausal pts was 0.47 (p=0.032, 95% CI 0.24-0.94). At this time, there is no differential effect with CT in regard to other stratification factors.

Conclusions: There is a significant differential treatment effect of CT benefit based on RS for premenopausal vs. postmenopausal women requiring separate analyses. While only 54% of the protocol specified events are recorded and pts will be followed for 15 years, the current data show that adjuvant therapy can be de-escalated to ET alone in postmenopausal pts with a RS $\leq$ 25 and 1-3 +LN. However, there is a strong IDFS benefit for CET in premenopausal pts, with an early indication of an OS improvement.

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