"An international scientific symposium for interaction and exchange among basic scientists and clinicians in breast cancer."

SAN ANTONIO BREAST CANCER SYMPOSIUM®

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Newsletter 2014

ISSUE 4

The Connecticut Experiment: Supplemental Screening of Dense Breasts

Not only are dense breasts an independent risk factor for breast cancer (BC), they can also mask small cancers, thus lowering the sensitivity of standard BC screening mammography. In 2009, the state of Connecticut became the first state to enact legislation mandating radiologists to inform women with dense breasts on mammography that they may benefit from supplemental screening, such as ultrasonography. Since then, 19 states have followed with similar legislation.

This has sparked the debate about whether women with dense breasts should undergo a supplemental screening modality.

"Screening breast ultrasound in women with mammographically dense breast tissue does find occult cancers," Dr. Jean Weigert said.

On Friday, Dr. Weigert presented data that she collected from 5 practice sites in Connecticut. She looked at the number of screening ultrasounds performed over 4 years, and saw a stable, incremental cancer detection rate of 3.2 per 1000 women per year (similar to findings from the 2008 ACRIN 6666 study). She reported a doubling in the positive predictive value (PPV) between the third and fourth years to almost 18%, "indicating that there is a learning curve in deciding which lesions to follow and which to biopsy, " she said. Shortly after, discussant Dr. Jafi Lipson pointed out that most of the improvement in PPV that Dr. Weigert saw was due to a shift from patients recommended to biopsy to patients recommended for short-term follow-up. "Some might argue that that shift to short-term follow-up is a benefit, but some might argue that short-term follow-up is still considered a harm of screening," Dr. Lipson said.

Dr. Weigert also reported that only 30% of eligible patients presented for supplemental screening. She attributed the low number to lack of education and cost issues, but Dr. Lipson suggested that patients might understand the significant risk of a false-positive biopsy and are choosing not to pursue supplemental testing.

Changing Paradigms of Screening for Breast Cancer

Scan the QR code to hear an in-depth conversation with Jean M. Weigert, MD and Jafi Lipson, MD

"We need a new paradigm for how we view screening women for breast cancer. And it should be based on a risk assessment," Dr. Weigert said. She added "in women who have no significant other risk than density, combining a bilateral screening mammogram with a bilateral breast ultrasound is perhaps the best way we have for finding early cancer."

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Issue at a GLANCE

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After Dr. Weigert's talk, Dr. Lipson pointed out some of the drawbacks and challenges of screening ultrasonography, such as the lack of control groups and long-term follow-up in the data. She also pointed out that screening ultrasonography generates many more biopsies than mammography does, and most end up being false-positives.

Dr. Lipson also referred to recent literature (Sprague et al) that concluded supplemental screening increases costs while producing relatively small benefits.

Women's Intervention Nutrition Study: Evaluating Dietary Intervention

Earlier preclinical and observational studies suggested that dietary fat intake may be related to outcomes of patients with BC. Dr. Rowan Chlebowski presented data from the Women's Intervention Nutrition Study (WINS), a randomized clinical trial designed to evaluate whether reduced fat intake influences outcomes in women with early-stage BC.

The WINS study recruited 2437 largely postmenopausal women between 1994 and 2001. All patients received the standard systemic therapy that was available at the time, and were randomized to a 5-year low-fat diet intervention or not. Those in the intervention group were counseled about fat gram intake and goals by trained, registered dietitians during 8 biweekly counseling sessions and subsequent monthly group sessions. The control group only had contact with dietitians every 3 months.

Dr. Chlebowski presented previous data that showed that at the end of 5 years, there was a 24% improvement (statistically significant) in relapse-free survival in the women in the dietary group. These women had significantly reduced their dietary fat intake, and had an average weight loss of 5.5 lb.

Then Dr. Chlebowski presented updated WINS data. Looking at the groups 19.4 years after entry, he saw that there were fewer BC deaths in women in the intervention group, compared to the control group (13.6% vs 17%), but this finding was not statistically significant.

Findings from exploratory subgroup analyses were more interesting. Among the 748 women with ER-negative disease, there was a 36% reduction in mortality, with a hazard ratio of 0.64. Median survival was 11.7 years vs 13.6 years. The difference was even greater among women with estrogen receptor (ER)-negative and progesterone receptor (PR)-negative BC. Based on a recent Surveillance, Epidemiology, and End Results (SEER) update, Dr. Chlebowski said these would include 73% triple-negative difficult-to-treat cancers. In this group, the hazard ratio was 0.46, with a 54% reduction in mortality. "At 10 years, it was even greater. There was a 69% reduction in mortality with over 2.3 years improvement in median survival," he said.

What conclusions can be drawn from the WINS study? The lifestyle intervention of targeting fat intake reduction associated with weight reduction did not significantly increase overall survival in women with resected BC, but exploratory analyses suggest beneficial influences on survival in women with hormone receptor-negative disease, and during active intervention. According to Dr. Chlebowski, "given emerging evidence, future lifestyle interventions should best target weight loss maintenance and increased physical activity."

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Advancing Targeted Therapies

Studying various patient populations when using targeted therapies and advanced endocrine therapies drives the development of new treatment strategies.

Dr. Sara Hurvitz presented data from BOLERO-1, a study that randomized 719 patients to paclitaxel plus trastuzumab with either everolimus or placebo. The study also looked at progression-free survival (PFS) in the hormone receptor-negative (HR-) subpopulation.

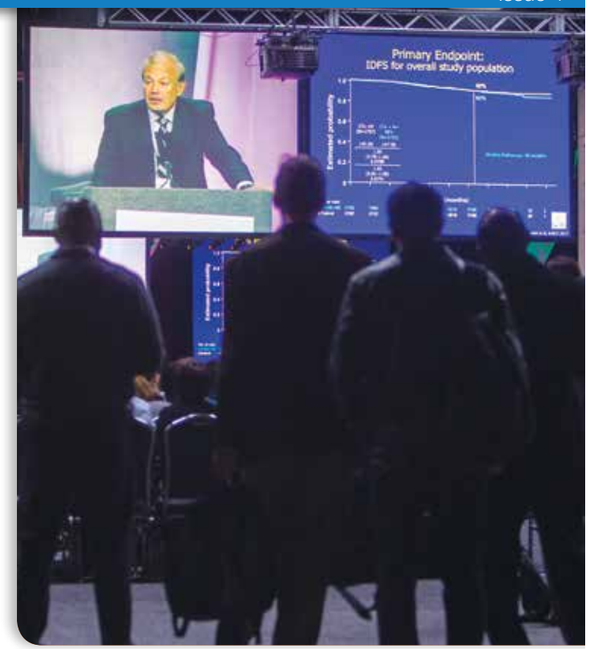
Dr. Hurvitz reported that in the full population, there was no statistically significant difference between the 2 treatment arms. The median PFS in the everolimus arm was 14.95 months, and14.49 months in the placebo arm. In the HR- subgroup, PFS was prolonged by 7 months in the everolimus group, but did not meet significance.

Dr. Hurvitz also noted that there was a higher rate of adverse event-related on-treatment deaths for everolimus in this study. She also pointed out neither the BOLERO-1 nor the BOLERO-3 study utilized endocrine therapy, which may contribute to differential results according to HR expression.

Next, Dr. Mothaffar Rimawi presented data from TBCRC023, a trial that hypothesized that in HER2+ BC, longer treatment with anti-HER2 therapy (and endocrine therapy if tumors are ER+), will result in higher pathologic complete response (pCR) rates. His group randomized patients with HER2+ BC to 12 or 24 weeks of lapatinib and trastuzumab. Endocrine therapy was added to patients with ER+ tumors.

The data showed that the overall pCR in the 12-week arm was 12%, vs 28% in the 24-week arm. This increase was seen entirely in the ER+ subgroup, where pCR was 9% in the 12-week arm and 33% in the 24-week arm. In the ER- subgroup, pCR was similar between arms (20% and 18%).

"This is the first trial to show that longer treatment with dual anti-HER2 therapy in combination with endocrine therapy in patients who are ER+/HER2+, without chemotherapy, leads to a meaningful increase in pCR," Dr. Rimawi said.



Next, Dr. Kerin Adelson presented results of a randomized trial of fulvestrant alone or in combination with the proteasome inhibitor bortezomib in 118 postmenopausal women with HR+ metastatic BC resistant to aromatase inhibitors.

She reported that for the first 3 months, PFS rapidly declined in both arms. However, after 3 months, they saw improvement in the fulvestrant plus bortezomib arm. The hazard ratio of 0.73 favored the combination, and this finding was significant. The PFS rate at 6 months was also greater in the combination arm, but not statistically significant. PFS rates at 12 months doubled in the combination arm (13.6% to 28%), which was statistically significant.

Dr. Adelson noted that the combination was associated with more nausea, diarrhea, sensory neuropathy, and thrombocytopenia, but very little grade 3 toxicity, and no attributable grade 4 toxicity.

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