Women With Luminal A Subtype of Breast Cancer Did Not Benefit From Adjuvant Chemotherapy

Patients with other subtypes had benefit

SAN ANTONIO — Premenopausal women whose invasive breast cancers were of the luminal A subtype had comparable 10-year disease-free survival rates regardless of whether or not they received adjuvant chemotherapy, according to data from the phase III DBCG77B clinical trial presented at the 2015 San Antonio Breast Cancer Symposium, held Dec. 8–12.

“Luminal A is a relatively common subtype of breast cancer, and is defined by high expression of hormone receptors [estrogen receptor (ER) and progesterone receptor (PR)], and low expression of the cell-growth marker Ki67 and the oncoprotein HER2. It is the form of breast cancer with the best prognosis,” said Torsten Nielsen, MD, PhD, professor of pathology at the University of British Columbia in Vancouver, Canada.

“We wanted to address the clinical question of whether or not women with molecularly low-risk luminal A breast cancer actually benefit from chemotherapy,” added Nielsen. “Instead of starting a new trial and waiting for 10 years to find answers, we used an older, completed trial that had saved tissue samples for future studies.”

Between 1977 and 1983, 1,146 premenopausal women who had lymph node-positive invasive breast cancer that was larger than 5 cm were randomized to two chemotherapy arms and two no-chemotherapy arms in the Dutch Breast Cancer Cooperative Group 77B trial. Women in the chemotherapy arms received either cyclophosphamid or a combination of cyclophosphamid, methotrexate, and fluorouracil. All women received radiotherapy but no endocrine therapy.

Nielsen and colleagues analyzed the tissue samples that were available from 709 patients for the presence of ER, PR, HER2, and Ki67, and identified 165 of them as having had the luminal A subtype.

The researchers found that there was no difference in 10-year invasive disease-free survival rates between women with luminal A disease who did and did not receive chemotherapy. Patients with
nonluminal A disease (which included the luminal B, HER2E, and triple-negative subtypes) who received chemotherapy were 50 percent less likely to have their disease recur in 10 years, compared with women with nonluminal A disease who did not receive chemotherapy.

Nielsen explained that none of the women in this trial received hormone therapy as adjuvant treatment. In that respect, the trial used in this study may not mirror the current standard of care. However, endocrine therapies are known to decrease the tumors’ sensitivity to chemotherapy. “Given that women with luminal A subtype of breast cancer did not benefit from chemotherapy in our study, it would certainly be expected that women with similar tumor characteristics getting endocrine therapy would also receive no benefit from chemotherapy,” he said.

“The trial was positive for chemotherapy benefit because women who had the luminal B and basal subtypes, in contrast to those who had luminal A, greatly benefited from cyclophosphamide-based adjuvant chemotherapy,” Nielsen said. “We would like to thank the women of Denmark who agreed to sign up to be randomized to different treatments. Even decades later, they are contributing to our scientific understanding of breast cancer and have helped a new generation of women make better-informed decisions about what treatments they need, or do not need,” he added.

This study was supported by the Canadian Breast Cancer Foundation, the IM Daehnfeldt Foundation, and the Danish Research Council. Nielsen has ownership interest in Bioclassifier LLC, and holds patent with, consults for, and has received royalty and fees from NanoString Technologies (who were not part of this study).

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The mission of the 2015 San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR), and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational, and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. For more information about the symposium, please visit www.sabcs.org.

Abstract: S1-08

Title: High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: Results from DBCG77B randomized trial

Authors: Torsten O Nielsen¹, Maj-Britt Jensen², Dongxia Gao³, Samuel Leung³, Samantha Burugu¹, Shuzhen Liu¹, Charlotte L Tykjær Jørgensen², Eva Balslev² and Bent Ejlertsen². ¹Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; ²Danish Breast Cancer
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Cooperative Group, Copenhagen, Denmark; 3Genetic Pathology Evaluation Centre, Vancouver, BC, Canada; 4Canadian Immunohistochemistry Quality Control, Vancouver, BC, Canada and 5University of Ottawa, Ottawa, ON, Canada.

Body:
Aim: To determine the predictive value of intrinsic subtypes for response to adjuvant chemotherapy using specimens from a randomized clinical trial.

Background: Several studies have shown distinct clinical profiles of intrinsic breast cancer subtypes. The Luminal A subtype has a favorable prognosis with higher survival rate and lower recurrence in comparison to other breast cancer subtypes (luminal B, HER2 and basal-like). In addition, there is mounting evidence suggesting that intrinsic breast cancer subtypes differ in their responsiveness to adjuvant chemotherapy. Based on these data, we hypothesized that Luminal A breast cancer patients derive no benefit from adjuvant chemotherapy whereas other intrinsic subtypes do. Randomized breast cancer trials with a no chemotherapy arm and available tissues are rare, but represent the best materials to test for markers predicting chemotherapy benefit. The 77B clinical trial from the Danish Breast Cancer Cooperative Group (DBCG) offers a unique opportunity to test such hypotheses as it randomized 1146 premenopausal women, who had positive axillary lymph nodes or tumors >5 cm, to two chemotherapy arms (single-agent oral cyclophosphamide, or cyclophosphamide-methotrexate-fluorouracil (CMF)), and two no chemotherapy arms (levamisole, or no agent). All arms included radiotherapy but no endocrine therapy.

Methods: We performed a full intrinsic subtype analysis on the 709 breast cancers available from DBCG77B on tissue microarrays using previously published, locked-down immunohistochemical (IHC) methods and intrinsic subtype definitions based on ER, PR, HER2, Ki67 and basal markers (Prat et al. JCO 2014). Biomarker scoring was performed in Vancouver by researchers with no access to the clinical database. A full statistical plan was prespecified in the Material Transfer Agreement and executed accordingly by the DBCG Statistical Office. 10-year invasive disease-free survival (IDFS) was the primary end point in DBCG77B; overall survival was also a predefined endpoint. The primary hypothesis was to assess interaction between benefit of chemotherapy (chemotherapy yes vs no) and subtype (Luminal A vs non-luminal A). This was analyzed in multivariate Cox proportional hazards models using the Wald test for interaction.

Results: 709 patients had tissue available and completed IHC intrinsic subtyping. The effect of chemotherapy in this subset of patients was similar to the original trial: hazard ratio 0.56, favoring chemotherapy for 10-yr IDFS. IHC classified 165 as luminal A, 319 luminal B, 58 HER2E and 91 as triple negative (including 82 core basal). Patients with luminal A breast tumors did not benefit from chemotherapy (HR = 1.07, 95% CI = 0.53-2.14, p = 0.86), whereas patients with non-luminal A subtypes did (HR = 0.50, 95% CI = 0.38-0.66, p < 0.001). This heterogeneity was statistically significant (p=0.048). A similar trend for 25-yr OS was seen, although not significant.

Conclusions: In a formal prospective-retrospective analysis of the DBCG 77B study randomizing women to adjuvant cyclophosphamide-based chemotherapy vs. no chemotherapy arms, patients with non-luminal A breast tumors (defined by IHC), but not luminal A tumors, benefit from adjuvant chemotherapy.