Highlights in Breast Cancer from the 2014 American Society of Clinical Oncology® Annual Meeting

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Selected by Edith A. Perez, MD

Genomic Analysis Predicts Response to Trastuzumab

Trastuzumab (Herceptin, Genentech) is more likely to benefit women with HER2-positive breast cancer if their tumors display heightened immunological function, according to the results of a recent study. The study found improved relapse-free survival (RFS) with adjuvant trastuzumab plus chemotherapy compared with chemotherapy alone, but only for women whose tumors displayed heightened immunity by genomic analysis.

"Genomic analysis revealed a major immunological component that predicted clinical benefit of adjuvant trastuzumab," said Dr Edith Perez of the Mayo Clinic in Jacksonville, Florida, speaking about her team's results.

The study was based on 1282 patients with HER2-positive breast cancer from the NCCTG N9831 adjuvant trastuzumab trial, which is part of the Alliance for Clinical Trials in Oncology; 433 had been assigned to receive adjuvant chemotherapy alone and 849 had been assigned to receive adjuvant chemotherapy plus trastuzumab. Patients were followed for a median of 6 years, 11 months.

The researchers used the whole-genome DASL assay to analyze mRNA information from the patients' tumor samples, and identified 14 genes that had a significant relationship to RFS. Approximately 52% of the tumors had high levels of expression of these genes, and were categorized as having enhanced immunological function. Among women whose tumors exhibited enhanced immunological function, PFS was longer with trastuzumab plus chemotherapy than with chemotherapy alone. Women whose tumors did not exhibit enhanced immunological function gained no additional benefit in PFS with the addition of trastuzumab.

Dr Sherene Loi of the Peter MacCallum Cancer Centre in Victoria, Australia, whose own research (FinHER, published online on April 29, 2014, in the *Annals of Oncology*) found that high levels of tumor-infiltrating lymphocytes in HER2-positive breast tumors were associated with improved response to trastuzumab and chemotherapy, told the audience that there is increasing evidence that immunity is important in HER2-positive and triple-negative breast cancer.

"Now we have 2 biomarker studies from randomized controlled trials that support the concept that adaptive immunity is important for trastuzumab efficacy," she said, referring to her own work and that of Dr Perez.

She said that although these data need further validation, immunological function testing might someday be used to select patients most suitable for immunomodulation, which might be accomplished using genetic engineering of chimeric antigen receptor T cells, T cell checkpoint inhibition, or radiotherapy.

Perez EA, Thompson A, Anderson SK, et al. Association of genomic analysis of immune function genes and clinical outcome in the NCCTG (Alliance) N9831 adjuvant trastuzumab trial [ASCO abstract 509]. *J Clin Oncol*. 2014;32(5 suppl).

Bevacizumab Does Not Benefit Women With High-Risk HER2-Negative Breast Cancer

Women with high-risk HER2-negative breast cancer do not benefit from the addition of bevacizumab (Avastin, Genentech) to standard chemotherapy, according to results from the Eastern Cooperative Oncology Group 5103 (E5103) trial.

"Our results are quite similar to those reported previously for the BEATRICE and the BETH trials, which enrolled patients with HER2-positive disease," said presenter Dr Kathy Miller of the Indiana University School of Medicine in Indianapolis. (BEATRICE refers to the Adjuvant Bevacizumab-Containing Therapy in Triple-Negative Breast Cancer trial, and BETH refers to the Treatment of HER2 Positive Breast Cancer With Chemotherapy Plus Trastuzumab vs Chemotherapy Plus Trastuzumab Plus Bevacizumab trial).

The E5103 study included 4994 patients with a median age of 52 years who had HER2-negative breast cancer that was considered high risk because of positive lymph nodes, negative estrogen receptor status in a tumor of at least 1 cm, or positive estrogen receptor status in a tumor of at least 5 cm or with an oncotype recurrence score of 11 or higher. All patients received doxorubicin and cyclophosphamide followed by weekly paclitaxel, and were randomly assigned to receive placebo, bevacizumab during chemotherapy, or bevacizumab during chemotherapy followed by bevacizumab monotherapy.

After a median follow-up of 47.5 months, invasive disease–free survival was 77% in the placebo group, 76% in the bevacizumab during chemotherapy group, and 80% in the bevacizumab during chemotherapy followed by bevacizumab monotherapy group. The hazard reduction between the bevacizumab during chemotherapy followed by bevacizumab monotherapy group and the

placebo group was not statistically significant for either invasive disease–free survival (HR, 0.87 [0.7-1.08]; *P*=.17) or overall survival (HR, 0.89 [0.68-1.17]; *P*=.41).

The rates of adverse events, including myelosuppression and neuropathy, were similar across the 3 arms of the trial, but there was a small, statistically significant increase in heart failure among patients who received bevacizumab compared with those who did not. Early discontinuation of therapy was more common among women who took bevacizumab than among those who did not.

Pathological and preclinical studies have shown that bevacizumab improves PFS but not overall survival in metastatic breast cancer. Dr Miller said that she and her coinvestigators had theorized that bevacizumab might be most effective when used in the adjuvant setting because proangiogenic pathways become more numerous and more redundant as cancer progresses, but this study did not support this hypothesis.

Commenting on the findings immediately after the presentation, Dr Erica Mayer of the Dana-Farber Cancer Institute in Boston, Massachusetts, pointed out that despite the success of antiangiogenesis inhibitors in gastric cancer, numerous trials have found these agents to be unsuccessful in breast cancer.

Miller K, O'Neill AM, Dang CT, et al. Bevacizumab (Bv) in the adjuvant treatment of HER2-negative breast cancer: final results from Eastern Cooperative Oncology Group E5103 [ASCO abstract 500]. *J Clin Oncol*. 2014;32(5 suppl).

Addition of Lapatinib to Adjuvant Trastuzumab Does Not Improve Outcomes in HER2-Positive Early Breast Cancer

A combination of lapatinib (Tykerb, GlaxoSmithKline) and trastuzumab was no more effective than trastuzumab alone as adjuvant treatment for women with HER2-positive early breast cancer, according to the first results of a new study presented by Dr Martine Piccart of the Jules Bordet Institute in Brussels, Belgium.

Results at 4.5 years from the phase 3 ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial, which is the first trial designed to explore whether dual HER2 blockade would improve disease-free survival (DFS) in the adjuvant setting, found no statistically significant difference in DFS between the 2 treatment groups. ALTTO is a global trial led by the Breast International Group and the North Central Cancer Treatment Group (now part of the Alliance for Clinical Trials in Oncology), with Drs Piccart and Perez as its principal investigators.

For the study, researchers randomly assigned 8381 patients to receive either lapatinib plus trastuzumab, trastuzumab followed by lapatinib, trastuzumab alone, or lapatinib alone; the lapatinib-alone arm was halted for futility.

The number of DFS events at 4.5 years of follow-up was 555, which was less than the target of 850. The 4-year DFS was 88% in the lapatinib plus trastuzumab group and 86% in the trastuzumab-alone group, a statistically nonsignificant difference. Rash, hepatobiliary adverse events, and especially diarrhea were more frequent with lapatinib plus trastuzumab than with trastuzumab alone. One encouraging finding was that cardiac toxicity was low in all treatment arms, despite the use of anthracycline-based chemotherapy followed by trastuzumab.

The disappointing results with lapatinib in this trial were surprising given the results of previous trials, including NeoALTTO, which looked at neoadjuvant rather than adjuvant dual HER2 blockade.

"The doubling in pathologic complete response rate observed with lapatinib plus trastuzumab in the NeoALTTO trial did not translate into improved survival outcomes in ALTTO at 4.5 years of median follow-up," concluded Dr Piccart.

Commenting on the results in a follow-up presentation, Dr George Sledge of Stanford University in California said that the lack of benefit and increase in toxicity with the addition of lapatinib in the adjuvant setting represented "a serious disappointment" that will require oncologists to rethink their approach to adjuvant therapy.

Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC) [ASCO abstract LBA4]. *J Clin Oncol*. 2014;32(5 suppl).

Exemestane More Effective Than Tamoxifen in Premenopausal Hormone Receptor–Positive Breast Cancer

Exemestane is more effective than tamoxifen at reducing recurrence in premenopausal women with hormone receptor–positive early breast cancer who received ovarian function suppression (OFS), according to a joint analysis of 2 trials.

The analysis, which was presented by Dr Olivia Pagani of the Oncology Institute of Southern Switzerland in Bellinzona, Switzerland (on behalf of the International Breast Cancer Study Group), and also published online in the *New England Journal of Medicine,* included 4690 women, whose average age was 43 years, from the phase 3 TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) studies. In both trials, women were randomly assigned to adjuvant OFS plus either exemestane 25 mg daily or tamoxifen 20 mg daily for 5 years. OFS was accomplished using the gonadotropin-releasing hormone agonist triptorelin, bilateral oophorectomy, or ovarian irradiation.

At a median follow-up of 5.7 years, patients who received exemestane had a significantly reduction in DFS hazard (HR, 0.72; 95% CI, 0.60-0.86; *P*=.0002) compared with those who received tamoxifen. The 5-year DFS rate was 91.1% with exemestane and 87.3% with tamoxifen. Exemestane also improved breast cancer–free interval and distant recurrence–free interval compared with tamoxifen, although no significant effect on overall survival was seen at this early follow-up.

Looking at the nearly 2000 women who did not receive chemotherapy, more than 97% in the exemestane group remained free from breast cancer at 5 years and only 1% in the exemestane group experienced a distant recurrence at 5.7 years. "These results suggest that some premenopausal women have an excellent prognosis with highly effective endocrine therapy without chemotherapy," said Dr Pagani.

About 30% of the women in both groups had grade 3 or 4 targeted adverse events, the most common being hot flashes, musculoskeletal symptoms, and hypertension. The side effects of exemestane in this study, which included vaginal dryness, decrease in libido, and dyspareunia, mirrored what is seen when aromatase inhibitors are used in postmenopausal women. Early cessation of treatment was more common with exemestane (16%) than with tamoxifen (11%), but overall adherence was very good.

Discussing the results of the analysis, Dr Nancy Davidson of the University of Pittsburgh Cancer Institute in Pennsylvania said she agreed that exemestane plus OFS is a "treatment option for premenopausal women with hormone responsive early breast cancer," and that it was too early to evaluate the impact on overall survival. Although the side effect profile is similar for exemestane and tamoxifen, she pointed out that the use of triptorelin requires monthly injections. She said that further follow-up would be required to determine the message to take from these trials.

Pagani O, Regan MM, Walley B, et al. Randomized comparison of adjuvant aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) versus tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): joint analysis of IBCSG TEXT and SOFT trials [ASCO abstract LBA1]. *J Clin Oncol*. 2014;32(5 suppl).

Commentary

Edith A. Perez, MD
Deputy Director at Large
Mayo Clinic Cancer Center
Director, Breast Cancer Translational Genomics Program
Serene M. and Frances C. Durling Professor of Medicine
Mayo Clinic
Jacksonville, Florida

All of the selected trials supply important data, and address principles that are pertinent to breast cancer research and treatment.

First, our whole-genome analysis that correlated biological pathways with patient outcome provided us with significant insights into the relevance of immune responsiveness genes and benefit from adjuvant trastuzumab. Validation with another genomic platform and other specimens should provide further paths for research and patient care.

The data on the addition of lapatinib or bevacizumab to treatment in the adjuvant setting were both sobering and highly important, for a variety of reasons. Adding either lapatinib (in HER2-positive disease) or bevacizumab (in HER2-negative disease) has been shown to produce measurable improvements in pathologic complete response, but neither has been shown to improve event-free or overall survival in the adjuvant setting. Thus, these studies seriously call for all of us to reevaluate the previously held concept that changes in neoadjuvant pathologic complete response could be correlated to changes in event-free or overall survival in breast cancer.

Finally, regarding the data related to hormonal adjuvant therapy for premenopausal women who undergo OFS to induce menopause: Exemestane appeared to be more effective than tamoxifen at reducing recurrence. Of course, the central question is whether OFS is really needed. The answer to this question will be available in December 2014, when the full results of SOFT will be presented at the San Antonio Breast Cancer Symposium.