Test Predicts Chemo Benefit in Breast Cancer

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SAN ANTONIO — A commercially available genetic test reliably predicts the magnitude of chemotherapy benefit in women with estrogen receptor–positive, lymph node–negative breast cancer, potentially enabling tens of thousands of women per year to safely avoid the toxicity and expense of adjuvant chemotherapy.

"This is a major breakthrough for the individualized treatment of patients diagnosed with early breast cancer," Soon-Myoung Paik, M.D., declared at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

The 21-gene test, known as the Oncotype DX, was the subject of two large clinical studies and a favorable cost-benefit analysis presented at the San Antonio breast cancer symposium.

The test, developed and marketed by Genomic Health Inc., previously was shown to predict the likelihood of distant recurrence of tamoxifen-treated node-negative breast cancer.

In a new study, Dr. Paik applied the Oncotype DX to standard, routinely available tumor samples from 651 participants in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial, in which women with node-negative, estrogen receptor–positive breast cancer were randomized 1:2 to tamoxifen alone or tamoxifen plus chemotherapy.

The rationale for applying the tumor gene–expression assay to this patient population lies in the fact that current guidelines recommend adjuvant chemotherapy in the great majority of such patients, yet prior studies demonstrate the clinical benefit is concentrated in only about 15% of the treated population. That means roughly 85% of early-stage breast cancer patients are being overtreated with chemotherapy, explained Dr. Paik, director of the division of pathology at the NSABP in Pittsburgh.

A total of 25% of participants in the B-20 trial had a high recurrence score on the Oncotype DX, meaning at least 31 out of a possible 100 points. Women in this group experienced a dramatic benefit from adjuvant chemotherapy. Their 10-year distant recurrence–free survival rate was 88% with chemotherapy and 60% without it.

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DR. PAIK

A total of 54% of B-20 participants had an Oncotype DX score below 18, defining them as low risk. They derived essentially no benefit from chemotherapy.

Dr. Paik's study was supported by the National Cancer Institute, as well as Genomic Health. He is coholder of a patent for the polymerase chain reaction (PCR) assay used in the study.

"These data advance the state of the art in cancer care and call for a reevaluation of treatment practice. By using the Oncotype DX assay, physicians can more effectively optimize a treatment plan and avoid undertreating and overtreating breast cancer patients," commented NSABP Chair Norman Wolmark, M.D., who is also chair of the department of human oncology at Allegheny General Hospital, Pittsburgh.

In a separate presentation, Laurel A. Habel, Ph.D., reported on a large population-based, case-control study involving patients with node-negative, estrogen receptor–positive early breast cancer treated at 14 Northern California Kaiser Permanente hospitals. The study population consisted of 220 women who had died of their disease and 570 matched controls who had not.

Tamoxifen-treated patients with a low recurrence score on the Oncotype DX test had a 2.8% mortality rate at 10 years, compared with 10.7% in those with an intermediate score of 18-30 and 15.5% in women with a high score.

In a multivariate analysis, recurrence score on the Oncotype DX test was by far the strongest independent predictor of 10-year breast cancer death, with an odds ratio of 6.5. In contrast, a tumor grade of moderate as compared with well-differentiated was associated with an odds ratio of 2.3. Another standard prognostic factor—tumor size—had an odds ratio of just 1.7, noted Dr. Habel of the Kaiser Permanente division of research, Oakland, Calif.

Continued on following page

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Continued from previous page

The Kaiser study is important because it replicates the NSABP validation study findings in a real-world community-based population. Nearly one-third of participants in the Kaiser study had tumors of 1 cm or less, as is increasingly the case in the contemporary era of widespread mammographic screening, she added.

The Oncotype DX assay uses reverse-transcriptase PCR to measure expression of 16 genes involved in cancer proliferation, cancer invasion, estrogen receptor activity, and *HER2*, along with five reference genes. At a cost of $3,460, the test is pricey, although Steven Shak, M.D., chief medical officer at Genomic Health, is quick to add that it's a highly complicated assay requiring 1,000 individual steps. For reasons of quality control, it must for the time being be performed on samples shipped to the company's core laboratory.

Despite the test's high price tag, a cost-benefit analysis reported at the meeting by Gary H. Lyman, M.D., concluded that routine use of the assay in early-stage breast cancer patients who are estrogen receptor–positive, node-negative, and tamoxifen-treated is cost-effective.

Taking into account the costs of five commonly used chemotherapy regimens, the use of empiric chemotherapy in such patients costs an average of $12,923 per year of life gained, compared with $5,124 per year of life gained with the use of a strategy of selective chemotherapy guided by the Oncotype DX score. The potential savings through routine use of the 21-gene assay were greatest among patients at least 50 years of age, for whom empiric chemotherapy cost an average of $28,742 per year of life gained, compared with $16,108 using a selective strategy of Oncotype DX–guided chemotherapy, according to Dr. Lyman of the University of Rochester (N.Y.).

He added that his figures understate the test's true value because they don't factor in the quality-of-life issues that further enhance the attractiveness of a test that safely enables many patients to avoid chemotherapy. Patients dread the toxicities of chemotherapy, including nausea and vomiting, hair loss, profound fatigue, and infections. His study was funded by Genomic Health, as was the Kaiser epidemiologic study.

Future projects will include tweaking the 21-gene assay so it can be applied to patients with node-positive breast cancer, and research on the value of chemotherapy in patients with an intermediate score on the Oncotype DX. ■

Blood Test Predicts Breast Ca Outcome

SAN ANTONIO — An elevated circulating tumor cell count at any point during systemic therapy for metastatic breast cancer indicates a high likelihood of rapid disease progression and mortality from that time on, Daniel F. Hayes, M.D., said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This implies that circulating tumor cell count, as measured by a commercially available blood test, may have an important role in patient monitoring and treatment. A randomized prospective clinical trial is now underway to evaluate the impact of switching therapy in patients who develop an elevated circulating tumor cell (CTC) count during therapy, added Dr. Hayes, clinical director of the breast cancer program at the University of Michigan Comprehensive Cancer Center, Ann Arbor.

In a previously reported double-blind multicenter study of 177 women who were about to start a new therapy for metastatic breast cancer, Dr. Hayes and his coinvestigators showed that the presence of at least 5 CTCs per 7.5 mL of whole blood using the CellSearch test was associated with significantly reduced progression-free and overall survival.

The same held true for patients with a positive test at their first follow-up visit after treatment initiation. They had a median 2.1-month progression-free survival from that time, compared with 7.0 months in women with 0-4 CTCs on the test. Their median overall survival was 8.2 months, compared with more than 18 months in those with a negative CellSearch test, said Dr. Hayes, a consultant to Immunicon, the company that developed the test.

In a multivariate regression model, CTC count at baseline and first follow-up visit were the strongest predictors of progression-free and overall survival, outperforming *HER2/neu* status, tumor receptor status, type of therapy, and other standard predictors (N. Engl. J. Med. 2004;351:781-91).

In Dr. Hayes's new analysis of the same patient cohort, he demonstrated that patients who developed an elevated CTC count at the second, third, or fourth follow-up visit also fared significantly worse than those who continued to have fewer than 5 tumor cells at their blood draw.

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