Urine Test for Breast Cancer Risk Shows Promise

For high-risk women, early signs of change in status could be detected between scheduled mammograms.

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SAN ANTONIO — A simple urine test for selected matrix metalloproteinases may provide a novel noninvasive means of assessing a woman's risk of developing breast cancer, Dr. Susan E. Pories reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Urinary levels of two biomarkers—matrix metalloproteinase-9 (MMP-9) and a disintegrin and metalloprotease 12 (ADAM12)—appear to be independent predictors of the presence of breast atypical hyperplasia or lobular carcinoma in situ (LCIS), both of which are well established predictors of increased risk of breast cancer, explained Dr. Pories of Beth Israel Deaconess Medical Center, Boston.

Dr. Pories and her coworkers had previously found that levels of MMP-9 and ADAM12 increase with more advanced disease status in patients who have breast cancer.

In the current study, she reported on urine samples obtained from 44 women with atypical ductal or atypical lobular hyperplasia, 24 with lobular carcinoma in situ, and 80 healthy controls.

For a 30-mL urine sample testing positive for both MMP-9 and ADAM12, the probability that the sample belonged to a woman with LCIS or atypical hyperplasia was 100%.

A urine sample that was MMP-9 negative but ADAM12 positive, had a 67% probability of being associated with atypical hyperplasia and a 50% likelihood that the patient had LCIS.

An MMP-9–positive/ADAM12-negative urine sample conferred a 40% chance that the patient had LCIS and a 25% chance that she had atypical ductal hyperplasia or atypical lobular hyperplasia.

And finally, a sample that proved negative for both biomarkers was associated with a zero probability of atypical hyperplasia.

The urine test has the advantages of being less invasive, less costly, and less uncomfortable than mammography. Asked how she envisions the urine test being used, Dr. Pories said in an interview that although it will never replace mammography, it could end up as a useful adjunct, serving, for example, as a tie breaker in helping to decide whether to biopsy a woman with a Breast Imaging Reporting and Data System (BI-RADS) stage 3 or 4 mammogram.

In high-risk women, the test could also be performed between scheduled mammograms in order to provide early warning of a change in status even before a mass appears.

She added that further studies with larger numbers of patients are needed to be sure the test is valid. The investigators are looking for a commercial partner to develop their assay. ■

Barring Cardiotoxicity, Drug Is Safe

Trastuzumab *from page 1*

the presentation of three very positive, large, randomized, phase III trials, which collectively demonstrated that a year of adjuvant trastuzumab in patients with HER2-positive early breast cancer resulted in roughly a 50% reduction in the relative risk of recurrence, compared with various conventional chemotherapy regimens. More recently, essentially the same results were found in an interim analysis of a fourth phase III trial—the 3,222-patient Breast Cancer International Research Group trial 006 (BCIRG 006).

But expanding the use of this very expensive agent to include patients with early-stage breast cancer creates a dilemma: Why expose all of these women to the risk of trastuzumab-induced cardiotoxicity, given that many would not go on to develop advanced breast cancer if initially treated instead with conventional adjuvant systemic therapy? Two promising methods of reducing trastuzumab's cardiotoxicity risk were presented at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Dr. Dennis J. Slamon, who presented the interim BCIRG 006 results at the symposium, said the study provided both good news and bad regarding trastuzumab's cardiotoxicity. The bad news is that the problem appears to be significantly worse than previously reported by other investigators.

BCIRG 006 randomized 3,222 patients with HER2-positive breast cancer and positive lymph nodes or other high-risk features to one of three treatment arms: a control group given a standard potent anthracycline-based chemotherapy regimen consisting of four cycles of doxorubicin and cyclophosphamide followed by four of docetaxel, the same regimen with the addition of 1 year of adjuvant trastuzumab beginning concurrent with the docetaxel, or a year of trastuzumab starting at the outset of six cycles of docetaxel and carboplatin.

In terms of the primary efficacy end point, at a median follow-up of 23 months the disease-free survival rate was 84% with the anthracycline/trastuzumab regimen and 80% with docetaxel/carboplatin/trastuzumab—significantly better than the 73% rate among the controls, who received anthracycline-based chemotherapy without trastuzumab.

But it was the safety data that Dr. Slamon focused on. As in other studies, trastuzumab wasn't associated with hematologic toxicity or other side effects common to chemotherapy.

"Trastuzumab doesn't cause neutropenia, nausea and vomiting, hair loss. The big issue with trastuzumab is cardiotoxicity. This drug is otherwise enormously safe," observed Dr. Slamon, professor of medicine, chief of hematology/oncology, and director of clinical/translational research at the University of California, Los Angeles.

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The major new cardiotoxicity finding in BCIRG 006 was that the asymptomatic decline in left ventricular ejection fraction known to be induced by trastuzumab in a substantial portion of treated patients is far more persistent than reported by other investigators. The lengthier persistence may be explained by the fact that BCIRG 006 featured seven serial echocardiograms, whereas previous trials have used far less intensive monitoring of left ventricular function in asymptomatic participants, he said.

The incidence of a subclinical relative decline of greater than 10% in left ventricular ejection fraction was 9% in the control group, 17.3% in patients who got trastuzumab in conjunction with anthracycline-based chemotherapy, and 8% in the group that received trastuzumab along with docetaxel and carboplatin. While others have reported that this reduction in heart function is typically reversed when trastuzumab is discontinued, that wasn't the case in patients in the anthracycline/trastuzumab arm in BCIRG 006; their decline in ejection fraction persisted beyond 550 days in most cases.

The cardiotoxic interaction between trastuzumab and anthracycline also came to the fore in terms of an increased incidence of severe chronic heart failure, as noted in other studies. There were 17 cases in the anthracycline/trastuzumab group, compared with 4 with docetaxel/carboplatin/trastuzumab and 3 among controls. The overall incidence of clinically significant cardiac events, including MI and serious arrhythmia, was 2.62% in the anthracycline/trastuzumab arm, 1.04% in controls, and 0.86% in the docetaxel/carboplatin/trastuzumab arm.

The good news regarding cardiotoxicity came from a BCIRG 006 substudy that suggests it may be possible through a simple genetic test to reduce cardiac risk by roughly two-thirds in patients with HER2-positive early breast cancer. Thirty-five percent of the 2,120 study participants tested so far demonstrated coamplification of the topoisomerase II alpha (topo II) gene, which is known to be the target of anthracycline-based therapy. Patients in this subgroup who received the anthracycline/trastuzumab combination had a significantly higher disease-free survival rate than those on either of the other two study regimens. In contrast, the 65% of patients without coamplification of topo II and HER2 had similarly favorable disease-free survival on either trastuzumab-containing regimen.

"Coamplification of topo II with HER2 may identify a subset of the HER2-positive group that might benefit from anthracycline, making it worth taking the risk of cardiac dysfunction. Conversely, the 65% of patients who are not coamplified with topo II do not appear to have this same benefit and may be better candidates for non–anthracycline-based chemotherapy in combination with trastuzumab," Dr. Slamon said.

Testing needs to be completed on the remainder of the 3,222 BCIRG 006 patients, and other investigators will want to replicate these data before topo II testing becomes part of clinical practice, but "we're pretty confident that this is correct …so I think this is something that will be done routinely, probably within the next several months," predicted Dr. Slamon, who is on the speakers' bureaus for Sanofi-Aventis and Genentech, sponsors of BCIRG 006.

An alternative approach to reducing trastuzumab cardiotoxicity was reported by Dr. Heikki Joensuu, who presented the interim results of the 1,010-patient Finnish Herceptin (FinHer) trial. The 23% of participants with HER2-positive early breast cancer received chemotherapy and were randomized to weekly trastuzumab for the first 9 weeks of therapy or to no trastuzumab.

The 3-year disease-free survival rate in these HER2-positive patients was 89.3% with short-course trastuzumab and 77.6% without it. Of particular interest was the finding that there was no increase in heart failure or subclinical left ventricular dysfunction in the trastuzumab arm. Nine weeks of trastuzumab seems to be effective as well as far less expensive and cardiotoxic and more convenient for patients than the standard 1-year course, according to Dr. Joensuu of the University of Helsinki.

Dr. Harold J. Burstein commented that the current standard 1-year duration of adjuvant trastuzumab is "entirely arbitrary" and that the optimal duration remains "a critical open question."

"Many of us are interested in waiting for the results of the third arm of the Herceptin Adjuvant (HERA) trial, which is 2 years versus 1 year of trastuzumab. I think if 2 years doesn't look a lot better than 1 year, then going back and asking these questions about shorter durations of therapy is going to be very important," said Dr. Burstein of Harvard Medical School, Boston.

"Remember," added the oncologist, who is on the speakers' bureau for Genentech, "chemotherapy was first used for a year, and now we're actually down to 3 or 4 months of adjuvant chemotherapy for most of our patients and we don't think we're doing any worse." ■