Chemo Is Key Benefit in BRCA1, BRCA2 Carriers

BY JANE SALODOF MACNEIL
Senior Editor

STOCKHOLM — Adjuvant chemotherapy appears critical to overcoming adverse prognostic factors for recurrence and survival in women with BRCA1 or BRCA2 breast cancer, according to a large prospective study presented at the annual meeting of the European Society for Medical Oncology.

Although BRCA1 and BRCA2 carriers presented at a younger age and with more advanced disease than patients with sporadic breast cancers, those who had adjuvant chemotherapy fared as well overall as comparable patients in the control group.

Hazard ratios for distant disease recurrence and for death were far worse in the absence of adjuvant chemotherapy, however: 1.69 and 1.97, respectively, in BRCA1 carriers; 2.13 and 3.62 ($P = .005$), respectively, in BRCA2 carriers. That just one of these ratios is statistically significant owes to only a small number of carriers not receiving adjuvant chemotherapy, said study investigator Dr. Pamela J. Goodwin, Marvelle Koffler Chair in Breast Research and professor of medicine at the University of Toronto. In all, 87% of BRCA1 carriers and 79% of BRCA2 carriers had adjuvant chemotherapy. Those who did not have adjuvant therapy were likely treated 10 to 15 years ago, Dr. Goodwin suggested.

"The vast majority [of BRCA1 carriers] receives chemotherapy, and what seems to be happening is that the chemotherapy is overcoming the effect of the adverse prognostic factors," she said in an interview.

Although adjuvant chemotherapy was slightly less frequent in BRCA2 carriers, the investigators saw a similar pattern. She added: "It seems to overcome the adverse prognosis. ... Not getting chemotherapy is a major, major negative."

Dr. Goodwin and her coinvestigators selected participants for the prospective study from population-based cancer registries in Ontario, Canada (1996-98), Northern California (1995-2000), and Australia (1992-1999). DNA samples were required. The population compared in the analyses comprised 92 BRCA1 carriers, 72 BRCA2 carriers, and 1,549 women with sporadic breast cancer.

Another 1,510 women were identified with other familial breast cancers. Although she did not discuss this population, Dr. Goodwin told her audience that "their results were virtually identical to the sporadic group."

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DR. GOODWIN

Analysis of the impact of adjuvant hormonal therapy is in progress, she added, and will be presented in December at the San Antonio Breast Cancer Symposium.

Compared with women with sporadic disease, the BRCA1 carriers tended to be younger and have higher-grade disease with negative receptors, Dr. Goodwin said. BRCA2 carriers presented with high-grade disease but had more nodal involvement. Tumor characteristics such as T stage, nodal status, and grade appeared to have similar prognostic effects in carriers and patients with sporadic disease, she said, but "effects of grade were less apparent in carriers." Carrier status did not appear to have a significant effect on distant disease-free survival or overall status in BRCA1 carriers.

The effect was significant with respect to both in univariate analysis for BRCA2 carriers, but disappeared after adjustment for age and tumor characteristics. The unadjusted prognosis is important when counseling individual patients, Dr. Goodwin advised. "They are more concerned about how they will fare as individuals than whether their outcomes are swayed by age or tumor characteristics," she said.

"Adjuvant chemotherapy appears to play a particularly important role in mutation carriers," Dr. Goodwin said, concluding, "understanding the relative efficacy of different chemotherapeutic agents in the adjuvant setting in mutation carriers should be an important priority."

In a discussion of the study, Dr. Judith Balmaña of the Hospital Universitari Vall d'Hebron in Barcelona cited numerous limitations, including selection bias, short follow-up, and small populations in earlier analyses that compared BRCA1 and BRCA2 carriers with women who had sporadic disease. The current study had a well-documented cohort, she said, and shows that the prognostic effects of BRCA status depend on chemotherapy use.

BRCA deficiency is a predictive biomarker of response to chemotherapy, said Dr. Balmaña, but "there is still no definitive word on the best treatment regimen for BRCA breast cancer." ■

Assay Predicts Metastasis in Early Breast Ca

BY PATRICE WENDLING
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STOCKHOLM — The genetic assay MammaPrint was able to identify a substantial proportion of women with small, early-stage breast tumors who were at risk for distant metastases, according to a study in 319 women.

The study included women with lymph node–negative T1 breast cancer, a group generally regarded as low-risk patients. Among 39 women with tumors smaller than 11 mm, 19 (49%) had a good-prognosis signature as determined by the MammaPrint assay, and 20 (51%) had a poor-prognosis signature.

Overall, the 10-year distant metastasis–free survival rate was greater than 90% among those with a good-prognosis signature, compared with 60% among those with a poor-prognosis signature, according to results reported in a poster presentation at the European Society for Medical Oncology Congress.

In the 280 women with tumors measuring 11-20 mm, the probability of remaining free of distant metastases at 10 years was 85% for those with a good-prognosis signature and 60% for those with a poor-prognosis signature.

The probability of remaining metastasis free was significantly different between prognosis-signature groups for either tumor size. "We've already shown that MammaPrint can distinguish high-risk patients with poor survival rates, but even in patients who are considered clinically to have a good outcome, we see that 50% of these patients actually have a poor prognosis," coinvestigator Dr. Femke de Snoo, director of medical affairs, Agendia BV, Amsterdam, said in an interview.

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DR. DE SNOO

The MammaPrint breast cancer prognostic test measures the expression of 70 genes in tumor samples. It is cleared for use by the Food and Drug Administration, and made by Agendia BV, which sponsored the study.

In an effort to underscore that the MammaPrint assay adds information to all risk categories, the investigators performed a subgroup analysis in 145 women with lymph node–negative, estrogen receptor–positive, grade 2 tumors.

The 10-year overall survival rate was significantly different among 90 women with a good-prognosis signature, as compared with 55 women with a poor-prognosis signature (92% vs. 60%), according to the investigators, led by Dr. Annuska M. Glas, also of Agendia BV.

Poster discussant Dr. Fabrice André of the Gustave-Roussy Institute in Villejuif, France, said that the number of women with small tumors of the breast is increasing with mass screening. If the current data are reproduced in cross-validation retrospective studies, MammaPrint could be used in clinical practice to identify women who are eligible for chemotherapy among this good-prognosis population, Dr. André said. He cautioned, however, that randomized, controlled trials are needed before molecular assays should be used to decrease the use of adjuvant treatment in this population. ■