Bone Marrow Micrometastases Predict Ca Risk

BY BRUCE JANCIN
Denver Bureau

San Antonio — The presence of disseminated tumor cells in bone marrow at initial diagnosis of nonmetastatic breast cancer independently predicted a greater than twofold increased relative risk of overall mortality and other end points in a pooled analysis of 4,703 patients, Dr. Stephan Braun reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

"This is level 1 evidence of the prognostic significance of disseminated tumor cells in bone marrow for patients with stage I-III breast cancer," said Dr. Braun of the department of ob.gyn. at the Medical University of Innsbruck, Austria.

These disseminated tumor cells (DTC), also known as bone marrow micrometastases, have generally been thought to be predictive only of distant bone metastases, but that wasn't so in the pooled analysis of nine clinical trials conducted in Europe and New York. Instead, DTC-positive patients had an increased risk of multiple distant metastases to both visceral organs and bone, he said. Based on the pooled analysis findings, a multicenter randomized clinical trial will begin this spring in Austria, Norway, and Germany in which DTC will be put to the test prospectively both for risk stratification and as an early surrogate for therapeutic efficacy. Postmenopausal women with hormone receptor–positive early breast cancer and DTC will be randomized to adjuvant anastrozole with or without fulvestrant. The primary end point will be the presence or absence of DTC after 12 months.

In the pooled analysis, 31% of the 4,703 women were found to have DTC at diagnosis of stage I-III breast cancer. Although the prevalence increased with greater tumor size and more extensive lymph node involvement, it's worth emphasizing that fully one in four women with no positive lymph nodes had DTC, as did a similar fraction of women with T1 tumor size, according to Dr. Braun. During a median 5.2-year follow-up, 32% of patients with DTC developed distant metastases, compared with 15% of those without DTC. Among the nearly 1,500 patients with T1 tumors and no lymph node involvement who received no systemic adjuvant therapy, those who had no DTC at baseline had a 94% 5-year survival, whereas those with DTC fared much worse.

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DR. BRAUN

A major goal of this research is to determine if DTC testing provides a reliable means of identifying a subgroup of early breast cancer patients for whom systemic adjuvant therapy is not warranted. However, it's proving difficult to find commercial sponsorship for such a clinical trial, Dr. Braun said.

In a separate presentation, Dr. Matthew J. Ellis described an easier, less invasive way to detect DTCs than by bone marrow biopsy: namely, identifying them in the circulation. He is a consultant to Immunicon Corp. in Huntingdon Valley, Pa., a company that has developed a Food and Drug Administration–approved, commercially available test to do just that for the purpose of monitoring and providing treatment guidance in patients with metastatic breast cancer.

Prior studies have utilized five or more circulating tumor cells per 7.5 mL of whole blood as the dividing line between favorable and unfavorable prognosis. That now appears to have been overly simplistic. A new analysis of the assay's performance in 223 metastatic breast cancer patients showed that in the 35% of women with estrogen receptor (ER)–negative breast cancer who had no detectable circulating tumor cells, the median survival was 22 months. In contrast, even a single circulating tumor cell in 7.5 mL of whole blood in ER-negative patients was associated with a median 8-month survival, and there was no further survival decrease with increasing numbers of circulating tumor cells.

"For ER-negative patients, the assay cutoff for a poor prognosis may simply be the presence of a single circulating cell," said Dr. Ellis of the oncology division of Washington University at St. Louis. ■