Cutting Anthracycline Use in Breast Ca Debated

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — The anthracyclines, in recent decades the mainstay of adjuvant chemotherapy for breast cancer, should now assume a greatly reduced role in treatment, Dr. Dennis Slamon asserted at the annual San Antonio Breast Cancer Symposium.

The anthracyclines are notoriously cardiotoxic. They also cause leukemia. Physicians and patients were willing to assume those risks because of presumed greater efficacy. But recent evidence indicates the efficacy of anthracyclines is superior to that of far less toxic nonanthracycline regimens in only about 8% of breast cancer patients—those who are both HER2 positive and who amplify or overexpress the topoisomerase II alpha gene (TOP2A) encoding a protein critical to DNA replication and function.

The strong benefit buried within this small subgroup has driven a misleading impression of across-the-board superiority for anthracyclines in large trials and meta-analyses, according to Dr. Slamon, professor of medicine and director of clinical/translational research at the Jonsson Comprehensive Cancer Center, University of California, Los Angeles.

There is no evidence that the anthracyclines are more effective than non–anthracycline-based chemotherapy in the 75%-80% of women who have HER2-negative breast cancer, nor in the two-thirds of HER2-positive patients who don't overexpress TOP2A, he said.

Dr. Slamon cited a recent meta-analysis by Dr. Alessandra Gennari and her coworkers at the Italian National Cancer Research Institute, Genoa, which included eight studies with more than 5,300 breast cancer patients. The investigators concluded that the added benefit of anthracyclines over non–anthracycline-based adjuvant chemotherapy in terms of disease-free and overall survival was confined to women with HER2-positive disease (J. Natl. Cancer Inst. 2008;100:14-20).

In vitro studies by Dr. Slamon and others have demonstrated that the increased anthracycline sensitivity in HER2-positive patients is not due to HER2 overexpression, but rather to the TOP2A gene amplification that is present in one-third of HER2-positive patients.

Amplification of TOP2A appears to occur only in conjunction with HER2 amplification. In a recent analysis of more than 1,600 HER2-normal patients in the Breast Cancer International Research Group (BCIRG) study 005, there was not a single case of TOP2A amplification, the oncologist noted.

A new retrospective analysis of the trial that led to approval of trastuzumab (Herceptin) as first-line treatment in HER2-positive metastatic breast cancer showed that anthracyclines alone resulted in a mean survival of 18.2 months in patients without TOP2A coamplification, compared with 38.5 months in those with it. Adding trastuzumab to the anthracycline regimen brought survival of the patients without coamplified TOP2A up to the same level as for those with coamplification.

Audience reaction to Dr. Slamon's call for sharply reduced use of anthracyclines was mixed.

"No one would like to get rid of anthracyclines more than I would, but I'm not ready to do it across the board," Dr. Eric Winer said in an interview. "Many of us would like to see a little more data and examine the alternatives before we say that anthracyclines are gone and gone for good. Particularly for patients who have HER2-negative disease, one of the big questions will be what will we use in their place," added Dr. Winer, director of the breast oncology center at Harvard Medical School, Boston.

But conference codirector Dr. C. Kent Osborne said he thought Dr. Slamon's analysis could change the way physicians practice. "It depends on how much data you think one needs to have before something becomes clinically useful. My own feeling is that this is probably enough, even without doing a large randomized trial. I think the data are pretty convincing and make biologic sense," said Dr. Osborne, director of the Dan L. Duncan Cancer Center and professor of medicine and cellular and structural biology at Baylor College of Medicine, Houston.

Dr. Slamon's research was supported by the Revlon Foundation. He is on the speakers bureaus for Sanofi Aventis and Genentech. ■