

Trastuzumab-Tied Cardiotoxicity Same at 5 Years

BY FRAN LOWRY
Orlando Bureau

CHICAGO — No increase was seen in the cumulative incidence of cardiac dysfunction associated with trastuzumab for HER2-positive, node-positive breast cancer after 5 years of follow-up, said Dr. Priya Rastogi, who reported on behalf of the National Surgical Adjuvant Breast and Bowel Project B-31 trial.

Updated results of the NSABP B-31 trial, which compared treatment regimens with and without trastuzumab (Herceptin), showed that the incidence of cardiac events in patients taking trastuzumab remained essentially unchanged from its value 2 years before, at 3.8%, Dr. Rastogi said at the annual meeting of the American Society of Clinical Oncology.

Trastuzumab, a monoclonal antibody that blocks human epidermal growth factor receptor 2 (HER2) from instigating the growth of breast cancer cells, has been a major advance in the treatment of both early- and late-stage breast cancer, but at the price of increased cardiotoxicity.

In the original NSABP B-31 trial (N.

Engl. J. Med. 2005;353:1673-84), the addition of trastuzumab significantly improved 3-year disease-free survival and overall survival when combined with anthracycline-based chemotherapy plus paclitaxel.

However, the incidence of cardiotoxicity, specifically congestive heart failure, among the 850 patients randomized to the regimen with trastuzumab, was 4.1%, compared with 0.8% among the 814 patients who did not get trastuzumab (J. Clin. Oncol. 2005;23:7811-9).

With an additional 2 years of follow-up, the cumulative incidence of cardiac events in the patients who received chemotherapy plus trastuzumab was 3.8%, compared with 0.9% in those who received chemotherapy alone.

Importantly, the majority of patients who had a decline in cardiac function experienced a recovery in ejection fraction within 18 months of taking trastuzumab.

"We were very heartened by this result," Dr. Rastogi, also of the University of Pittsburgh Medical Center, said at a press briefing.

The update also allowed the NSABP investigators to create a model to predict

which women would be most likely to develop cardiotoxicity from trastuzumab. (See box.) Age, use of antihypertensive medications, and poor heart function as measured by a low ejection fraction at baseline were the most important predictors of risk.

"Incorporating these factors into the model allows us to calculate a cardiac risk score, which gives a percentage of risk of a cardiac event within 3 years. This is important because it now lets us choose trastuzumab-containing regimens based on an individual patient's risk and benefit profile," Dr. Rastogi said in an interview.

She added that the next step is to validate the model in a similar group of patients. "But we do have the model now, and it can be used. So you can tell the patient who is sitting face to face with you that, based on these risk factors of age, hypertensive medication, and baseline cardiac function, this is her risk for developing a cardiac event."

Dr. Julie Gralow, moderator of the press briefing, told reporters that such a model represented a very important development for women with HER2-positive breast cancer, who account for roughly 25% of breast cancer patients. "I am thrilled to have a new risk model to help me discuss with my patients the risks and benefits from adding trastuzumab," said Dr. Gralow of the University of Washington, Seattle.

Dr. Gralow also reminded reporters that trastuzumab cut the incidence of recurrences by almost 50% and deaths by ap-

proximately one-third in such patients, and that it was very reassuring to see no increase in cardiotoxicity in the B-31 update.

In the discussion that followed Dr. Rastogi's formal presentation, Dr. Sharon Hunt, professor of medicine at Stanford (Calif.) University, cautioned that 5 years of follow-up is not long enough to assuage concerns about the cardiotoxic effects of

trastuzumab.

The cardiotoxicity that is being noted with these 3- and 5-year follow-ups is "probably the tip of a very big iceberg. Left ventricular dysfunction, which you are rather simply measuring as

You can tell the patient that, based on the factors in our model, this is her risk for a cardiac event.

DR. RASTOGI

ejection fraction, is a lifelong problem in many patients, and even though the numbers may improve, the structural damage done to the heart persists for the life of the patient," Dr. Hunt said.

Decrying the lack of information in the B-31 study about whether any therapy for heart failure had been given to patients, Dr. Hunt called for greater collaboration between oncologists and cardiologists.

"We need to know the time course of this cardiotoxicity. Is the optimistic view that it is reversible and not a cause for concern valid? Will preemptive therapy with well-proven heart failure prevention medications such as ACE inhibitors and β -blockers abrogate any of this cardiotoxicity?"

Finding the balance between improved survival from breast cancer and the down side of cardiotoxicity "is one of the most important things we need to do in the field," she said. ■



Cardiotoxicity Prediction Model

$$\frac{[7.4 + (0.03 \times \text{age}) - (0.1 \times \text{LVEF}) + (0.68 \text{ if on blood pressure medication, } 0 \text{ if not}) \times 100]}{4.82}$$

4.82

To obtain the cardiac risk score (percentage of risk of a cardiac event within 3 years), take the constant of 7.4 plus 0.03 times the patient's age, minus 0.1 times the baseline left ventricular ejection fraction plus the addition of 0.68 if the patient is on blood pressure medications or 0 if the patient is not on blood pressure medicines times 100 divided by 4.82.

Healthy Diet Fails to Reduce Breast Cancer Recurrences

BY MARY ANN MOON
Contributing Writer

A low-fat diet very high in vegetables, fruit, and fiber failed to decrease recurrences in women who had survived early-stage breast cancer, reported Dr. John P. Pierce and his associates in the Women's Healthy Eating and Living study.

Even though the women substantially increased their intake of vegetables, fruit, and fiber and cut down on fat consumption, their rates of breast cancer recurrence, new primary cancers, metastases, and mortality were no different from those of control subjects after a mean of 7 years of follow-up, the researchers said.

The WHEL study was a randomized trial "based on the recommendations of a national committee of experts called to respond to a 1993 challenge grant from a private philanthropist who believed that the role of diet in preventing cancer progression deserved scientific study," said Dr. Pierce of the University of California, San Diego, and his associates.

Subjects were 3,088 women aged 18-70 years who had been treated with axillary

dissection and total mastectomy or lumpectomy followed by radiation at seven medical centers between 1995 and 2000. A total of 1,537 women were randomly assigned to a dietary intervention involving frequent telephone consultation, cooking classes, and monthly newsletters.

The daily dietary target was intake of five vegetable servings plus 16 ounces of vegetable juice, three fruit servings, 30 g fiber, and 15%-20% of total energy intake from fat.

The remaining subjects, who constituted the control group, were given print materials encouraging them to follow the government's recommended daily intake of five servings of vegetables and fruit, 20 g or more of fiber, and less than 30% total energy intake from fat. They also were offered cooking classes and newsletters, but most did not participate.

The dietary patterns of the intervention group changed dramatically with the introduction of the diet, and most of the women maintained their healthy eating patterns throughout follow-up. For example, at 1-year follow-up the intervention

group averaged approximately eight servings of vegetables each day. Total plasma carotenoid level, a biomarker of vegetable and fruit intake, was 73% higher in the intervention group than in the control group.

However, the same proportion of subjects in both groups—16%—developed a breast cancer recurrence, metastasis, or a new primary cancer, and "the disease-free survival curves were virtually identical across groups," the investigators said (JAMA 2007;298:289-98).

All-cause mortality was 10% in both groups. More than 80% of the deaths in both groups were caused by breast cancer.

There were no differences between the intervention and control groups in depression, social support, or quality of life during the first year of treatment, when the intervention was most intense. "Therefore, we believe that our investigation provides an adequate test of whether the study dietary pattern provided an added benefit

over the dietary pattern of the comparison group of women," Dr. Pierce and his associates said. ■



The study diet included five vegetable servings, 16 oz vegetable juice, and three fruit servings.