

SHOULD CARDIAC PROTECTION BE CONSIDERED FOR PATIENTS WITH HER2+ BREAST CANCER ON TRASTUZUMAB?

“The addition of lisinopril or carvedilol should be considered to reduce risk for cardiotoxicity in patients with HER2+ breast cancer treated with trastuzumab and an anthracycline,” said Dr. Pamela Munster, from the University of California, San Francisco.

While trastuzumab is a highly effective agent for HER2+ breast cancer, its cardiac side effects often result in the need for frequent monitoring, dose interruptions, and discontinuation of treatment. Small studies have suggested the use of prophylactic agents to prevent cardiotoxicity in patients on chemotherapy.

On Friday morning, Dr. Munster presented findings from a randomized community-based trial looking at the use of lisinopril (an angiotensin-converting enzyme inhibitor) or carvedilol (a β -blocker) for the prevention of cardiotoxicity in patients with early stage HER2+ breast cancer receiving adjuvant trastuzumab.

In their study, Dr. Munster and her colleagues stratified 468 trastuzumab-treated patients based on whether they also received an anthracycline or not. Patients were then randomized to carvedilol, lisinopril, or placebo at start of trastuzumab therapy. The primary endpoint was cardiotoxicity defined as a fall in left ventricular ejection fraction of $>10\%$, or at least a 5% decrease in patients whose left ventricular ejection fraction was already $<50\%$.

Study results showed that cardiotoxicity ($\approx 30\%$) and cardiotoxicity-free survival were similar for all cohorts.

However, among patients who received an anthracycline, significant benefits in cardiotoxicity-free survival were associated with carvedilol (HR 0.49) and lisinopril (HR 0.54), compared to placebo. Among patients who did not receive an anthracycline, there were no significant differences.

Dr. Munster pointed out that among the anthracycline cohort, 23% of patients on lisinopril, 20% of patients on carvedilol, and 40% of patients on placebo required interruptions of trastuzumab for any reason. Also, patients on lisinopril experienced more fatigue, dizziness, cough, and hypotension than patients who were assigned to carvedilol or placebo.

“We will now analyze whether there are long-term symptomatic changes or just changes in left ventricular ejection fraction,” Dr. Munster concluded.

General Session Discussant, Dr. Jennifer Ligibel, of the Dana-Farber Cancer Institute in Boston, MA, feels that further work needs to be done.

While she described much of Dr. Munster’s findings as “reassuring,” Dr. Ligibel said that it must be determined whether a new medication should be added for “a change on the echocardiogram without clinical congestive heart failure, and without an LVEF fall below an established limit of normal, either 50% or 55%.”

CONTINUED ONTO PAGE 2

ISSUE 4 AT A GLANCE

- 1 Should Cardiac Protection Be Considered for Patients With HER2+ Breast Cancer on Trastuzumab?
- 2 Cardiovascular Effects of a Tailored Exercise Regimen
- 3 Impact of Lifestyle Intervention on Overall and Disease-Free Survival
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- P6-17-29
- P6-21-02

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Dr. Ligibel also hopes for more information about trastuzumab interruptions in different patient populations. “I think the high rate of disruption of trastuzumab in the control arm in patients treated with anthracycline needs to be explored further,” she said.

She added that further investigation of patients with cardiac risk factors, who are being increasingly treated without an anthracycline, should also be conducted.

“In my mind, we still need a bit more information in order to be routinely prescribing these medications for patients receiving trastuzumab and an anthracycline,” she concluded.

**CARDIOVASCULAR EFFECTS OF A
TAILORED EXERCISE REGIMEN**

New evidence suggests that rigorous adherence to a tailored exercise regimen may counteract some of the cardiovascular decline associated with breast cancer, particularly among women who receive chemotherapy, Inger Thune, MD, PhD, reported here this morning.

The findings are the first to be presented from the Energy Balance and Breast Cancer Aspects-II (EBBA-II) study, which examined whether a year-long program of endurance and strength training exercise could improve survival rates among women undergoing adjuvant therapy for breast cancer, said Dr. Thune, of the Department of Oncology, Oslo University Hospital, Oslo, Norway.

Patients ranging in age from 18 to 75 years (mean age at diagnosis: 55.2 years) and with stage I or II breast cancer were stratified according to menopausal status and randomized to undergo either treatment plus the exercise intervention or treatment as usual. The intervention was led by physiotherapists, who worked with the participants in groups of 10-12 women each. It consisted of two 60-minute outdoor sessions per week, which included stretching and weight bearing exercises considered to be of moderate to high intensity. In addition, the women engaged in two more 60-minute exercise sessions at home each week, for a weekly total of 240 minutes of exercise. Women in the control group received usual care, with no restrictions placed on their activity.

VO2 max was assessed in each patient at baseline and at six and 12 months thereafter. Patients also underwent cardiopulmonary exercise testing at similar time points. The primary study outcome was change in VO2 max at 12 months, compared with baseline.

The original cohort consisted of 545 women: 271 in the exercise group and 274 in the control group. However, after accounting for the withdrawal of some participants during the course of the study, the final counts in each group were 237 in the exercise intervention group and 258 in the control group.

Women in both groups had a mean body mass index at baseline of 25.6 kg/m². Slightly more patients in the control group had undergone breast conservation treatment (74.4% vs. 68.9% in the intervention group). However, about 85% of patients in both groups had undergone sentinel node examination and about 12% had had axillary node dissection. Similarly,

roughly 55% of all patients had undergone chemotherapy.

Adherence to the exercise intervention program was 70%: “high, despite being on chemotherapy,” Dr. Thune said. In an analysis of final results, which included all of the original 545 participants, VO2 max among women in the intervention group showed a decrease at 6 months of 2.7% compared with baseline, but by 12 months this had increased to 0.3% over baseline. Women in the control group, however, experienced an 8.9% decline at the six-month point which improved somewhat over the next six months, but was still markedly below their baseline values at 12 months.

These differences were even more pronounced among women who had not undergone chemotherapy, whose 12-month VO2 max values were 1.6% over and 2.7% below baseline for participants in the intervention and control groups, respectively (<0.001). All of the patients who underwent chemotherapy with taxanes experienced a decline in VO2 max compared with baseline, but these were significantly less among women in the exercise group (p=0.002).

In a discussion following Dr. Thune’s presentation, Jennifer Ligibel, MD, of the Dana-Farber Cancer Institute, Boston, MA, noted that “chemotherapy can have a profound and long-lasting effect on cardiorespiratory function.” However, she said, the findings of the EBBA-II trial provide “lovely confirmation” of prior studies showing a beneficial effect of exercise on the cardiovascular function of these patients.

**IMPACT OF LIFESTYLE INTERVENTION ON
OVERALL AND DISEASE-FREE SURVIVAL**

A program that emphasizes weight loss through dietary change and exercise may improve disease-free survival (DFS) and overall survival (OS) among overweight or obese breast cancer patients, Wolfgang Janni, MD, PhD, said on Friday.

However, the findings must be interpreted with caution due to the low adherence rate among participants in the intervention group, said Dr. Janni, of the University Hospital in Ulm, Germany.

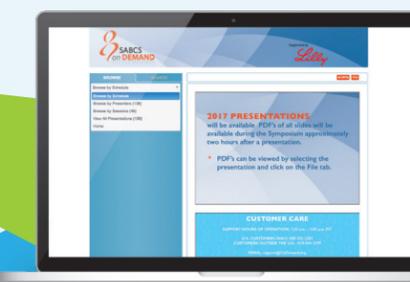
The findings come from an interim analysis of data from SUCCESS-C, the first randomized phase III study to evaluate the effect of intensive lifestyle modification on DFS following adjuvant chemotherapy for early-stage HER2-negative breast cancer.

SUCCESS-C consisted of two parts: the first was a comparison of two chemotherapy regimens, and the second, which Dr. Janni covered in this presentation, was an examination of the efficacy of diet and exercise. Patients with a body mass index of 24 kg/m² to 40 kg/m² were randomized to either the lifestyle intervention (LI) or control (non-LI) arm of the study. The lifestyle intervention program lasted for 2 years and consisted of instruction on diet and exercise, as well as psychological interventions addressing issues such as motivation, anxiety, and time management. Specially trained coaches

CONTINUED ONTO PAGE 4



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maintained contact with the patients through regular mailings of materials on various aspects of weight management, plus 19 telephone calls to address key issues or problems. The non-LI program consisted of general recommendations for a healthy lifestyle. Patients in this arm received regular support materials in the mail plus a 2-year subscription to a publication offering lifestyle information.

A total of 2,292 patients participated, with 1,146 assigned to each arm. Median follow-up times were 64.6 months for OS and 64.2 months for DFS. Patients in both arms of the study had a mean age of 57 years and a mean body mass index of approximately 28 kg/m². They were also roughly similar with respect to tumor size and stage, menopausal status, and chemotherapy history.

Patients in the LI group lost an average of 1.0 kg, while patients in the non-LI group gained an average of 0.95 kg ($p < 0.001$). Overall, 552 (48.2%) of patients in the LI arm of the study and 925 patients in the non-LI arm (80.7%) completed the study. Patients who did not complete the LI arm were significantly older (mean age, 58.0 years, versus 56.0 years for completers; $p = 0.0013$), more likely to have grade 3 tumors ($p = 0.043$), and to have hormone receptor-negative tumors ($p = 0.004$) than study completers.

An intention-to-treat analysis that included all of the patients showed no differences in OS or DFS between the groups. However, in a subgroup analysis of participants who completed the study, there were 82 DFS events among patients in the non-LI arm, versus 28 events in the LI arm (hazard ratio, LI arm vs. non-LI arm, 0.51; $p = 0.002$). In a comparison of patients who completed and did not complete the study, both OS and DFS were significantly greater among women who completed either arm ($p < 0.001$ for both arms).

In a discussion following the presentation, Jennifer Ligibel, MD, of the Dana-Farber Cancer Institute, Boston, MA, commented on the “clear differences” between patients who did and did not complete the study, especially in the LI arm. “There are a lot of differences between people who complete an intervention and those who don’t that we don’t fully understand,” she said.

“Lifestyle intervention research is hard,” Dr. Ligibel concluded. “I don’t think we can take from [this study] that we know there’s an impact of a weight loss intervention on disease outcomes.”

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