

Adjuvant Chemoendocrine Therapy Ups CV Risk

Resting echocardiography may not be sufficiently sensitive to detect subtle cardiac dysfunction.

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SAN ANTONIO — Breast cancer patients who receive adjuvant chemoendocrine therapy experience a marked reduction in cardiac reserve and diminished peak oxygen consumption, placing them at increased long-term risk for cardiovascular events, Dr. Mark Haykowsky reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This risk is further compounded by a tendency for worsening lipid profiles in women on aromatase inhibitors, which are increasingly replacing 5 years of tamoxifen as the standard for adjuvant endocrine therapy.

Indeed, as breast cancer mortality continues to decline because of earlier diagnosis and improved therapies, late-occurring cardiovascular disease is becoming an increasingly important source of compet-

ing mortality in the estimated 2.3 million U.S. women living with a history of breast cancer, added Dr. Haykowsky of the University of Alberta, Edmonton.

He reported on 47 postmenopausal patients who had hormone receptor-positive early-stage breast cancer treated with surgery followed by adjuvant radiotherapy, anthracycline-containing chemotherapy, and endocrine therapy. All participants had completed radiation and chemotherapy at the time of the cardiac function study. Of the total, 26 women were on adjuvant tamoxifen for their endocrine therapy, while 21 were on an aromatase inhibitor; 11 age-matched healthy women served as controls.

The mean peak oxygen consumption in the breast cancer patients was 17.9 mL/kg per minute, significantly worse than the 22.2 mL/kg per minute in controls.

This impairment in peak oxygen consumption appeared to result from a lower stroke volume and cardiac output at peak exercise. Stroke volume at peak ex-

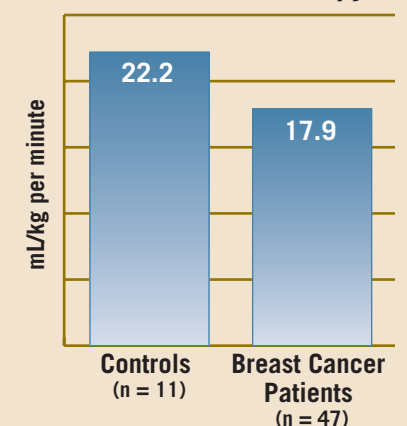
ercise was 68 mL/beat in the breast cancer patients, compared with 76 mL/beat in controls. Cardiac output at peak exercise averaged 10.4 L/minute in the cancer patients and 11.7 L/minute in controls. And cardiac reserve averaged 1.7 watts (W) in women with breast cancer, compared with 2.4 W in controls. All of this adds up to diminished oxygen delivery to skeletal muscles in breast cancer patients receiving standard adjuvant therapies.

The patients' low stroke volume was probably the result of impaired ventricular preload, since systemic vascular resistance as reflected in peak heart rate and afterload didn't differ between patients and controls, Dr. Haykowsky continued.

Of note, the breast cancer patients with the greatest impairment in peak oxygen consumption also tended to have the worst cardiovascular risk profiles. And those on an aromatase inhibitor had worse lipid profiles and higher levels of C-reactive protein, insulin, and glucose than did those on tamoxifen.

This study was the first to scrutinize the mechanisms responsible for exercise limitation in recipients of chemoendocrine therapy for early-stage breast cancer. An

Reduced Mean Peak Oxygen Consumption Linked to Breast Cancer Therapy



Source: Dr. Haykowsky

important clinical implication of the results is that resting echocardiography—the imaging tool oncologists and clinical trialists most often turn to in order to check cancer patients' heart function—appears to be insufficiently sensitive for early detection of treatment-associated subtle cardiac dysfunction. ■

Cardiovascular Risk From Radiotherapy Higher in Patients With Prior MI

SAN ANTONIO — A history of MI in women who subsequently develop breast cancer sharply increases their risk of radiotherapy-induced MI, Sarah Darby, Ph.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

She presented an update from the ongoing observational Radiation-Associated Cardiac Events (RACE) study involving nearly 63,000 Danish and Swedish patients diagnosed with early-stage breast cancer during the late 1970s through the beginning of the current decade.

By cross-referencing RACE participants against Danish and Swedish national hospital registries, investigators determined 1.1% of the women had an MI prior to their diagnosis of breast cancer. A history of previous MI was equally common in the 32,485 women with left-sided breast cancer and the 30,468 diagnosed with right-sided breast cancer.

Cancer sidedness is a key element of RACE because most radiotherapy regimens—particularly those popular until the early 1980s—direct a larger dose of ionizing radiation to the heart when applied to the left breast, noted Dr. Darby, professor of medical statistics at University of Oxford (England).

Further cross-checking of the Scandinavian national registries revealed 2,244 subjects had a fatal or nonfatal MI after being diagnosed with breast cancer. Of those, 41% had undergone radiotherapy. Nonirradiated patients had a similar risk of subsequent MI regardless of whether they had cancer of the left or right breast. This was true whether or not they had a history of MI prior to breast cancer.

The story was very different in women who underwent adjuvant radiotherapy. Those with a previous history of MI had a 2.1-fold greater rate of MI after breast cancer if they had left-sided as opposed to right-sided cancer.

Irradiated women with no history of MI had a 12% greater risk of MI after breast cancer with left-sided disease, compared with right-sided, although this modest increase didn't reach statistical significance, it was of similar magnitude as the increase in risk Dr. Darby found in an earlier study, which did achieve significance because of greater patient numbers (Lancet Oncol. 2005;8:557-65). ■

Tamoxifen Superior to Raloxifene for Noninvasive Breast Ca in STAR Trial

SAN ANTONIO — The landmark Study of Tamoxifen and Raloxifene had an intriguing paradoxical outcome: Although the two drugs proved equally effective in preventing invasive breast cancer, tamoxifen turned out to be far better at preventing noninvasive breast cancers, Dr. Victor G. Vogel said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

"This was somewhat surprising," he admitted. "I really don't have a biologic or molecular explanation for these data at this time."

STAR involved 19,747 postmenopausal women at high risk for breast cancer who were randomized to daily tamoxifen or raloxifene and followed for an average of 4 years. Invasive breast cancer—the primary study end point—occurred in 163 women on tamoxifen and 168 on raloxifene, compared with a predicted 312 cases per study arm, based on use of the Gail breast cancer risk model in lieu of a placebo arm.

This worked out to a cumulative incidence of 25.1 cases of invasive breast cancer per 1,000 patients at 6 years with tamoxifen and an almost identical 24.8/1,000 with raloxifene, noted Dr. Vogel of the University of Pittsburgh and the National Surgical Adjuvant Breast and Bowel Project.

In contrast, the 80 cases of in situ breast cancer—either ductal carcinoma in situ, lobular carcinoma in situ, or mixed lesions—in the raloxifene arm constituted a rate 40% higher than with tamoxifen, although the difference in this secondary end point was of only borderline statistical significance. The finding was unexpected in light of the fact that in situ breast cancer is a well-established powerful risk factor for development of invasive breast cancer.

A gratifying and clinically important related finding

in STAR was that tamoxifen and raloxifene proved of equal benefit in preventing invasive breast cancer in women with a history of precancerous breast lesions at study entry, he added.

Dr. Leslie G. Ford commented that despite the apparently higher rate of noninvasive breast cancer with raloxifene compared with tamoxifen in STAR, the overall advantage goes to raloxifene because of its lower rates of thromboembolic events, endometrial cancer, and cataracts.

"We consider raloxifene the winner of STAR," declared Dr. Ford, associate director of clinical research in the division of cancer prevention at the National Cancer Institute, the trial's primary sponsor.

She noted that while the 38% reduction in the relative risk of uterine cancer in the raloxifene arm didn't quite reach statistical significance, more than twice as many women in the tamoxifen arm underwent hysterectomy for noncancer indications. And a finding of endometrial hyperplasia at hysterectomy was six times more frequent in tamoxifen users.

"There's no question that if these hyperplasias had gone on without the uterus being removed, we would have had a highly significant result in terms of uterine cancer," Dr. Ford observed.

The cumulative 6-year incidence of thromboembolic events was 21 cases/1,000 treated women in the tamoxifen arm and 16/1,000 with raloxifene, for a highly significant 30% relative risk reduction.

"This was another surprise to us. Although both tamoxifen and raloxifene carry in their labels an increased risk for thromboembolic events, in fact raloxifene was better than tamoxifen," she said.

The raloxifene group also had a 21% reduction in the relative risk of developing cataracts. ■



The in situ breast cancer rate in the raloxifene arm was 40% higher than with tamoxifen.

DR. VOGEL