LHRH Agonists of Benefit in Early Breast Cancer

BY BRUCE K. DIXON
Chicago Bureau

Ovarian suppression with luteinizing hormone-releasing hormone agonists is an effective adjuvant treatment for premenopausal women with hormone receptor–positive early breast cancer, according to a meta-analysis of published trials.

"Our results broadly support those of the previous analyses, but also show other important details. Of particular importance is the benefit of LHRH agonists after chemotherapy in women younger than 40 years … and the equivalence of LHRH agonists with chemotherapy" in hormone receptor–positive cancers, wrote Dr. Jack Cuzick of the University of London, and colleagues.

The study of nearly 12,000 premenopausal women randomized in 16 trials showed that luteinizing hormone-releasing hormone (LHRH) agonists were beneficial when used alone, and effective in addition to tamoxifen or chemotherapy, or as an alternative to chemotherapy. Only trials in which more than half the treatments were with an LHRH agonist were included in the analysis (Lancet 2007;369:1711-23).

Hormone-containing drugs used in the studies included goserelin (10,450 patients), triptorelin (821), and leuprorelin (589). Most of the chemotherapy given was cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) based, but anthracycline-based chemotherapy was used for 38% of the patients who received randomized chemotherapy. No patients received taxanes.

The use of an LHRH agonist had similar absolute results for rates of recurrence, death after recurrence, and death from any cause, versus chemotherapy.

The duration of LHRH treatment was 2 years in most trials, but 18-month, 3-year, and 5-year regimens also were used. Treatment duration was 3 years in the two trials using triptorelin.

From the entire cohort of women, the investigators focused on 9,000 hormone receptor–positive patients, who accounted for 76% of all randomized patients. Of these, 92% were estrogen receptor–positive, whereas the remainder were estrogen receptor–negative but progesterone receptor–positive.

The use of an LHRH agonist, compared with no systemic treatment, did not have a significant effect on recurrence, death after recurrence, or death from any cause, but the effect size was large, the authors said, noting that the number of patients included in this comparison was very small.

The use of an LHRH agonist had similar absolute results for rates of recurrence (3.9% increase), death after recurrence (6.7% decrease), and death from any cause (14.9% decrease), compared with chemotherapy.

The addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced the hazard rate for recurrence by 12.7% and for death after recurrence by 15%, the researchers said, adding that LHRH agonists showed similar efficacy to chemotherapy.

LHRH agonists were ineffective in hormone receptor–negative tumors.

"The scope, focus, and rigor of this overview lend substantial weight to its findings," Dr. Nicholas Wilcken and Dr. Martin Stockler wrote in an accompanying editorial. They pointed out that a previous meta-analysis on the subject was reported in 2005, with data obtained in 2000, lending this newer and larger study additional weight (Lancet 2007;369:1668-70).

This meta-analysis "has established that ovarian suppression is an active treatment" in the setting of hormone receptor–positive breast cancer in premenopausal women, and "one that can be regarded as a reasonable alternative to chemotherapy in women with low-risk disease," said Dr. Wilcken and Dr. Stockler of the University of Sydney. "In women with higher-risk disease, chemotherapy followed by tamoxifen should still be the standard approach, with the addition of an LHRH analogue a reasonable consideration for those who remain premenopausal."

They added that it is not yet known whether ovarian suppression is as effective as chemotherapy when tamoxifen is used.

Another important question is whether adding an LHRH agonist is only useful when amenorrhea is not achieved with chemotherapy, said Dr. Cuzick and colleagues. "Some trials have shown a worse outcome after chemotherapy in women who did not experience amenorrhea after chemotherapy, and these women could be the ones who benefit most from the addition of an LHRH agonist," they said. ■

Depression Tied to Insomnia In Breast Cancer Survivors

BY HEIDI SPLETE
Senior Writer

MINNEAPOLIS — Depression is what keeps breast cancer survivors up at night, according to data from a study of more than 2,000 women.

"Depression is consistently the strongest predictor of insomnia in these breast cancer survivors," Wayne A. Bardwell, Ph.D., said at the annual meeting of the Associated Professional Sleep Societies.

In general, women who have survived breast cancer report a high rate of insomnia, compared with the general population, he said.

To determine the relative importance of a range of risk factors for insomnia in breast cancer survivors, Dr. Bardwell and his colleagues at the University of California, San Diego, surveyed 2,101 women at four time points: at baseline, at 1 year, at either 2 or 3 years, and at 4 years after they had completed their cancer treatments. The study was supported by several organizations including Susan B. Komen for the Cure (formerly the Susan G. Komen Foundation), the Lance Armstrong Foundation, and the Walton Family Foundation.

The women were classified as having persistent insomnia, remittent insomnia, or normal sleep based on their responses on the Women's Health Initiative Insomnia Rating Scale (WHIIRS).

Overall, 14% of the women met the criteria for persistent insomnia (scores of 9 or higher on the WHIIRS at all time points). Another 45% fell into a pattern of mixed or remitting insomnia (scores of 9 or higher at some, but not all, time points), and 40% were consistently normal sleepers (scores lower than 9 at all time points).

After controlling for multiple variables, including cancer data, personal characteristics, health behaviors (such as diet and exercise), physical health, and emotional health, only depression and night sweats were significantly associated with chronic insomnia.

All the women in the study had early-stage breast cancer (ranging from stage I to stage IIIA), with no metastases. "Most of the women were stage II and they averaged 2 years since their diagnoses," Dr. Bardwell noted. About 40% of the women had been initially treated with surgery.

Cancer-specific variables were unimportant in predicting whether the women experienced persistent or remittent insomnia, the researchers concluded.

The findings supported Dr. Bardwell's recent study of baseline insomnia (rather than chronic insomnia) in the same group of women, which also showed that only depressive and vasomotor symptoms in the form of night sweats were significantly associated with insomnia immediately after the completion of treatment for early-stage breast cancer (Psychooncology 2007 Apr. 11 [Epub doi:10.1002/pon.1192]).

Dr. Bardwell's study did not address how or whether the women were treated for their insomnia and depression. The use of low-dose sedating antidepressants is becoming more common as a way to manage chronic insomnia, but more dose-related studies of safety and effectiveness are needed in a range of patient populations. ■

Pedometer, Exercise Guidebook Help Ca Survivors Enhance Life

BY JEFF EVANS
Senior Writer

WASHINGTON — Breast cancer survivors may be more likely to increase their physical activity and quality of life if they are given step pedometers and an exercise guidebook, Jeffrey K.H. Vallance reported at the annual meeting of the Society of Behavioral Medicine.

In a recent prospective observational study, exercising after treatment for breast cancer and into breast cancer survivorship was associated with a 26%-40% reduction in the risk of breast cancer recurrence, breast cancer–specific mortality, and all-cause mortality (JAMA 2005;293:2479-86).

Since most breast cancer survivors do not meet the physical activity recommendations, there is a need for studies that don't require patients to come to a clinic to exercise under supervision and for distance- and home-based behavior-change interventions, said Mr. Vallance, a Ph.D. candidate in the faculty of physical education at the University of Alberta, Edmonton.

In preliminary results of a randomized trial of 377 breast cancer survivors from the Alberta Cancer Registry, Mr. Vallance and his colleagues found that patients who received an exercise guidebook alone (94), a step pedometer alone (94), or both (93) all reported significantly greater increases in moderate to vigorous physical activity per week and self-reported brisk walking at the end of 12 weeks than did patients who were given the standard physical activity recommendation over the telephone (96). The increases amounted to an additional 40-60 minutes a week of moderate to vigorous physical activity and an additional 60-90 minutes a week of brisk walking, compared with patients who were given the standard recommendation.

But only the patients who used both the guidebook and the step pedometer had significant changes in their quality of life and level of fatigue at the end of 12 weeks. There were no significant differences in quality of life and fatigue among the three intervention groups. The changes in quality of life and fatigue for patients in the combined treatment group "approached the minimal cut points for what we can term a clinically important difference," which is any difference that might necessitate or qualify for change in a patient's management or approach to her management, Mr. Vallance said.

"This study provides some preliminary support for more distance-based behavior-change approaches," he said, adding that it was relatively inexpensive at only $30 a person.

"I think we need to start pushing these distance-based approaches. If we consider that there are approximately 10 million cancer survivors in the [United States] alone today, then it's these novel, public health–based, distance-based approaches that might be able to target and have an impact on the greatest number of survivors."

The investigators are currently analyzing 6-month follow-up data. ■