Vaginal Estrogen Therapy Ups Serum Estradiol

BY BRUCE JANCIN

SAN ANTONIO — Vaginal estrogens for treatment of atrophic vaginitis result in significant systemic absorption, leading to increased serum estradiol levels that are of concern in breast cancer survivors, a study indicates.

"All we can say now to patients is that the use of vaginal estrogens does increase the serum estrogen level. There isn't any information out there to say whether this is going to increase their risk of recurrence or not," Shannon Wills, Ph.D., said in presenting her study findings at the San Antonio Breast Cancer Symposium.

But that's a distinct possibility. It is well established that adjuvant aromatase inhibitors are more effective than tamoxifen at preventing breast cancer recurrences and that they drive serum estrogen levels lower, noted Dr. Wills of William Beaumont Hospital, Royal Oak, Mich.

She reported on the use of a highly accurate radioimmunoassay to measure serum 17-beta-estradiol levels in 24 postmenopausal women who had completed chemotherapy and/or local therapy for breast cancer. All of the women were on an adjuvant aromatase inhibitor or selective estrogen receptor modulator and had been using a vaginal estrogen for an average of 20 months to treat severe atrophic vaginitis. Fourteen women were using one vaginal estrogen tablet (Vagifem) inserted twice weekly, and 10 were using the vaginal estradiol ring (Estring), which was inserted every 3 months.

'The use of vaginal estrogens does increase the serum estrogen level.'

DR. WILLS

Twenty-four postmenopausal breast cancer patients on adjuvant therapy who were not using vaginal estrogens served as controls.

Preinsertion serum estradiol levels in the patients who were using vaginal estrogen tablets averaged 4.7 pmol/L—not significantly different than controls. Twelve hours post insertion, however, their average serum estradiol level was 76 pmol/L. One patient had a level of 300 pmol/L, and two others were in the 200-250 pmol/L range.

Preinsertion serum estradiol levels in vaginal ring users averaged 14.2 pmol/L. Eight weeks post insertion, the average serum level was 30 pmol/L, with one patient having a level approaching 180 pmol/L.

Previously, all 24 patients on vaginal estrogens had unsuccessfully tried all the other methods of improving atrophic vaginitis. They were still suffering, and vaginal estrogens were the only option left, Dr. Wills noted.

The session chair, Dr. Charles L. Loprinzi, asked Dr. Wills which type of product she'd recommend in these desperate situations—tablets or ring?

"I would have to say the vaginal tablets are probably a better option for the patient, based on our results," she replied. "The Estring had continuous absorption throughout the entire 3-month period. Our pharmacist said it gives a dose of 2 mcg/day for the 3 months of insertion. With the vaginal tablets there appears to be a spike, then the serum level goes back down to baseline."

Dr. Loprinzi observed that vaginal dryness is a major problem for many postmenopausal women who haven't had breast cancer and even more of a problem for those who have, "if we ask about it."

Among the old-school potential alternatives to vaginal estrogens for these patients are nonestrogenic vaginal lubricants such as K-Y Jelly and Replens. But the most exciting work in this area involves the use of intravaginal dehydroepiandrosterone (DHEA) capsules (prasterone), according to Dr. Loprinzi, professor of oncology at the Mayo Clinic, Rochester, Minn.

In a series of papers that were based on a recent phase III randomized, double-blind, placebo-controlled, 12-week clinical trial involving 216 postmenopausal women with vaginal atrophy, Dr. Fernard Labrie and coworkers at Laval University, Quebec, showed that intravaginal DHEA was highly and rapidly effective for the treatment of vaginal atrophy (Menopause 2009;16:907-22), significantly improved the patients' libido and sexual function (Menopause 2009;16:923-31) and did so with no suggestion of an increase in serum sex steroid levels (Menopause 2009; 16:897-906).

"I believe this is something that ideally should be replicated by another group. But it does look quite interesting," Dr. Loprinzi commented.

He and his coworkers recently completed an as-yet unpublished phase III clinical trial of pilocarpine (Salagen) for atrophic vaginitis based on a favorable preliminary report in patients with Sjögren syndrome. "Unfortunately the data do not look promising. There's some toxicity associated with this, so this will not be a new treatment to utilize," he said. ■

Distant Metastasis More Likely in Obese Breast Ca Patients

BY BETSY BATES

VITALS

Major Finding: Women who had a BMI higher than 25 were more likely than normal-weight women to die of breast cancer 10 or more years after diagnosis.

Data Source: Analysis of a registry of nearly 19,000 breast cancer patients.

Disclosures: The investigator received a grant from Novartis Pharmaceuticals, and GlaxoSmithKline sponsored her trip to the meeting. The study was conducted without support from pharmaceutical companies.

SAN ANTONIO — Obese women are substantially more likely than women of normal weight to die of breast cancer, a large Danish registry study concluded.

Researchers from the Danish Breast Cancer Cooperative Group examined extensive health information from nearly 19,000 women with breast cancer, with follow-up data available for up to 30 years post diagnosis.

Breast cancer patients who had body mass indexes greater than 25 kg/m^2 faced a 42%-46% increased risk of developing distant metastasis, even after the investigators adjusted for numerous other prognostic factors such as age, tumor size, histologic characteristics, estrogen receptor status, and lymph node involvement.

The disparity showed up early in the course of their disease, Dr. Marianne Ewertz reported at the annual San Antonio Breast Cancer Symposium.

"For distant metastasis, the curves begin to separate after 3 years," said Dr. Ewertz, professor of oncology at Odense (Denmark) University Hospital.

By 5 years, women who had a BMI of 25-30 had an increased adjusted hazard ratio of developing distant metastasis of 1.42. For those who had a BMI greater than 30, the adjusted hazard ratio of distant metastasis beginning at 5 years was 1.46.

Women with a BMI of 25-30 were 26% more likely and those with a BMI greater than 30 were 38% more likely than normal-weight women to die of their disease 10 or more years after diagnosis, and more likely to die of other causes as well.

Heavier women in the study were older, were more likely to be postmenopausal, had larger tumors, had more positive lymph nodes, and had more tumor invasion into deep fascia than did those with a BMI less than 25. They also had more grade 3 tumors.

However, all of these factors were statistically accounted for in the multivariate analyses of distant metastasis and overall survival.

Poorer outcomes over time may indicate that adjuvant therapy is less effective in obese women than in normal-weight women, Dr. Ewertz suggested.

Inadequate dosing or biologic factors could account for the study's findings, said Dr. Michelle D. Holmes of the Dana-Farber/Harvard Cancer Center in Boston, who was the formal discussant of the presentation.

The impact of lifestyle factors on cancer risk can be "confounding" because they cannot be studied in prospective, randomized trials. Therefore, prospective observational evidence is gathered from huge, well-controlled population databases such as the Danish health registries.

"This is kind of as good as it gets, and it's pretty good," Dr. Holmes said.

The findings add weight to previous smaller studies, most of which have also found associations between mortality and BMI.

The "vast amount of data" in the Danish registries "allows for a very detailed look at subgroups," she said.

Dr. Holmes specifically highlighted findings that point to heightened risks of distant metastasis despite equivalent locoregional control, and "a loss of treatment benefit over time in the obese."

The findings dovetail nicely with recent clinical literature on obese patients with breast cancer that documents profoundly reduced complete responses to neoadjuvant therapy and a two- to four-fold-increased likelihood of receiving substandard doses of initial chemotherapy (J. Clin. Oncol. 2008;26:4072-7; J. Clin. Oncol. 2008;26:4060-2).

Social bias, a reluctance on the part of medical oncologists to prescribe full weight-based dosages of medications, and as-yet unidentified biologic differences each may play a role in the poorer outcomes of obese women, Dr. Holmes said. ■

Updated Breast Health Guide

The National Cancer Institute has updated its booklet "Understanding Breast Changes: A Health Guide for Women."

To download the free booklet, visit the NCI Web site at www.cancer.gov/cancertopics/understanding-breast-changes.