Breast Density Predicts Drug's Preventive Benefit

BY BRUCE JANCIN
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SAN ANTONIO — A reduction in mammographic breast density after 12-18 months of tamoxifen use—prescribed for primary prevention of breast cancer—is an excellent early predictor of subsequent treatment efficacy, according to a new report from the landmark International Breast Intervention Study I.

Women who showed at least a 10% decrease in breast density by visual assessment on routine mammography 12-18 months into their 5-year course of tamoxifen experienced a 63% reduction in breast cancers compared with placebo through 8 years of follow-up in IBIS-I, Jack Cuzick, Ph.D., reported at the San Antonio Breast Cancer Symposium.

"This is the first time in cancer we've found a biomarker that predicts response to preventive treatment. … The point is, if your preventive intervention doesn't work, there's no point in pressing on for 5 years," explained Dr. Cuzick, chairman of the IBIS-I steering committee and head of the Cancer Research UK Centre for Epidemiology, Mathematics, and Statistics, London.

Many healthy women at high risk for breast cancer are reluctant to take tamoxifen because of concerns about toxicity. The new IBIS-I findings have the potential to increase adoption of tamoxifen therapy in eligible women because after just 12-18 months they'll have a good indication of whether it's working for them.

IBIS-I randomized 7,154 women at high risk for breast cancer to 5 years of tamoxifen or placebo. At the latest follow-up, the tamoxifen group had a significant 27% decrease in breast cancer risk (J. Natl. Cancer Inst. 2007;99:272-82).

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The new mammographic density analysis included 126 IBIS-I participants who developed breast cancer after their 12- to 18-month mammogram and 942 controls who remained free of breast cancer during the first 5 years of the study. At baseline, 47% of the women had at least 50% of their breasts covered by densities.

Among the roughly 40% of tamoxifen-treated subjects who showed at least a 10% reduction in breast density at their 12- to 18-month mammograms, there was a 63% reduction in breast cancer risk compared with placebo after adjustment for age, body mass index, and baseline breast density. In contrast, tamoxifen-treated women who did not have at least a 10% reduction in breast density went on to have essentially the same breast cancer incidence as did those on placebo.

In an analysis restricted to participants with baseline atypical hyperplasia or lobular carcinoma in situ, a 10% or greater decrease in breast density in response to tamoxifen was associated with a 71% reduction in breast cancer risk compared with placebo, Dr. Cuzick continued.

"Mammographic density is a very simple thing to measure that really isn't very much used at the moment," he noted in an interview. Visual estimates of breast density to the nearest 5% as employed in IBIS-I show "very good" reproducibility, Dr. Cuzick added.

Multiple studies have established that baseline breast density has the highest attributable risk of all known breast cancer risk factors. In an earlier IBIS-I analysis, a baseline density of 51%-75% was an independent risk factor associated with a 2.7-fold increased risk of breast cancer, while a density in the 76%-100% range conferred a 3.9-fold increased risk.

Dr. Cuzick stressed that the new findings apply specifically to tamoxifen for prevention. Whether the same holds true for tamoxifen in the adjuvant setting in women being treated for breast cancer remains to be seen.

Dr. Cuzick is now looking at the ongoing IBIS-II trial database to learn whether early change in breast density is also a predictor of efficacy for the aromatase inhibitor anastrozole (Arimidex) when used for primary prevention in high-risk postmenopausal women. It will also be important to scrutinize mammograms collected in the clinical trials that led to approval of raloxifene (Evista) for breast cancer prevention in high-risk women to determine whether change in breast density is predictive of efficacy for that drug as well.

"If this turns out to be a general phenomenon that applies to any kind of preventive activity, it might mean we can begin to evaluate breast cancer preventive strategies in trials of 1-2 years rather than 10 years to find out if something works," Dr. Cuzick said.

Dr. Cuzick said he has no financial conflicts of interest regarding the study. ■

Complication Rate Low

Brachytherapy *from page 1*

15, or 20 years ago are growing into the age where they are developing breast cancer," said Dr. Kuske, noting that one-third of his patients have had breast augmentation.

Previous trials have shown excellent overall outcomes and in-breast control rates with multicatheter brachytherapy following lumpectomy in patients with selected early-stage cancers (Int. J. Radiat. Oncol. Biol. Phys. 2008;72:467-73). The results presented at the RSNA meeting provide the first evidence of brachytherapy's potential as an early-stage treatment alternative for women with saline or silicone breast implants. So far, "early tumor control is 100% [in this group of patients], but obviously more follow-up is necessary," Dr. Kuske said.

Between June 2003 and June 2008, 70 patients (median age 50 years) were treated with multicatheter brachytherapy following lumpectomy in select early-stage cancers. Eligibility criteria were stage I or II breast carcinoma confirmed to be less than 3 cm, and 0-3 positive axillary nodes without extracapsular extension.

A mean of 17 plastic catheters were placed with CT guidance using a template with predrilled holes to map catheter positioning. The catheters rest on the surface of the augmentation, Dr. Kuske noted, but no punctures occurred in any of the patients. The target volume was the lumpectomy cavity plus 2 cm. Treatment was delivered with 34 Gy in 10 fractions twice daily over 5 days with high-dose–rate iridium 192. The end points evaluated were tumor control, complications, and cosmesis.

No breast or nodal recurrence or capsular contracture was noted in any of the patients after a median follow-up time of 26 months (range of 3-60 months). Cosmesis ratings were either excellent (91%) or good (9%) for all patients.

Clinical infections, a concern with multicatheter placement, occurred in four patients, and all were successfully treated with antibiotics. More than half of patients (40) received brachytherapy without antibiotics; 26 patients received antibiotics prophylactically. Other complications included one wound dehiscence, two minor cases of telangiectasia, one pneumothorax, and one persistent seroma.

Dr. Kuske is a consultant for Nucletron. ■

Lasofoxifene Shown to Sharply Reduce Incidence of Breast Cancer

BY BRUCE JANCIN
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SAN ANTONIO — The investigational selective estrogen-receptor modulator lasofoxifene is shaping up as a PEARL of a drug for the prevention of breast cancer.

Lasofoxifene (Fablyn) slashed the incidence of estrogen receptor–positive breast cancer by 81%, compared with placebo, over a 5-year period in the 8,556-woman, phase III PEARL (Postmenopausal Evaluation and Risk Reduction With Lasofoxifene) trial, Andrea Z. LaCroix, Ph.D., reported at the San Antonio Breast Cancer Symposium.

That's a considerably more dramatic preventive effect than the roughly 50% reductions seen in earlier placebo-controlled trials of tamoxifen and raloxifene, the two approved agents for primary prevention of breast cancer, added Dr. LaCroix, a professor of epidemiology at the University of Washington, Seattle.

Reduction of estrogen receptor–positive breast cancer was a coprimary end point in PEARL, together with nonvertebral fractures, which were decreased by a highly significant 24% in women randomized to lasofoxifene at 0.5 mg/day.

The PEARL participants (aged 59-80 years) were enrolled in 32 countries. All had osteoporosis at entry. They were randomized to placebo or lasofoxifene at 0.25 or 0.5 mg/day.

During 5 years of follow-up, 21 women in the placebo arm developed estrogen receptor–positive breast cancer, as did 11 in the lower-dose and 4 in the higher-dose lasofoxifene arms. The incidence was 0.3 cases per 1,000 patient-years in women on lasofoxifene at 0.5 mg/day, 0.9 cases per 1,000 patient-years with lasofoxifene at 0.25 mg/day, and 1.9 cases per 1,000 patient-years with placebo.

Women on lasofoxifene at 0.5 mg/day had a 35% reduction in breast biopsies, compared with the 2.8% incidence in the placebo arm. As expected, the SERM had no effect on the rate of estrogen receptor–negative breast cancers. The risk of ductal carcinoma in situ was similarly unaffected.

Dr. LaCroix noted that lasofoxifene had its greatest breast cancer reduction benefit among women with above-average levels of estradiol. Other benefits included a reduction of 42% in vertebral fractures, a decrease of 32% in major coronary heart disease events, and a 36% reduction in strokes.

The chief risk associated with the SERM was a twofold increase in venous thromboembolic events (from 0.4% over 5 years in the placebo arm to 0.8% with 0.5 mg lasofoxifene).

In September 2008, the Food and Drug Administration's Reproductive Health Advisory Committee recommended approval of Pfizer Inc.'s application for an indication for lasofoxifene at the 5-mg dose for treatment of osteoporosis. One oncologist in the San Antonio audience shrugged off Pfizer's failure to seek an additional indication for breast cancer prevention, noting that once lasofoxifene is approved for osteoporosis, physicians will readily be able to prescribe the drug in postmenopausal women for breast cancer prevention as well.

Dr. LaCroix disclosed that she is on the advisory boards for Pfizer, Sanofi-Aventis, and Procter & Gamble Co. ■

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