Cyclic Mastalgia Eased by Topical Afinoxifene Gel

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Topical afinoxifene proved effective for the treatment of cyclic mastalgia and also showed potential for reduction of mammographic breast density in separate phase II clinical trials presented at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Afinoxifene is a highly potent tamoxifen metabolite formulated in a topical alcohol-based gel. Applied to the breast, it avoids first-pass liver metabolism and thereby results in high levels of the antiestrogen in target breast tissue with very low systemic exposure. The result is an agent designed to have a far quicker onset of benefit than oral tamoxifen, which is prescribed for 5 years for chemoprevention.

Dr. Robert E. Mansel reported on 130 premenopausal women with a history of moderate to severe cyclic mastalgia who were randomized to receive 2 mg or 4 mg/day of afinoxifene or placebo for four menstrual cycles in a double-blind multicenter trial.

The primary end point was change in breast pain assessed by patients on a visual analog scale from baseline through the fourth treatment cycle. The 4-mg dose significantly outperformed placebo as evidenced by a mean 32-point reduction from a baseline of 72 points on the 0-100 scale, compared with reductions of 19 points with placebo and 25 points with 2 mg/day of afinoxifene.

The 4-mg dose also outperformed placebo in the secondary end points of blinded physician-assessed breast pain, nodularity, and tenderness, with 67%-70% reductions being recorded relative to placebo in each of these domains, added Dr. Mansel, professor and chairman of the department of surgery at the University of Wales, Cardiff.

Rates of hot flashes, night sweats, and nipple discharge were similar in the three groups. Application site skin reactions occurred in 4% of women on 4 mg/day of the topical antiestrogen. Duration of menses, cycle length, and estrogen and progesterone levels were unaffected in the three study arms.

Dr. Jennifer A. Harvey reported on 61 premenopausal women with 50%-80% breast tissue density and 19 with greater than 80% breast density on a screening digital mammogram performed within the prior 42 days who were randomized to 2 mg/day of afinoxifene or placebo in a double-blind study.

Mammographic breast density in the 80% range has been shown to be a biomarker conferring a four- to fivefold increased risk of developing cancer. But unlike many breast cancer risk factors, breast density is modifiable.

Radiodense glandular epithelium and connective tissue also interfere with early diagnosis of breast cancer by hiding mammographic abnormalities, explained Dr. Harvey of the University of Virginia, Charlottesville.

Results of the trial were mixed: Five of 32 afinoxifene-treated patients and 0 of 29 placebo-treated patients with 50%-80% baseline mammographic breast density showed at least a 10% reduction in density after 4 months, but there was no significant difference between the two study arms at 6 months. Moreover, none of the 19 patients with greater than 80% baseline breast density showed a 10% improvement at 4 months. In light of the success of 4 mg but not 2 mg/day of afinoxifene in the mastalgia trial, further studies using the higher dosage are planned.

Four of five afinoxifene responders were aged younger than 40 years. This suggests afinoxifene may have potential as a chemopreventive agent in young high-risk women who avoid oral tamoxifen because of side effects, she added.

The trials were sponsored by Ascend Therapeutics. ■

Tomosynthesis May Eventually Rival Screening Mammography

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Breast tomosynthesis was equivalent or superior to conventional diagnostic mammography in 9 of 10 women in a preliminary study of 98 women.

"In a screening capacity, we estimate about a 40% decrease in screening mammography, which would be a huge benefit to women and public health to save the patient the anxiety, cost, and time of going for diagnostic evaluation," lead author Dr. Steven P. Poplack said at the annual meeting of the Radiological Society of North America. Nationally, about 12% of all screening mammograms are recalled for additional evaluation.

'Not only are we going to get benefit in specificity, but we're also going to get a benefit in sensitivity and decrease our false-negative rate.'

The investigational three-dimensional technique uses conventional x-ray tubes and digital imaging plates. But a series of low-dose exposures are made every few degrees while the x-ray tube is rotated over the patient in a 30-degree arc, creating a series of digital images.

The individual digital images are then reconstructed into a series of thin, high-resolution slices that can be displayed individually or in a dynamic cine mode, said Dr. Poplack, who serves as a scientific advisory board member for Hologic Inc., which sponsored the study.

He presented data from a study in which 98 women with abnormal digital screening mammograms were sequentially recruited and underwent tomosynthesis of the affected breasts.

Tomosynthesis images were evaluated prospectively and compared with the initial screening mammography exams showing 112 findings in the women.

Tomosynthesis detected five invasive carcinomas in 4 of the 98 women, including one lesion that was not apparent on digital mammography.

As a diagnostic imaging technique, tomosynthesis was equivalent (60/112) or superior (39/112) to diagnostic mammography in 86 of 98 (88%) women. Half (49) of the women would not have been recalled if tomosynthesis had been used on the first screening.

The advantage of tomosynthesis is its ability to reduce or eliminate the tissue overlap and structure noise seen in single-slice two-dimensional mammography, said Dr. Poplack of Dartmouth Medical School, Hanover, N.H.

"It's my own belief that not only are we going to get benefit in specificity, but we're also going to get a benefit in sensitivity and decrease our false-negative rate," he said.

Another benefit of tomosynthesis is that it builds on a huge base of knowledge already established in mammography, so the images will not be foreign to radiologists. It requires the same amount of compression as film or digital mammography, so the discomfort is no less for the patient, however.

Dr. Poplack cautioned that the results are preliminary, and that the study was too small to identify characteristics of women in whom tomosynthesis might offer the greatest benefit. ■

HT Ineffective for Hot Flashes In Tamoxifen-Treated Women

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Hormone therapy is not effective for hot flashes in women on tamoxifen, Ivana Sestak, Ph.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This was the clear-cut conclusion of a new secondary analysis of the International Breast Cancer Intervention Study I (IBIS-I), in which 7,152 postmenopausal women at increased breast cancer risk were randomized to 20 mg/day of tamoxifen or placebo.

The new finding is unwelcome news for women on tamoxifen for breast cancer chemoprevention who find their vasomotor symptoms intolerable. Those who don't solve their problems by discontinuing tamoxifen have often turned to hormone therapy (HT) in an effort to find relief, despite the fact that HT is believed to confer a modest increase in breast cancer risk.

The primary results of IBIS-I, in which tamoxifen reduced the risk of breast cancer by one-third over 4 years, have been published (Lancet 2002;360:817-24). The new secondary analysis focused on quality of life issues, chief of which for many women on tamoxifen are vasomotor symptoms.

Indeed, 71% of women in the tamoxifen group of IBIS-I reported hot flashes during 84 months of follow-up, compared with 57% on placebo. Most were rated mild to moderate. But 12% of affected women in the tamoxifen group had severe hot flashes, a rate twice that in the placebo group, said Dr. Sestak of Cancer Research UK, London.

Menstrual irregularities and night sweats were also 33%-54% more common among tamoxifen-treated women than placebo-treated women. These vasomotor symptoms were much less of an issue than the hot flashes, as they affected only 11% and 4%, respectively, of women on tamoxifen.

HT was effective in curbing hot flashes in the placebo group. For example, among placebo-treated women who were current HT users at study entry, the prevalence of hot flashes at the 6-month follow-up visit was 23%, compared with 34% among HT-nonusers. Similarly, women in the placebo group using HT at study entry and still using it during months 6-12 had a 20% rate of hot flashes at the 12-month follow-up visit, compared with a 39% rate among women who entered IBIS-I on HT but discontinued it during the first 6 months.

In contrast, women in the tamoxifen arm who entered the trial on HT and continued using it during months 6-12 had a 48% prevalence of hot flashes at 12 months, which wasn't significantly different than the 51% rate among tamoxifen users who were on HT at entry but who quit using it during the first 6 months.

Among 2,658 women in the tamoxifen group who had never used HT or stopped prior to study entry, 43% were experiencing hot flashes 6 months into the study. Among those who went on HT at that point, the rate of hot flashes at 12 months was 74%, which wasn't significantly different than the 67% rate among non-HT users.

It was quite a different story in the placebo group. One-quarter of the 2,613 women not on HT at entry had hot flashes at 6 months. Among those who went on HT at that point, the rate of hot flashes at 12 months was 43%, compared with 65% in those who didn't.

Physicians will need to come up with an effective therapy for tamoxifen-induced vasomotor symptoms to improve adherence. Agents worthy of further study by dint of having mechanisms of action not mediated solely by estrogen levels include progestins, clonidine, tibolone, some of the selective serotonin reuptake inhibitors, and black cohosh, she added. ■

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