Afinofin Effective Therapy for Cyclic Mastalgia

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SAN ANTONIO — Topical afinofin proved effective for the treatment of cyclic mastalgia and also showed potential for re-duction of mammographic breast density in separate phase II clinical trials presented at a breast cancer symposium sponsored by the Cancer Therapy and Research Center. Afinofin is a highly potent tamofoxifen metabolite formulated in a topical alcohol-based gel. The breast, it avoids first-pass liver metabolism, thus resulting in high levels of the antiestrogen in target breast tissue with low systemic exposure.

The result is an agent designed to have a far quicker onset of benefit than oral tamofoxifen, which is prescribed for 5 years for chemoprevention—and afinofin also is intended to span women over the entire spectrum of the female oral drug, including increased risks of venous thromboembolism, endometrial cancer, and hot flashes.

Dr. Robert E. Mansel reported on 130 premenopausal women with a history of moderate to severe cyclic mastalgia who were randomized to 2 mg or 4 mg/day of afinofin in a double-blind multicenter trial. The primary endpoint 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 vs. reductions of 19 points with placebo and 25 points with 2 mg/day of afinofin.

The 4-mg dose also outperformed place-bo in the secondary endpoints of oral cup size, demonstrated by a physician assessed breast pain, nodularity, and tenderness, with 67%-70% reductions being recorded relative to placebo in each of these domains, said Dr. Mansel, who is professor and chairman of the depart-ment 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. Menses duration, cycle length, and estrogen and proges-terone levels were unaffected in the three study arms. Mammographic breast density was estimated by an estimated 8 million premenopausal American women for at least 2 weeks during their menstrual cycles. There are at present no approved treatments for mastalgia.

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 afinofin or placebo in a double-blind study.

Mammographic breast density in the 80% range has been shown to be a bio-marker confirming a four- to fivefold increased risk of developing cancer. But unlike many breast cancer risk factors such as age, family history, and early age at menar-ché, breast density is modifiable. Radiogenic ductal epithelial and connective tissue also interferes with early diagnosis of breast cancer by hiding mammographic abnormalities, said Dr. Harvey of the University of Virginia Charlottesville.

Results of the trial were mixed. Five of 32 afinofin-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. None of the 19 patients with greater than 80% baseline breast density showed a 10% reduction in density at 4 months.

In light of the success of 4 mg but not 2 mg/day of afinofin in the mastalgia trial, more breast density reduction studies with the higher dosage are planned. An intriguing finding was that 1 of the five afinofin responders were younger than 40 years, suggesting afinofin may have potential as a chemopreventive agent in young high-risk women who avoid oral tamoxifen because of side effects.

The trials were sponsored by Afin Pharmaceuticals.