Development Pipeline Full of Breast Ca Preventors

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SAN ANTONIO — Substantially boosting the uptake of pharmacotherapy for primary prevention of breast cancer will probably require the development of new agents that are more effective, better tolerated, or have bonus benefits beyond the breast, according to speakers at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Among the drugs potentially meeting these requirements that are now in various stages of the developmental pipeline are celecoxib, rexinoids, novel selective estrogen-receptor modifiers (SERMs), tyrosine kinase inhibitors, and the third-generation aromatase inhibitors (AIs).

The biggest buzz in the pharmacologic prevention of breast cancer concerns the AIs. Based on their ability to block two carcinogenic pathways, the AIs are expected to be markedly more effective for primary prevention than are SERMs, which block only one pathway. This notion is supported by the halving of contralateral cancers in the AI arms, compared with tamoxifen, in landmark trials of adjuvant hormonal therapy.

These findings have spawned three ongoing megatrials of AIs for primary prevention in postmenopausal high-risk women: The 10,000-patient International Breast Cancer Intervention Study–II (IBIS-II) features anastrozole; the 5,100-patient MAP.3 trial involves exemestane; and the nearly 13,000-subject National Surgical Adjuvant Breast and Bowel Project's P-4 Study to Evaluate Letrozole and Raloxifene (STELLAR) is about to enroll participants.

The SERMs are not far behind. Dr. Carol J. Fabian observed that women at moderately elevated risk of breast cancer—and that's the majority of patients at increased risk who show up in physicians' offices—often balk at the prospect of the side effects and 5-year treatment course of tamoxifen, which at present is the sole approved drug for breast cancer prevention. What they want are new agents that benefit multiple organ systems and have no negative quality of life effects.

"The SERMs will always be in the forefront of drugs that can benefit multiple organs. We simply need to develop SERMs that have less thromboembolic potential—in my view, that can be done relatively simply by making some that are transdermal—and SERMs less likely to cause perimenopausal symptoms," said Dr. Fabian, professor of medicine and director of the breast cancer prevention program at the University of Kansas, Kansas City.

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DR. BROWN

She has been extensively involved in animal and clinical studies of arzoxifene, a third-generation SERM with less uterine-agonist activity, better preservation of bone density, and greater bioavailability than tamoxifen or raloxifene. Arzoxifene is now in a phase III clinical trial for prevention of breast cancer and fractures in at-risk women.

But as Dr. Powel H. Brown noted, SERMs only prevent estrogen receptor–positive breast cancer. There is an urgent need to develop agents that prevent both receptor-positive and receptor-negative disease.

One candidate having that potential is the cyclooxygenase-2 (COX-2) inhibitor celecoxib, which reduces the incidence of both types of breast cancer in animal studies. Celecoxib is the subject of five phase II clinical trials for breast cancer prevention using biomarker modulation end points, including one directed by Dr. Brown and another headed by Dr. Fabian.

Celecoxib has attractive multiorgan benefits: It is useful for musculoskeletal aches and pains, and it is also under study for colorectal cancer prevention. Of course, its well-publicized cardiovascular risks make it less than ideal for widespread use in breast cancer prevention. But it does target a promising disease pathway, and if results of the ongoing trials prove favorable, there will be a concerted effort to develop COX-2 inhibitors without celecoxib's side effects, predicted Dr. Brown of Baylor College of Medicine, Houston. ■