The Breast Cancer Chemoprevention Debate

By Charlie Schmidt

The latest data on breast cancer chemoprevention appeared in the New England Journal of Medicine on June 23, showing that exemestane (Aromasin), an aromatase inhibitor, reduced annual tumor risk by 65% compared with placebo. Generated by Paul Goss, Ph.D., a professor at Harvard Medical School and director of breast cancer research at Massachusetts General Hospital, in Boston, and colleagues, that finding drew widespread media attention after it was first announced on June 4 at the American Society of Clinical Oncology’s (ASCO) annual meeting in Chicago.

Going Nowhere Fast
But as of this year, exemestane’s patents worldwide have expired, and Pfizer has shown little inclination to pursue a prevention indication for the drug, which is now approved for use in postmenopausal women with tamoxifen-resistant, estrogen receptor–positive breast cancer. After decades of investigation, and multiple large-scale clinical trials, breast cancer chemoprevention is languishing with little hope of revival. Neither the drug industry nor the National Institutes of Health seems ready to promote breast cancer chemoprevention in the way they promoted statins for heart disease. Meanwhile, advocacy groups, including the National Breast Cancer Coalition (NBCC) in Washington, D.C., are openly skeptical of chemoprevention. In an updated, seven-page position statement, issued in June 2011, the NBCC described efforts to market chemopreventive agents to otherwise eligible women as irresponsible without more data on their long-term effects. “Remember that with chemoprevention, these drugs are given to healthy women, most of whom will never get breast cancer anyway,” said Laura Nikolaides, NBCC’s director of research and quality care programs. “Risks in healthy women are a totally different story than risks in women who take the drugs for treatment.”

Only two drugs—tamoxifen and raloxifene, both selective estrogen receptor modulators (SERMs)—are currently approved for chemoprevention. Tamoxifen’s prevention approval dates back to 1998, after results from the Breast Cancer Prevention Trial (BCPT), co-sponsored by the National Cancer Institute, showed a 49% reduction in the incidence of invasive, estrogen receptor–positive breast cancer in high-risk women. Likewise, raloxifene, a SERM used in osteoporosis treatment, reduced breast cancer risk by 50%, according to the NCI-cosponsored Study of Tamoxifen and Raloxifene (STAR). On the basis of that result, the U.S. Food and Drug Administration approved raloxifene for breast cancer prevention in 2007. According to Rowan Chlebowski, M.D., a medical oncologist at the Los Angeles Biomedical Research Institute, raloxifene is limited to postmenopausal women, whereas tamoxifen is not.

But despite these positive findings, the public’s attitude toward breast cancer chemoprevention is largely ambivalent, says Erika Waters, Ph.D., M.P.H., an assistant professor at the Washington University School of Medicine in St. Louis. According to Water’s findings, published last year in Cancer Epidemiology, Biomarkers, and Prevention, the number of U.S. women who use tamoxifen for chemoprevention fell from 120,000 in 2000 to 60,000 in 2005, even though more than 2 million women are eligible for treatment.

Supporters of chemoprevention lament those figures. “We’ve invested decades and a commitment from tens of thousands of women in running chemoprevention trials; it’s a great sadness that we would do all this work and not take advantage of the results,” said Nancy Davidson, M.D., director of the University of Pittsburgh Cancer Institute. “What are we waiting for?” she asked.

Patients Need More Information
Andrew Freedman said it’s unclear why so few women partake in breast cancer chemoprevention. It could be that their doctors don’t know about it, he said, or that potential candidates worry about side effects, which can include hot flashes, blood clots, and elevated risks for endometrial cancer.

According to Ford, broadening awareness about chemoprevention would require a promotional campaign on the scale of that which drove statins toward blockbuster status. The National Heart, Lung, and Blood Institute; the American Heart Association; and the American College of Cardiology joined forces in that effort during the 1980s, and now tens of millions of people take statins for prevention, making them the most prescribed drugs in the world. “[The campaign] turned high blood pressure into a disease that needs to be treated rather than a risk factor for heart attack or stroke,” Ford said.

In contrast, promotional campaigns aiming to boost SERMs for cancer chemoprevention have backfired. When Zeneca Pharmaceuticals (now AstraZeneca) launched a multimillion-dollar effort to market tamoxifen prevention in 1999, the FDA intervened, claiming that the campaign was misleading because it didn’t give enough

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information about side effects. One ad featured a young woman wearing a lacy bra, under a caption that read, “If you care about breast cancer, care more about being a 1.7 than a 36B.” The 1.7 figure referred to a statistically defined threshold for elevated cancer risk generated by the GAIL model, which predicts cancer according to a woman’s age and medical history, among other factors. But Breast Cancer Action, an advocacy group based in San Francisco, attacked the ad, claiming that it played on breast cancer fears.

Understanding the GAIL Model

Meanwhile, unlike statins, which lower cholesterol levels, chemotherapies for breast cancer prevention lack a measurable goal that individuals can monitor to assess benefits from treatment. Instead, decisions to use chemotherapy depend on risk factors and models that can be difficult to grasp. The FDA defines eligibility in terms of GAIL model scores that predict cancer risks over a 5-year period. According to Ford, the highest breast cancer risk occurs between the ages of 60 and 65 years, and the average GAIL score for all women in this age group is 1.66%. This means that on average, 1.66 of 100 women aged 60–65 years will develop breast cancer over the next 5 years. According to FDA criteria, any woman older than 35 years with a GAIL score of 1.66% is eligible for chemoprevention. Age is the model’s most important risk factor, so young women, by definition, have fewer risks. A young woman with a GAIL score of 1.66% or higher has other major risk factors beyond age, such as a close family history of breast cancer or a finding of atypical ductal hyperplasia on biopsy, which can drive her lifetime risk of breast cancer to nearly 50%. On the other hand, lifetime risks for a 50-year-old woman with the same GAIL score are much lower.

BRCA mutations, which confer much higher risk, do not factor into the GAIL model. Neither SERMs nor exemestane acts on the appropriate target. Specifically, insufficient data are available regarding tamoxifen’s effect on breast cancer incidence in women with inherited mutations to enable specific recommendations on its effectiveness in these patients. BRCA mutations can warrant mastectomy.

Benefits from chemotherapy must be balanced against side effects from treatment that can be more life-threatening than the dizziness, headaches, and muscle pains that statins induce in some patients at risk of heart attack or stroke.

Two reports have aimed to integrate risks and benefits from chemoprevention in ways that might clarify clinical decision making. The first, by Mitchell Gail, M.D., Ph.D., from the NCI’s division of cancer epidemiology and genetics, published in JNCI in 1999, was limited to tamoxifen. More recently, Andrew Freedman, Ph.D., branch chief in clinical and translational epidemiology at the NCI, and colleagues, followed up with an analysis published in the Journal of Clinical Oncology in May 2011, pertaining to tamoxifen and raloxifene. According to Freedman, the study offers a tool that clinicians can use to balance risk and benefits according to age, ethnicity, and other factors. The analysis shows, said Karen Carlson, M.D., an associate professor at Harvard Medical School, that chemoprevention’s benefits outweigh its risks in just a small percentage of cases. “For a white woman in her 50s, it would take a GAIL score of around 3%, and for a black woman of the same age, it would have to be around 6%,” she said. Asked about the racial discrepancy, Carlson replied that stroke is twice as common in black women, who could face greater risks from treatment-induced blood clots.

Disagreements over chemoprevention also segregate with perceptions of lifetime breast cancer risk. Referring to the NBCC policy statement, Nikolaides said that widely cited figures suggesting that one in eight women will develop breast cancer are estimates that apply over the course of a 90-year life span, whereas annual risks hover around 1% or lower. Referring to Goss’ recent exemestane article, Nikolaides said that chemoprevention dropped the annual cancer incidence from just 0.55% to 0.19%—too little, she emphasized, to justify the hazards of treatment.

Carlson said she understands both sides of the chemoprevention debate. “If you’re a researcher working on prevention, then reducing cancer incidence is your main concern,” she said. “But if you’re a woman trying to decide on treatment, then the risk of blood clots, or perhaps hot flashes and joint pain from exemestane treatment, might not be worth it to you.”

Gauging Long-Term Effects

According to NBCC’s policy statement, scientists still need more information on chemoprevention’s long-term effects, including data on whether it prevents the initiation of disease and whether it reduces treatment efficacy (because of acquired resistance during its use for prevention) in the event of a future diagnosis, among other considerations.

Susan Love, M.D., an outspoken public advocate for breast cancer prevention, and president of the Dr. Susan Love Research Foundation in Santa Monica, Calif., claims that GAIL model outputs aren’t strong enough to capture the public’s attention. “It doesn’t measure anything you can see,” she says. “With drugs for low bone density, or statins, you have an endpoint that you can measure to see the effect of treatment. And then there’s the problem with hormones; we’ve been wrong in the past with hormonal therapy, and women feel betrayed by someone telling them ‘this is the answer’ and suddenly it’s not.”

Ford agrees that improved predictive tests are needed. “The ultimate goal is to develop better risk models so we intervene only on those most likely to get cancer—breast or any other,” she said. “This would improve the benefit–risk ratio. These could be molecular tests, genetics, or tissue changes like [lobular carcinoma in situ] or [ductal carcinoma in situ].”

Meanwhile, sources who would not go on record said that Pfizer abandoned its exemestane prevention trial after the study met its statistically defined goals after only 3 years’ follow-up. According to Ford, another ongoing study—the International Breast Cancer Intervention Study II, sponsored by Cancer Research UK—should supply more follow-up with yet another chemoprevention agent, anastrazole (Arimidex). The study is exploring whether anastrazole is a more effective chemopreventive agent than tamoxifen, with fewer risks for endometrial cancer and blood clots. However, anastrazole also elevates risks for osteoporosis, vaginal dryness, and hot flashes.

Rowan Chlebowski consults for Novartis, Pfizer, and AstraZeneca.

© Oxford University Press 2011. DOI: 10.1093/jnci/dj479

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