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New Treatment Options For Breast Cancer

Promising Drug May Work Better Than Longtime-Standard Tamoxifen

By Rachel Zimmerman And Scott Hensley

FOR OVER A QUARTER century, the standard treatment to keep breast cancer from recurring was tamoxifen—a powerful medication but one that sometimes loses effectiveness with long-term use. Now a new class of drugs is expanding the options.

In a study being released today, a next-generation drug called Aromasin appears to have an impressive ability to keep breast cancer at bay. The findings, published in the New England Journal of Medicine, are the latest in a wave of research suggesting there may be better options than tamoxifen, the old standby treatment for cases in which women have had a lumpectomy or mastectomy.

It's the third time in a year that cancer researchers, using a new class of drugs called aromatase inhibitors, are reporting better health outcomes—and a lower recurrence of tumors—for many breast-cancer patients. The new treatments, as well as tamoxifen, fall into the category of hormonal therapies, which can be used to treat about two-thirds of breast cancers.

In the U.S., one of out nine women develops breast cancer in her lifetime. In the U.S., breast cancer kills 40,000 women a year, making it the leading cause of cancer death for women, after lung cancer.

Reinforcements

New options show promise for breast-cancer patients

- **Tamoxifen:** Has long been the standard, but some women have severe side effect and can become resistant over time.
- **Aromasin, Femara and Arimidex:** These new "aromatase inhibitors" may be even more effective than Tamoxifen, but not all the data are in.

For more on breast-cancer treatments, see page D6.

In the study today, involving 4,700 postmenopausal women, switching to Aromasin after two or three years of tamoxifen therapy cut the risk of cancer recurring in either breast, or death from any cause, by 32%, compared with women who took tamoxifen for five years. The results were so strong that the trial was released earlier than planned to get the information to investigators and patients as soon as possible. The study was largely funded by **Pfizer** Inc., which sells Aromasin.

"Until last year, we've had one option for hormonal therapy," says Robert Morgan, staff physician with the division of medical oncology and therapeutics research at City of Hope Comprehensive Cancer Center in Duarte, Calif. "Now, three major papers all suggest we have multiple options."

The new class of drugs, which also includes **Novartis** AG's Femara and Astra **Zeneca** PLC's Arimidex, work by inhibiting the conversion of naturally produced hormones called steroids into estrogen. Estrogen is believed to stimulate the growth of breast-cancer cells.

The different options now provide some confusing choices for women. Tamoxifen, which is sold as a generic drug and also under the brand name Nolvadex by AstraZeneca, remains the standard treatment. However, the recent trial suggests strongly that switching to Aromasin after two or

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three years can improve the odds of staying cancer-free. Still, the data are incomplete and the side effects of the new treatments are not yet fully understood. Researchers still haven't analyzed the drug's effect on bone density (which can affect the propensity of fractures) or the risk of uterine cancer or other gynecological problems.

All three aromatase inhibitors are on the market for various uses, but only one, Arimidex, is FDA-approved for early stage breast cancer. Doctors armed with this new data can prescribe off-label.

When tamoxifen first hit the market in the mid-1970s, it was a revolutionary drug, dramatically reducing recurrence of cancer after surgery. Even today, it remains the standard treatment. Women whose tumors have been removed get a biopsy to see if they have estrogen "receptors," proteins on the outside of the tumor cells which recognize the hormone. If the answer is yes, they typically get tamoxifen.

But the downside of tamoxifen is that the therapy is generally limited to five years. Some women become resistant—even in the first one to two years—and also because side effects can be severe. Tamoxifen increases the risk of endometrial cancer and blood clots, and in a few cases, strokes.

"I think the standard of treatment is changing. It will take a little longer to determine what the standard will be, but it's definitely changing," says Julia Smith, a medical oncologist at the New York University Medical Center. However, the choices are complex. Any woman with early-stage breast cancer who is taking tamoxifen, or who has finished treatment with the drug "should speak to her doctor or a knowledgeable oncologist for an individual assessment," she says.

Another treatment option is to take Arimidex, which was approved in 2002 by the Food and Drug Administration as an alternative to tamoxifen for treatment of early-stage breast cancer. In a study of 9,300 postmenopausal women, those taking Arimidex after removal of a breast tumor had an 18% reduction in risk of tumor recurrence, compared with those taking tamoxifen. Another study found that switching to Arimidex after two to three years of tamoxifen was beneficial. But the drug carried a higher risk of joint pain and bone fractures, a key concern about this class of drugs in general.

In another big trial, Femara proved an excellent alternative for bridging the gap after five years of tamoxifen. The drug lowered the risk of returning cancer by 43% in a clinical trial of 5,000 postmenopausal women, compared with a placebo. But side effects included hot flashes, night sweats and impaired sexual function.

"When it was tamoxifen versus placebo, it was easy," says Cindy Pearson, executive director of the National Women's Health Network in Washington, D.C. "Tamoxifen is a bird in the hand, and with these aromatase inhibitors, it's more difficult. You still need to be able to compare all of the risks and benefits."

Woman are likely to have a clearer picture soon, with a flurry of new research. One trial, now under way, compares Aromasin directly to tamoxifen for the first five years after surgery. Another trial, paid for by Pfizer working jointly with the national cancer institutes in the U.S. and Canada, is a head-to-head comparison of Aromasin and Arimidex. Femara is also being tested both for use immediately after surgery, and as a drug to switch to after two or three years on tamoxifen.

Approved in the U.S. in 1999, Aromasin has been used to treat women with breast cancer that has progressed after treatment with tamoxifen. Aromasin is a small drug for Pfizer, racking up $88 million in sales last year. Pfizer said that, based on the New England Journal study results, it plans to ask the FDA to change the label of the drug to include earlier use. The company believes about 1.5 million women world-wide taking tamoxifen are candidates to be switched to Aromasin.

The Aromasin study is unusual in its large size and scope: 4,742 patients from 37 countries were followed for about 30 months. The researchers found that 266 women taking tamoxifen for five years experienced either a recurrence of their original cancer, a new cancer in the other breast, or died of any cause, compared with 183 in the Aromasin group. In addition, there was a more than 50% reduction in the risk of developing a new cancer in the other breast in the Aromasin group. The patients taking tamoxifen also had a higher rate of new non-breast cancers than those switching to Aromasin, for reasons which are not yet fully understood.

Breast Cancer Medications

How Aromasin, Femara and Arimidex—drugs in a newer class known as aromatase inhibitors—compare with tamoxifen to help prevent recurrences in post-menopausal women. (All the drugs are used in the two-thirds of breast cancers that respond to hormone therapy.)

DRUG	SOLD BY	WHAT IT CAN DO	SIDE EFFECTS	AVAILABILITY
Aromasin	Pfizer Inc.	Trial compared women who took tamoxifen for 5 years to women who switched to Aromasin after 2 or 3 years. Switchers had 32% lower risk of tumors in the same or the other breast, or death from any cause.	Diarrhea, joint aches.	FDA-approved for treating cases that progressed after tamoxifen therapy. Can be prescribed off-label for recurrence prevention.
Femara	Novartis AG	Lowered risk of recurrence by 43% in trial of 5,000 post-menopausal women who had taken tamoxifen five years.	Hot flashes, night sweats, impaired sexual function. May also increase osteoporosis risk.	Approved for advanced-stage cases; can be used off-label for preventing recurrences of early-stage cases.
Arimidex	AstraZeneca PLC	Study found women taking Arimidex after removal of tumor had 18% lower risk of recurrence compared with tamoxifen.	Increased risk of bone fractures, joint aches.	FDA approved for advanced cases and for treatment of early-stage cases in post-menopausal women after tumor removal.
Tamoxifen	Generic	Taken for five years, cuts recurrence 47% and risk of death 26%. But some women become resistant; recommended for five years only.	Muscle cramps. Higher risk of vaginal bleeding and blood clots. May raise risk of endometrial cancer.	Approved by the FDA in the 1970s.

Ford Motor Recalls Taurus, Sable Sedans

Dow Jones Newswires

DETROIT—**Ford Motor** Co. has recalled 1.3 million Taurus and Sable sedans to fix problems in the vehicles' brake lights and air filters.

A database at the National Highway Transportation Safety Administration shows the recall was initiated on March 1.

Some of the company's 2003 model Taurus and Sables have air-filter problems that can lead to fires, NHTSA said. And the 2000-2003 model year sedans also have an issue with the brake lights, which can make it difficult to shift the car out of park.

Ford said about 118,000 of the sedans involved in the two recalls have both problems in their cars. Those drivers will be able to have both issues fixed at the same time.

The recall is being enacted voluntaAbout 938,800 Taurus and Sables are affected by the braking problem. The cars were built at the Atlanta and Chicago assembly plants. The air-filter problem affects nearly 400,000 cars.