Can Topical Drugs Help Prevent Breast Cancer?

Clinical trials are testing gel forms of oral drugs to help prevent the disease in women at an increased risk.

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The drug tamoxifen can help prevent breast cancer in women at an increased risk of the disease. But many women who stand to benefit from tamoxifen do not take the drug—a pill—because of concerns about side effects, such as hot flashes and the increased risk of blood clots and stroke.

To explore alternatives to oral tamoxifen that might have fewer side effects, researchers are testing a topical form of the drug in two clinical trials. These randomized placebo-controlled studies are evaluating a gel formulation of tamoxifen called 4-hydroxytamoxifen (4-OHT) that women apply directly to the breasts.

The goal of this research is to find out if delivering a form of tamoxifen topically results in the same level of the drug in the breast but leads to lower levels of the drug in the blood and other parts of the body compared with oral delivery, according to Brandy Heckman-Stoddard, PhD, of NCI's Division of Cancer Prevention.

"With lower levels of the drug in the body, women would potentially have fewer side effects," she added.

Testing a Topical Drug for Breast Cancer Prevention

Four years ago, Seema Khan, MD, of Northwestern University Feinberg School of Medicine led a small study that compared the proliferation of abnormal cells in the lining of the breast duct—a condition known as ductal carcinoma in situ (DCIS)—among women treated with the gel applied to the breast skin and women treated with oral tamoxifen. (In women with DCIS, the abnormal cells have not yet spread to other tissues in the breast.)

"We found a similar reduction in the growth of DCIS cells from both the gel and the pill form of the drug, and the concentrations [of tamoxifen] in the breasts of women who were treated with the gel were quite good," said Khan, who is leading one of the new clinical trials of the tamoxifen gel. 4-OHT has the feel and consistency of hand sanitizer gel, she noted.

Women in the gel group also had lower blood levels of certain biomarkers associated with side

effects than women in the oral tamoxifen group, the researchers found.

Khan cautioned that those results need to be confirmed by the randomized placebo-controlled clinical trials now under way. She also noted that the 4-OHT gel is intended for use in a specific group of women.

“This approach is for healthy women who have an increased risk of breast cancer and for women with DCIS,” said Khan. “When the problem is confined to the breast, this approach would be appropriate.”

Using a topical drug would not be a viable approach once breast cancer cells have broken through the duct walls, because those cancer cells can go elsewhere in the body, she explained.

“In such cases, the treatment for invasive breast cancer needs to be systemic, and the local approach does not achieve that,” said Khan.

For women with DCIS, the topical application is “a local treatment for a local condition,” said Heckman-Stoddard.

Using Breast Density as an Indicator in Clinical Trials

NCI is cosponsoring one of the 4-OHT gel clinical trials, and the company that manufactures the gel, BHR Pharma, is sponsoring the other.

“There’s real excitement in the field for the results of the two studies,” said Heckman-Stoddard. “And if the trials demonstrate the effectiveness of the gel, then this could lead to the next large phase 3 breast cancer prevention trial for NCI.”

In both trials, researchers are assessing changes in breast density as a proxy for the anticancer effects of the drugs. Breast density has emerged as an important research area in breast cancer for two reasons: Dense breasts are a risk factor for breast cancer, and on mammograms dense breasts can mask breast cancers, making some tumors difficult to detect.

Clinical trials of oral tamoxifen have shown that people who have the greatest reduction in breast density also have the greatest reduction in breast cancer risk, noted Banu K. Arun, MD, of the University of Texas MD Anderson Cancer Center, who is leading a second tamoxifen gel clinical trial.

Participants in this study will apply the 4-OHT gel or placebo gel to the breasts for a year. “We are measuring mammographic breast density and hoping to see a decrease,” said Arun.

Although the evidence that a readily available drug—oral tamoxifen—can reduce breast cancer risk and breast density is strong, Arun continued, “new approaches are needed” to prevent breast cancer because many women who might benefit from oral tamoxifen do not take it because of side effects.

“We do not have a clear picture of whether the gel will avoid hot flashes,” said Khan. “But the ongoing clinical trials will give us information about whether the side effects are reduced.”

The clinical trials may also help answer questions about how well topical drugs are dispersed, or distributed, in the breast. Heckman-Stoddard noted that the distribution could be different for different topical agents.

Whether the amount of gel used to prevent breast cancer should differ based on breast size is also being explored in the clinical trials, Khan said.

Broadening the Approach to Include Other Drugs

In addition to its role in the 4-OHT gel studies, NCI is sponsoring two additional trials of topical drugs for breast cancer prevention. One trial is testing a gel form of the drug bexarotene (Targretin), and the other is testing a gel form of the drug endoxifen.

If the current clinical trials demonstrate the potential of using topical drugs for preventing breast cancer, Khan plans to investigate additional agents, including topical forms of some drugs that are too toxic for patients to take orally.

“We are giving drugs for cancer prevention to healthy women, so there has to be a high standard for safety and tolerability,” said Khan.

“Some drugs, such as certain types of retinoids, are not suitable for oral use by healthy women, but topical forms of these medicines might expand the options for cancer prevention if they get through the skin and have the desired effects,” she added.

For the moment, the researchers are focused on the current 4-OHT gel studies and the recruitment of the few hundred women needed to advance the research.

“I’m optimistic about this approach,” said Arun, referring to the use of the gel. “We know how tamoxifen works [to prevent breast cancer], and we have the results of trials testing oral tamoxifen.”

Khan agreed. “The momentum is building for this agent,” she said. “If both trials go in the right direction, then we’ll be poised to test the approach in a study of thousands of women.”

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