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Estrogen pills can benefit women with metastatic breast cancer

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For breast cancer survivors, the idea of taking estrogen pills is almost a taboo. In fact, their doctors give them drugs to get rid of the hormone because it can fuel the growth of breast cancer. So these women would probably be surprised by the approach taken by breast cancer physician Matthew Ellis, M.B., Ph.D., associate professor of medicine at Washington University School of Medicine in St. Louis — he has demonstrated that estrogen therapy can help control metastatic breast cancer.

In a study presented at the 31st annual San Antonio Breast Cancer Symposium, he showed that for about a third of the 66 participants — women with metastatic breast cancer that had developed resistance to standard estrogen-lowering therapy — a daily dose of estrogen could stop the growth of their tumors or even cause them to shrink. The study was funded by the Avon Foundation through the National Cancer Institute and included six cancer centers in the United States.

Ellis believes that estrogen therapy offers an appealing alternative to chemotherapy for metastatic breast cancer that has become resistant to estrogen-lowering agents called aromatase inhibitors, such as exemestane, anastrazole and letrozole. These drugs deplete the body of estrogen and are standard treatments for hormone-receptor positive breast cancers, which account for about 75 percent of breast cancer cases.

"By stabilizing or shrinking tumors in some women with metastatic

breast cancer, estrogen therapy can relieve pain and other symptoms of cancer and can potentially prolong lives," says Ellis, an oncologist with the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital. "And unlike chemotherapy, estrogen enhances the quality of life. For many of our patients, their hot flashes disappear, and they lose other symptoms of menopause. It's a natural treatment for breast cancer. Not only that, it's much cheaper than chemotherapy, costing less than a dollar a day."

Furthermore, estrogen seems able to return metastatic tumors to a vulnerable state in which they again can be affected by aromatase inhibitors. "We thought acquired resistance to aromatase inhibitor therapy was permanent," Ellis says. "But now we've shown that in some patients giving estrogen can make it possible to cycle back to aromatase inhibitors, and they can work again."

About 40,000 women die of metastatic breast cancer each year, and estrogen therapy potentially could help thousands of women with hormone receptor-positive disease, Ellis says.

The study measured how many women with aromatase inhibitor therapy-resistant metastatic breast cancer responded to estrogen therapy. All study participants had estrogen-receptor positive tumors that had spread to their bones, livers or lungs. The women were postmenopausal with an average age of 59.

Coming into the study, all the participants were taking aromatase inhibitors to slow or stop the growth of their tumors. But their tumors had stopped responding to the treatment and had begun to grow again. Half of the patients got a high dose of estrogen (30 milligrams a day) and half got a low dose (6 milligrams a day).

Ellis points out that decades ago, high-dose synthetic estrogen was an

accepted breast cancer therapy and was only abandoned when the estrogen-blocker tamoxifen came along in the 1970s and proved just as effective with fewer side effects. The high dose in the current study was based on the amount given to breast cancer patients in many of those earlier regimens.

Both the high- and low-dose treatments led to stabilization or shrinkage of metastatic tumors in about 30 percent of the participants. But the high-dose regimen had significant side effects such as nausea, vomiting, vaginal bleeding, fluid retention or calcium imbalances. In contrast, the low-dose regimen had few side effects and was well tolerated.

The researchers found that if study participants eventually experienced disease progression on estrogen, they could go back to an aromatase inhibitor that they were previously resistant to and see a benefit — their tumors were once again inhibited by estrogen deprivation. That effect sometimes wore off after several months, but then the tumors might again be sensitive to estrogen therapy. In fact, some patients have cycled back and forth between estrogen and an aromatase inhibitor for several years, thereby managing their metastatic disease.

The researchers also found that PET (positron emission tomography) scans could predict whose tumors would respond to estrogen therapy. They measured tumor glucose uptake before starting the women on estrogen and again 24 hours later. The patients whose tumors showed an increased glucose uptake, called a PET flare, were the same patients who benefited from estrogen therapy.

It's too early to know why estrogen has a negative effect on metastatic breast cancer tumors. But Ellis has found one clue — estrogen reduces the amount of a tumor-promoting hormone called insulin-like growth factor-1 (IGF1).

"I think that in order for breast cancer cells to survive in the absence of estrogen (when patients are on aromatase inhibitors), the cells have to learn to alter their cellular programs to utilize alternative growth signals like IGF1," Ellis says. "In theory, when you give estrogen back, IGF1 decreases and cancer cells die as a consequence. But surviving cancer cells prefer to switch back to living on estrogen — to them it's like eating out at McDonald's every day instead of foraging on roots and berries. These cells eventually reappear as estrogen dependent tumors and the cycle starts over."

Ellis plans to continue to follow metastatic breast cancer patients to quantify the response rate to retreatment with aromatase inhibitors when estrogen therapy stops working.

Source: Washington University School of Medicine