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hormonal therapy

TAMOXIFEN & AROMATASE INHIBITORS

by Beate Burdett and Maryjo Faith Morgan

In order to understand how hormonal treatment works it is important to have some basic understanding of how estrogen affects the breast. The term hormone therapy can be misleading because in breast cancer it refers to "anti-hormone" therapy. Most types of breast cancer depend on hormones for growth. Hormone-dependent breast cancers contain protein molecules called estrogen receptors. When the estrogen receptors are exposed to estrogen the result is tumor cell growth and multiplication. In other words, estrogen promotes the growth of breast cancer cells. Tumors that contain these estrogen receptors are known as estrogen receptor positive (ER+) tumors. These are the cancers that can be treated by hormonal therapies.

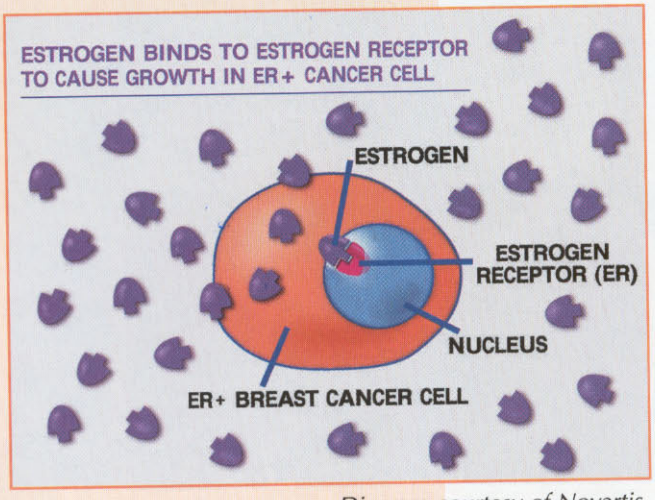


Diagram courtesy of Novartis.

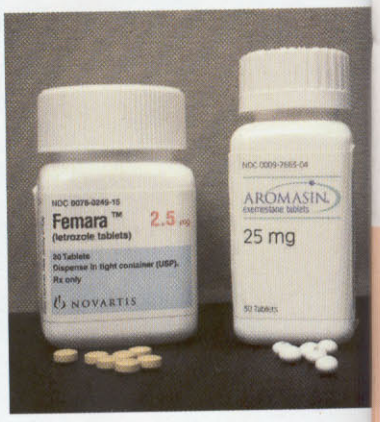
Hormonal therapy blocks the body's natural hormones from reaching any remaining cancer cells. The estrogen receptors and the related estrogen hormones are like interlocking pieces of a puzzle. They are "shaped" exactly right to fit each other. Hormone therapy is designed to either lower the total amount of estrogen available to fit ER+ receptors, or it mimics the shape of the hormone, fills the space in the receptor thus blocking the estrogen from matching up.

There are two classes of such drugs: selective estrogen receptor modulators (SERMs) such as Tamoxifen (tamoxifen citrate is manufactured by AstraZenea Pharmaceutical under the brand names Nolvadex, Apo-Tamox, Tamofen, and Tamone) and aromatase inhibitors such as Femara. Generally tamoxifen is tried first, and aromatase inhibitors are the second line of defense.

TAMOXIFEN

Tamoxifen is the most commonly used drug to block estrogen receptors. It fights breast cancer by competing with estrogen for space on estrogen receptors in the tumor tissue. Tamoxifen is a SERM engineered to behave like estrogen in some tissues while interfering with the action of estrogen in other tissues. Every tamoxifen molecule that hooks onto an estrogen receptor prevents and estrogen molecule from linking up on that same site. Without a steady supply of estrogen the tumor's ability to spread and thrive is reduced.

Tamoxifen has been used for more than 20 years to treat patients for early and advanced stage breast cancer. It was tested extensively in a nationwide Breast Cancer Prevention Trial with more than 13,000 women who were at high risk for breast cancer. Tamoxifen, as an adjuvant therapy, was found to substantially decrease the risk of breast cancer recurrence of the original cancer and also reduce the risk of developing new cancers in the other breast. Among the women taking tamoxifen, the risk of breast cancer was cut by 49%. Women who took tamoxifen also had 50% fewer diagnosis of non-invasive breast tumors, such as ductal or lobular carcinoma in situ.



However, there are risks associated with tamoxifen. In May 2002, the FDA issued a "boxed warning", a very high priority warning placed at the beginning of the label before any other instructions, concerning an increased risk for cancer of the uterus, stroke, and pulmonary embolism. The warning label of Nolvadex, a manufacturer of Tamoxifen, reads, "In clinical trials it has been shown that cancer of the uterus, stroke, and blood clots can occur approximately two to four time more frequently with Nolvadex than placebo, but each occurred in less than 1% of women. Some of these strokes, blood clots, and uterine cancers were fatal."

As with all drug treatments, the side effect can vary from individual to individual. It is important that you talk to your health care provider about the potential benefits and the potential risks and that you be closely monitored by your physician while on the drug. For most women the benefits outweigh the risks.

How long should you take tamoxifen? The prescribed length of time varies depending on our total medical situation. A study by the University of Pennsylvania's National Adjuvant Breast and Bowel Project concluded, "women do not receive any additional benefit from taking tamoxifen for

more than five years." Research conducted at Duke University Medical Center and the Novalon Pharmaceutical Corporation suggests that taking tamoxifen for over five years may reverse its beneficial effect, "because tamoxifen may begin to mimic estrogen in breast cells after five years, it may actually stimulate the growth of cancers after five years of use."

Aromatase Inhibitors

So where do you go from here? One second line of defense option for post menopausal women is to follow their five year Tamoxifen therapy with the nonsteroidal aromatase inhibitor Letrozole, which is manufactured under the brand name Femara® by Novartis. In post menopausal women, the body produces estrogen from other hormones known as androgens through the action of an enzyme called aromatase. Aromatase inhibitors bind to the enzyme aromatase and block it from converting androgens to estrogens in these tissues, thus decreasing tumor growth or delaying progression of tumor growth altogether.

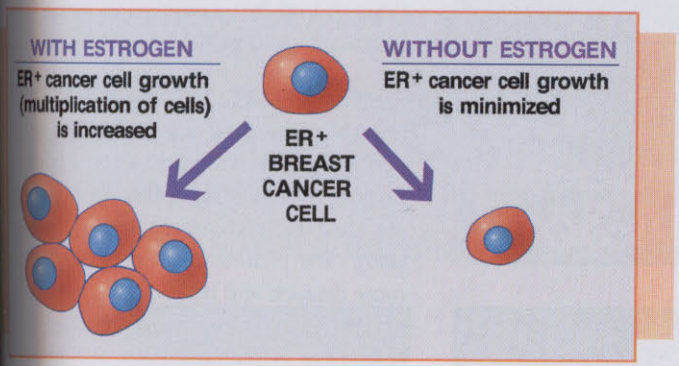


Diagram courtesy of Novartis.

As we've already discussed, the growth of some breast cancers is stimulated by estrogens; Femara reduces the total amount of estrogen in the body, effectively limiting the amount of estrogen that can reach cancer cells. Femara is contraindicated for pre-menopausal women; if taken during pregnancy there is risk of fetal damage and loss of pregnancy. Likewise, caution should be exercised by nursing women.

Although Femara seems to be generally well tolerated, it is necessary to strike a balance between risk of recurrence with potentially unpleasant side effects which may include bone pain, hot flashes, back pain, nausea, joint pain, shortness of breath, fatigue, coughing, constipation, chest pain, and headache.

In October 2003 the advance online New England Journal of Medicine published results from the Canadian-led international study on Femara which included 5,187 women from Canada, the United States, and Europe. Ninety-eight percent of the women had hormone-receptive positive breast cancer. The trial found post-menopausal survivors of early-stage breast cancer who took Femara after completing an initial five year Tamoxifen therapy had significantly reduced risk (43 percent) of cancer recurrence compared to women taking the placebo. This study was stopped early due to the significant decrease in recurrence among the group taking Femara. Due to this surprising efficacy the women taking the placebo were then given the opportunity to take Femara.

New on the horizon is Exemestane, manufactured by Pharmacia under the brand name Aromasin®. Although Aromasin is a steroidal inhibitor, and Femara, a non-steroidal inhibitor, they are very closely related. Both inhibit or block actions of the aromatase enzyme; the main difference seems to be that Aromasin has less effect on the bones and may have less associated risk of osteoporosis. In a recent trial, Intergroup Exemestane Study (IES), women who switched to Aromasin after two to three years of tamoxifen experienced a significant decrease in breast cancer recurrence. "This (IES) trial demonstrates that five years of tamoxifin therapy is likely to be suboptimal, and that switching patients from tamoxifin to Aromasin may be preferable in preventing breast cancer relapse. In addition, patients on exemestane had significantly fewer side effects as compared to patients on tamoxifin. this is an important advance at a stage of treatment when we are striving to eliminate cancer completely for our patients, says R. Charles Comes, MD, principal investigator of the IES trials and Head of Department Cancer Medicine, Imperial College School of Medicine Hammersmith Hospital in London, England.

In mid October, an international breast cancer prevention trail will launch to determine if two different drugs, Aromasin with or without Celebrex, could provide a preventive benefit for women at high risk for breast cancer. Celecoxib is generally used to treat symptoms of arthritis. It is a member of a class of drugs called COX-2 inhibitors which have been shown to have a possible role in the prevention of many types of cancer. Celecoxib reduces inflammation n the body and inflammation is linked to the development of some types of cancer. The combination of exemestane and celecoxib has shown to be very helpful in the treatment and prevention of breast cancer in experiments in animals.

Each patient and her specific circumstances are unique. According to local oncologist Dr. Miho Toi Scott, "It is essential for her, along with her medical team, to look at all the options of treatment currently available, and make choices that best fit her particular situation." New products, treatments, and the updating of proven methods are constantly changing. What is the norm in breast cancer treatment shifts rapidly as new information becomes available through longer term studies and clinical trials.

Editor's Note: Hormonal therapy is completely different from hormone replace therapy (HRT), which many women take during or following menopause. HRT is not a breast cancer treatment and in fact is contraindicated for women with diagnosed breast cancer.

To find out about current clinical trials, call 1-800-4CANCER to reach the Cancer Information Service, a program of the National Cancer Institute, or go to www.cancer.gov/clinical trials where you may search the Physicians Data Query (PDQ) database for trials by cancer type and by geographical area.

The facts presented here regarding Tamoxifen, Femara, and Aromasin are only a portion of the information you need to make informed decisions about your treatment. Talk to your doctor, do your own research, and along with your medical team, be an active partner in your healing process.

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