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TREATMENT UPDATE

Breast Cancer

With Highlights From the 2014 San Antonio Breast Cancer Symposium

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Treatment Update

Breast Cancer

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Editor

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For people coping with breast cancer, the number of treatment options continues to grow.

Each year in the United States, about 232,000 women and 2,350 men are diagnosed with breast cancer. In recent years, the number of effective treatments for breast cancer has increased. Because breast cancer is not just one disease—there are several types, each with its own unique features—doctors are able to tailor treatments. They prescribe specific medicines for specific types of breast cancer.

Although both women and men may be diagnosed with breast cancer, only about 1 percent of all cases occur in men. Because so few men have breast cancer, it is challenging for doctors to study the treatment of breast cancer in male patients separately in clinical trials. In this booklet, we refer only to women with breast cancer, but much of the information also applies to men. If you are a man affected by breast cancer, your health care team will tailor a treatment plan that best fits your situation.

In this booklet, we talk about the breast cancer treatments now available and new medicines in development. We also describe possible treatment side effects and how to prevent and cope with them, as well as how to communicate your needs to your health care team.

Biopsy Results Guide Treatment Decisions

Tests performed on tumor samples give valuable information that helps guide treatment decisions for breast cancer. One test your doctor may perform is a biopsy. For this test, he or she uses a hollow needle to remove a tissue sample from the tumor and examine it under a microscope. Some breast biopsies require surgery.

Tumor samples can help doctors determine whether the tumor is non-invasive (has not spread outside the milk duct or gland, where breast tumors usually begin) or invasive (has spread outside the duct or gland into nearby breast tissue). The tumor sample also helps identify the tumor's grade, which can be a clue as to whether it is a fast-growing or slow-growing form of breast cancer.

Another important piece of information your doctor may learn from the biopsy is whether the tumor's growth is driven by

hormones. This is known as the tumor's hormone receptor status. Receptors are specialized proteins to which hormones and other chemical messengers in the bloodstream, like HER2, can attach and fuel the growth of cancer cells. These receptors may lie on the surface of cancer cells or within them. When hormone receptors are present, the tumor's growth can be stopped or slowed by one of several hormonal therapies available. About 75 percent to 80 percent of breast cancers are estrogen receptor (ER)-positive. Of these cancers, nearly two thirds also have receptors for the female hormone progesterone (PR-positive).

About 20 percent to 25 percent of breast cancers are HER2-positive. These cancer cells have an abundance of HER2 receptors on their surface. The attachment of HER2 to these receptors stimulates the growth of the cancer. HER2-positive breast cancer usually responds well to targeted treatments that block the HER2 receptor. Targeted treatments are drugs that focus on specific cell mechanisms thought to be important for cancer cell survival and growth. These drugs tend to cause different side effects than chemotherapy.

Another 15 percent of women with breast cancer have a type called triple-negative. These tumors do not have receptors for estrogen or progesterone and do not have excess HER2 receptors on their surface. So certain drugs that work for hormone receptor-positive or HER2-positive tumors are not effective for women with triple-negative breast cancer. However, triple-negative breast cancer often responds well to chemotherapy. Clinical trials are pointing the way to new and even better treatments for triple-negative breast cancer.

Doctors also may order additional diagnostic tests to help choose the best treatment possible for each patient and to estimate the risk of cancer returning after treatment.

Current Treatments

Surgery

In the past, surgeons thought that mastectomy (full removal of the breast) was the best way to improve the chances that the cancer would not return. However, mastectomy does not reduce the chances of the tumor coming back, and for many women, lumpectomy (removal of just the tumor with some surrounding tissue) plus radiation is equally effective. Lumpectomy also has the advantage of offering a better cosmetic result than mastectomy.

Another surgical procedure that has been used to treat breast cancer involves removing the sentinel lymph node in the underarm. (Lymph nodes filter and trap bacteria, viruses and other unwanted substances in the body, so that white blood cells called lymphocytes can then destroy them.) The sentinel lymph node is the first lymph node into which breast cancer cells spread. If the sentinel lymph node is cancer-free, chances are that other, nearby lymph nodes are also unaffected and can be left in place. That's important because removing many lymph nodes from the underarm can lead to lymphedema, a painful swelling of the arm.

In certain patients, even if routine lab tests show that there are cancer cells in the sentinel lymph nodes, removing many nearby lymph nodes is not needed. Studies confirm that these patients can be treated successfully with lumpectomy followed by radiation. Long-term studies also show that the routine lab tests used to look for cancer in the sentinel lymph node give doctors the information they need to make an effective treatment plan. Using more complex tests to search for tiny single-cell amounts of cancer that may be present in the sentinel lymph node is not necessary. That's because

finding such small amounts of tumor cells does not seem to affect survival.

All women with breast cancer who have had surgery should talk with their health care team about whether they will need further treatment. This treatment could range from more surgery to radiation plus systemic treatment (chemotherapy, hormone blockers and/or targeted treatments) or systemic treatment alone. Each of these treatments is discussed below.

Radiation

Radiation to the entire breast has been the standard of care for women who have been treated with lumpectomy. However, any form of radiation can damage healthy tissues and cause cosmetic deformities or unpleasant swelling or scars. In fact, when radiation is given in a more concentrated form to a smaller area of the breast, the cosmetic outcome may be worse than the damage caused by whole-breast radiation.

The British START Trial showed that slightly higher daily doses of radiation given over as little as three to four weeks are as effective as and may cause less-severe side effects than the traditional practice of giving a higher total dose of radiation spread out over five to seven weeks. Additional benefits of the shorter treatment course include fewer visits for radiation treatments and lower out-of-pocket costs.

Several large clinical trials in Canada have since confirmed the findings of the START trial, and doctors have been encouraged to offer the shorter treatment schedule to all eligible women age 50 and older with ER-positive breast cancer after surgery. Women with early-stage breast cancer who have had a lumpectomy should discuss their treatment options with their doctors.

Chemotherapy

For many women, chemotherapy is an important part of treating breast cancer. It works by traveling through a patient's bloodstream to destroy cancer cells. Based on clinical trials over many years, doctors have learned how to more effectively use chemotherapy either alone or in combination with other treatments. They have refined the doses and schedules of these drugs so that women get the most benefit from treatment with the fewest side effects. Diagnostic tests, such as Onco*type* DX and MammaPrint, are now available to help identify those women with invasive ER-positive breast cancer who will likely benefit from the addition of chemotherapy to hormonal treatment (see page 8). These tests are run on a sample of the tumor that was removed during a biopsy or surgery and preserved. They often do not require another biopsy or further surgery.

The Importance of Clinical Trials

All of the advances that have been made in breast cancer treatment have been the result of clinical trials. These carefully controlled studies are the standard by which we measure the effectiveness of new treatments and their impact on patients' quality of life. Clinical trials also offer an additional treatment option. For these reasons, doctors and researchers urge women with breast cancer to take part in clinical trials.

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things you should know about clinical trials:

- People who take part in clinical trials often gain access to and benefit from new treatments.
- Before you take part in a clinical trial, you will be fully informed about the possible risks and benefits.
- Most clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- You can choose to stop taking part in a clinical trial at any time for any reason.

Hormone Blockers

Doctors generally recommend hormonal therapy for ER-positive or PR-positive breast cancer. These treatments work in different ways. Some are designed to prevent estrogen or progesterone from attaching to receptors in breast cancer cells. Others are designed to reduce the amount of hormones circulating in the body that attach to estrogen or progesterone

receptors. By blocking hormones, these treatments deprive tumor cells of the stimulation that fuels their growth.

Tamoxifen is an estrogen-blocking treatment given to both pre- and postmenopausal women with breast cancer. Taking tamoxifen after surgery for five years reduces by half the chances of the cancer coming back. It also lowers the risk of a new tumor developing in the other breast. Some recent studies show that taking tamoxifen for 10 years can be even more beneficial. For women with metastatic breast cancer—cancer that has spread from where it started to other parts of the body—tamoxifen can stop the growth of the cancer and shrink the tumor. It also has been shown to reduce the chance of breast cancer developing in healthy women at high risk.

Aromatase inhibitors (AIs) form another type of hormonal therapy. AIs are given to postmenopausal women with ER-positive breast cancer to help prevent the cancer returning after surgery or other treatment. Before menopause, AIs can stimulate a woman's ovaries to produce more estrogen, and so AIs are not effective in younger women with breast cancer. After menopause, however, the body can make estrogen from other sources using an enzyme called aromatase. AIs block the action of this enzyme, cutting off the supply of estrogen that can stimulate tumor growth.

Three types of AIs are available in the United States: anastrozole (Arimidex and others), letrozole (Femara and others) and exemestane (Aromasin and others). Taking AIs for five years has helped countless postmenopausal women with ER-positive breast cancer survive longer without their cancer coming back. Most of these breast cancer survivors in clinical trials took an AI for five years after being treated with tamoxifen for five years.

However, AIs can have side effects, including joint pain, bone loss, hot flashes and vaginal drying or itching. These side effects, which are similar to those experienced by many women after menopause, can become so bothersome to patients that they stop taking them. In fact, studies have shown that up to one third of women with breast cancer on AIs stop taking them as directed.

Women who are taking AIs and are thinking of stopping them for any reason should talk to their health care team first. Switching from one AI to another AI or switching to tamoxifen, taking vitamin D, exercising, and even acupuncture, among other options, may lessen the side effects of AIs and help women obtain the full benefit of hormone treatment.

According to a large clinical trial that is still ongoing, anastrozole may prove to be an effective way to prevent breast cancer in women at high risk of developing breast cancer, based on their family history. Researchers found that the chance of developing breast cancer was reduced by 53

percent in women at high risk who were given anastrozole compared with those who were not given it. Anastrazole also reduced the frequency of breast cancer metastases in other parts of the body. Researchers plan to follow the women who took part in this study to determine whether the benefits of anastrozole continue over time.

Another estrogen-blocking drug, fulvestrant (Faslodex), works in a slightly different way: It attaches to estrogen receptors and changes their shape. This prevents the receptors from working properly, which slows the growth of breast cancer cells. Fulvestrant is given as an injection and is approved only for postmenopausal women with metastatic breast cancer whose tumors have not responded well to other hormonal treatments such as tamoxifen.

Targeted Treatments

Trastuzumab (Herceptin) is one example of a targeted treatment designed for women whose tumor cells are HER2-positive. Since trastuzumab was approved, many women with HER2-positive tumors are surviving much longer.

Another medication, lapatinib (Tykerb), also targets HER2. Lapatinib is able to get inside cancer cells and block HER2 signals from within. Lapatinib has been shown to be effective in women whose HER2-positive breast cancer returned, spread or continued growing despite treatment with trastuzumab and chemotherapy. When medications that target HER2-positive breast cancer such as lapatinib are given along with chemotherapy, such as capecitabine (Xeloda and others), the combination of treatments can be effective at stopping cancer growth and shrinking tumors.

Another effective treatment for HER2-positive metastatic breast cancer is pertuzumab (Perjeta). Given through a

vein every three weeks, pertuzumab is used as a first-line (first-time) treatment in combination with trastuzumab and docetaxel (Taxotere and others). This three-drug combination can also be used to treat earlier-stage breast cancers before having surgery.

Ado-trastuzumab emtansine (Kadcyla), or T-DM1, is used to treat women with HER2-positive metastatic breast cancer who have already received treatment with trastuzumab and chemotherapy that included a taxane such as paclitaxel (Taxol and others) or docetaxel. T-DM1 is a combination of trastuzumab (T) with a chemotherapy drug (DM1). The combination is designed to block HER2 receptors on the surface of breast cancer cells to prevent HER2 from attaching to them and stimulating their growth, while delivering DM1 deep within the cells to damage their ability to multiply and killing them. T-DM1 also alerts the body's immune (defense) system to seek out breast cancer cells and destroy them.

Everolimus (Afinitor) is a type of targeted treatment that works inside cancer cells to restore their sensitivity to antiestrogen therapies such as AIs. In treating breast cancer, everolimus seems to help hormone therapy work more effectively, but it may cause increased side effects. Taken once a day with exemestane, everolimus treats advanced hormone receptor-positive, HER2-negative breast cancer in postmenopausal women whose cancer has continued to grow after treatment with other AIs.

Palbociclib (Ibrance) is a new targeted treatment that works by stopping breast cancer cells from dividing and growing. Palbociclib was recently approved for use in combination with letrozole for the treatment of locally advanced or metastatic ER-positive, HER2-negative breast cancer in postmenopausal women who have not received hormonal therapy previously.

Promising New Treatment Approaches: A Report From the 2014 San Antonio Breast Cancer Symposium

This section presents highlights from the 2014 San Antonio Breast Cancer Symposium, which took place December 9–13 in San Antonio, Texas. The information includes new findings on a number of currently used treatments, as well as promising new treatments that researchers continue to study in clinical trials.

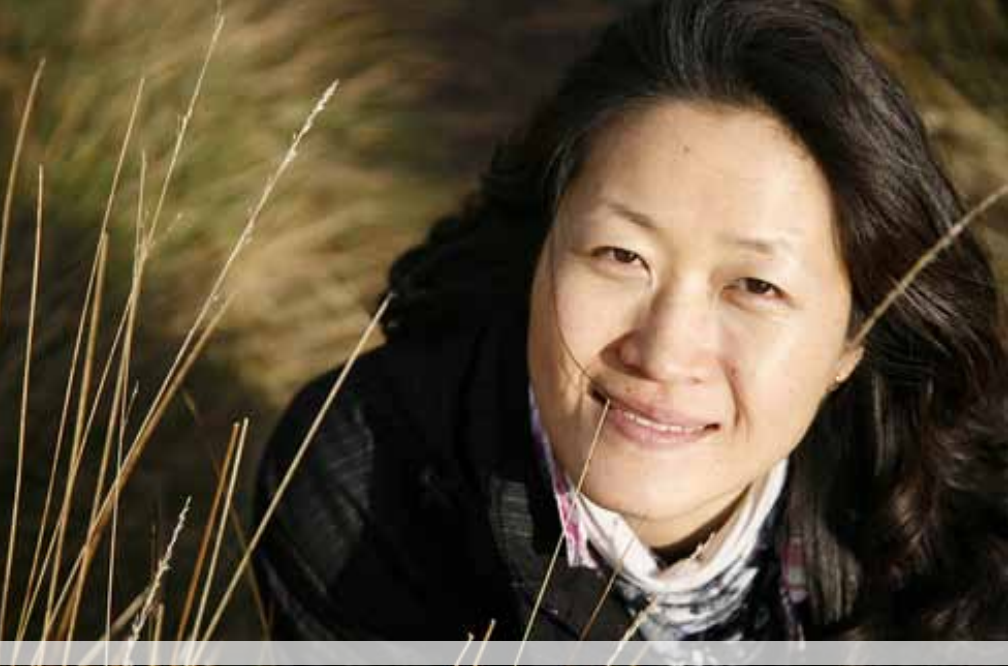
Some of these new treatments are still in the earliest phases of research and may not be available to the general public outside of a clinical trial. The information is intended for discussion with your doctor. He or she can let you know if these research findings affect your treatment plan and whether a clinical trial might be right for you.

HORMONE RECEPTOR-POSITIVE BREAST CANCER

Tamoxifen in Healthy Women at Risk of Developing Breast Cancer

Numerous clinical trials and clinical experience have shown that tamoxifen is an effective treatment for estrogen receptor (ER)-positive breast cancer. Until now, however, little has been known about how well this drug can prevent breast cancer in healthy women over the long term.

More than 7,150 pre- and postmenopausal healthy women whose risk of developing breast cancer was higher than normal participated in this study. Half of them received tamoxifen, and



the other half received placebo (a look-alike pill with no active ingredients) for five years to prevent breast cancer. After an average of 16 years, fewer women receiving tamoxifen developed breast cancer than those taking placebo (246 versus 343).

Tamoxifen was equally effective in preventing ER-positive breast cancer both before and after menopause. However, treatment with the drug did slightly increase the risk of other cancers developing in women who took it, including endometrial cancer, non-melanoma skin cancer and lung cancer.

What Patients Need to Know

The hormone treatment tamoxifen has been used to treat millions of women with breast cancer since it was approved by the FDA in 1977. Researchers now know that the benefits of tamoxifen may extend to healthy women to prevent the occurrence of breast cancer long after they stop taking the drug. The results of this large study suggest that tamoxifen may be an effective way to prevent ER-positive breast

cancer in both pre- and post-menopausal women but is not completely risk free. Tamoxifen did not have this same preventive effect against ER-negative breast cancer.

Fulvestrant Versus Anastrozole in Locally Advanced or Metastatic Breast Cancer

Women with breast cancer receiving fulvestrant (Faslodex) survived significantly longer than those receiving anastrozole (Arimidex and others), according to a clinical trial in 205 women with locally advanced or metastatic breast cancer.

Half of the women received fulvestrant, and the other half received anastrozole. Patients who received fulvestrant survived nearly six months longer than those receiving anastrozole (about 54 months versus 48 months). Side effects from the two drugs were slightly more frequent in women taking fulvestrant compared with anastrozole (24 percent versus 21 percent). None of the women in this study had received hormone therapy before.

What Patients Need to Know

Fulvestrant is approved by the FDA for use in women who have metastatic hormone receptor-positive breast cancer that no longer responds to other hormone treatment, such as tamoxifen. These new study results, which include women from more than 60 breast-cancer centers in nine countries, show that fulvestrant may prove to be an effective first-line (initial) hormone treatment as well.

Not only did fulvestrant stop their cancer from growing, it also helped these women to survive longer than did the current standard of care, anastrozole. The use of fulvestrant in women with metastatic hormone receptor-positive breast cancer is being studied further in a larger clinical trial. If the benefits are confirmed, researchers predict that fulvestrant may become

a new standard of care in the first-line treatment of locally advanced or metastatic hormone receptor-positive breast cancer.

Bortezomib in Metastatic Breast Cancer Resistant to Aromatase Inhibitors

In women with hormone receptor-positive metastatic breast cancer who are no longer responding to treatment with aromatase inhibitors like anastrozole, the addition of bortezomib (Velcade) to fulvestrant may be of benefit, according to a recent clinical trial. Bortezomib has been shown to be an effective treatment in patients with certain blood cancers. It is now under study as a treatment, either alone or in combination with other drugs, for the treatment of breast cancer.

Of 116 women with metastatic breast cancer that started growing again despite treatment with an aromatase inhibitor, 59 received fulvestrant alone and 57 received fulvestrant and bortezomib. One year later, there were no signs of cancer growth in more than twice as many patients who received fulvestrant plus bortezomib than those who received fulvestrant alone (28 percent versus less than 14 percent). Adding bortezomib to fulvestrant, however, did cause additional side effects, including nausea, diarrhea, tingling or numbness and swelling in the limbs.

During the study, 27 patients whose cancer continued to grow while receiving fulvestrant alone switched to fulvestrant and bortezomib. In four of these patients (15 percent), the cancer stopped growing for at least six months.

What Patients Need to Know

Many women with breast cancer eventually stop responding to their initial treatment, and so researchers continue to search for more effective treatment options. The results of this study

may signal a newer approach to treating women with hormone receptor-positive metastatic breast cancer. The addition of bortezomib to fulvestrant seems to be a more effective treatment than fulvestrant alone. In addition, bortezomib may even help these women to continue to respond to fulvestrant without their cancer resisting its benefits. Researchers are pleased with these early findings and plan to study this drug combination further in women with hormone receptor-positive metastatic breast cancer.

HER2-POSITIVE METASTATIC BREAST CANCER

Adding Everolimus to Trastuzumab and Paclitaxel

Researchers involved in a large clinical trial known as BOLERO-1 found that adding everolimus (Afinitor) to trastuzumab (Herceptin) and paclitaxel (Taxol and others) in women with advanced HER2-positive breast cancer offered no additional benefit, while causing more side effects. However, in patients with hormone receptor-negative breast cancer, there was a significant improvement in how long they managed their diagnosis before the cancer continued to grow. Of the 719 women in the BOLERO-1 study, 43 percent were hormone receptor negative, and the rest were hormone receptor positive.

Two thirds of the women participating in this study received the combination of everolimus, trastuzumab and paclitaxel. The remainder received trastuzumab and paclitaxel alone. Patients with hormone receptor-negative breast cancer receiving everolimus, trastuzumab and paclitaxel managed their diagnosis an average of seven months longer without their cancer coming back compared with those who received trastuzumab and paclitaxel alone (20.3 months versus 13.1 months).

The most common side effects observed in patients who received everolimus were inflammation of the mouth and lips (67 percent versus 32 percent among those who did not receive everolimus), diarrhea (57 percent versus 47 percent) and hair loss (47 percent versus 53 percent).

What Patients Need to Know

The BOLERO-1 researchers had hoped that adding everolimus to the combination of trastuzumab and paclitaxel might improve outcomes in women with HER2-positive breast cancer. However, initial results of this study seemed to show that the three-drug treatment is no more effective than trastuzumab and paclitaxel alone. Sometimes clinical trials do not achieve the desired effects, but they may offer some new information that may allow doctors to treat patients more effectively.

This was the case with the BOLERO-1 study. Researchers learned that combining everolimus with trastuzumab and paclitaxel did, in fact, help women with HER2-positive, hormone receptor-negative breast cancer go longer without their cancer growing. Thus, this three-drug combination will be studied further in this particular group of women and may prove to be of benefit in the future.

TREATMENT PRIOR TO BREAST CANCER SURGERY OR CHEMOTHERAPY

Lapatinib and Trastuzumab Prior to Surgery

In women with HER2-positive breast cancer, treatment with lapatinib (Tykerb) and trastuzumab before breast cancer surgery led to a significant response without using chemotherapy, according to a clinical trial in 95 women. The rate of response was not as high in a subgroup of women with ER-negative breast cancer.

All patients received lapatinib and trastuzumab. Women who were ER-positive also received letrozole (Femara and others), along with treatment to stop the production of estrogen by the ovaries if they were premenopausal. Letrozole is a drug that lowers the amount of estrogen in the body. About one third of the women received treatment for 12 weeks and the remainder for 24 weeks.

In women with ER-positive breast cancer, about 9 percent responded after 12 weeks of treatment and 33 percent after 24 weeks. In those with ER-negative breast cancer, however, the rate of response was 20 percent after 12 weeks of treatment but only 9 percent after 24 weeks. This result suggests that longer treatment with lapatinib and trastuzumab is better only in patients with ER-positive breast cancer.

The combination of these two drugs did have some adverse effects. They included mild-to-moderate diarrhea, rash and mucositis (inflammation of the mucous membranes lining the digestive tract).

What Patients Need to Know

Earlier studies had shown that the combination of lapatinib and trastuzumab is an effective way to treat women with advanced HER2-positive breast cancer. Researchers wanted to learn whether giving this drug combination for 24 weeks would be better than giving it for 12 weeks. They learned that women with ER-positive breast tumors who received longer treatment had better results than those who received shorter treatment. However, they also found out that women with ER-negative breast tumors actually did better with shorter treatment than with longer treatment. This promising drug combination will be studied further in women with advanced breast cancer in the hope that many of them may be spared the cost and side effects of chemotherapy.

Nab-Paclitaxel in Early-Stage Breast Cancer

In patients with early-stage breast cancer, more women receiving nab-paclitaxel (Abraxane) had a complete remission—no sign of cancer—than women receiving standard paclitaxel, according to a clinical trial in 1,204 women. Both drugs were given to the women prior to their receiving standard chemotherapy.

Nab-paclitaxel is a formulation of paclitaxel protected by a microscopic shell of human serum albumin. This formulation allows delivery of higher doses of the drug directly to the tumor without increasing its side effects. Studies have shown that nab-paclitaxel is superior to standard paclitaxel in patients with metastatic cancer.

In this study, 33 percent of the women had HER2-positive tumors, and the remainder had HER2-negative tumors. Of those with HER2-negative tumors, 23 percent had triple-negative breast cancer. Triple-negative breast cancer is more challenging for doctors to treat because the treatment options available are limited.

About half of the patients received nab-paclitaxel, and the remainder received standard paclitaxel. After 12 weeks, all patients were taken off nab-paclitaxel or paclitaxel and were given standard chemotherapy with epirubicin (Ellence and others) and cyclophosphamide. Patients who received nab-paclitaxel had a higher pathologic complete response (pCR) rate—the percentage of women who had no signs of cancer after treatment when tissue removed from their breast was examined under a microscope—than those who received standard paclitaxel (38 percent versus 29 percent). pCR is a predictor of a drug's long-term effectiveness in preventing a return of cancer after surgery. The difference in pCR rate between nab-paclitaxel and standard paclitaxel was even greater in patients with triple-negative breast cancer (48 percent versus 25 percent).

What Patients Need to Know

This large German study showed that nab-paclitaxel was more effective than standard paclitaxel in raising the pCR rate in women with early-stage breast cancer. In fact, the benefits of nab-paclitaxel were particularly noticeable in women who had triple-negative breast cancer, which is especially good news because this form of breast cancer tends to resist treatment. Following these women with early-stage breast cancer for a longer time also will show whether the use of nab-paclitaxel offers a survival benefit.

Carboplatin and Bevacizumab in Triple-Negative Breast Cancer

Adding either carboplatin or bevacizumab (Avastin) to standard chemotherapy significantly provided a better response in patients with early triple-negative breast cancer, according to a clinical trial in 360 women. Although carboplatin increased the pCR rate equally for women with basal-like and non–basal-like tumors, the addition of bevacizumab benefited only women with basal-like tumors. In addition, bevacizumab lowered the pCR rate in women with non–basal-like cancers. Standard chemotherapy consisted of paclitaxel, doxorubicin and cyclophosphamide.

Of the 360 patients, 87 percent had basal-like tumors. In those patients, the pCR rate rose from 47 percent to 61 percent with the addition of carboplatin. In contrast, the addition of bevacizumab increased the pCR rate from 45 percent to 64 percent, but lowered the pCR rate in women with non–basal-like tumors from 60 percent to 43 percent.

What Patients Need to Know

Researchers now know that how well a woman with triple-negative breast cancer responds to a given treatment may depend on the subtype of the tumor she has. The results of this study showed that women who had basal-like tumors and those who had non–basal-like tumors responded equally well to the addition of carboplatin to standard chemotherapy. However, although women with basal-like tumors responded to the addition of bevacizumab to standard chemotherapy, those who had non–basal-like tumors did not respond to bevacizumab and, in fact, had a poorer response to

carboplatin. Such information about tumor subtypes may help doctors in the future to select the right treatment with the best chance of success in women with triple-negative breast cancer.

Carboplatin in Triple-Negative Breast Cancer

In certain women with metastatic or locally advanced breast cancer, carboplatin was more effective in stopping their cancer from coming back than docetaxel (Taxotere and others), according to a clinical trial (TNT) in 376 women. These women had both triple-negative breast cancer and a BRCA gene mutation (change).

Half of the women in the study received carboplatin, and the other half received docetaxel. Overall, there was little difference between carboplatin and docetaxel in how soon their cancer started growing again (3.1 months versus 4.5 months). However, in women who had both triple-negative breast cancer and a BRCA gene mutation, more than twice as

many women responded to treatment with carboplatin than those who responded to docetaxel (68 percent versus 33 percent). In addition, women with a BRCA gene mutation who received carboplatin went longer without their cancer coming back than those who did not have a BRCA gene mutation (6.8 months versus 3.1 months). This benefit was not seen in women who received docetaxel.

What Patients Need to Know

The TNT study is a very important one for women who have advanced or metastatic triple-negative breast cancer. The results showed that neither carboplatin nor docetaxel is more effective than the other drug in the treatment of these patients. But when researchers looked more closely at these patients' genetic background, they found that women who had a BRCA gene mutation responded much better to carboplatin than to docetaxel, compared with women who did not have this gene mutation.

Additional studies are needed to understand more about how a BRCA gene mutation affects how a woman with triple-negative breast cancer responds to treatment. But the good news is that doctors may now start to make more informed choices on chemotherapy for women with this type of breast cancer based on genetic testing.

Treatment of Younger Women With Hormone Receptor-Positive Breast Cancer

The SOFT study was designed to answer the question of whether tamoxifen alone is the best treatment for hormone receptor-positive breast cancer in younger, premenopausal women. Tamoxifen is generally regarded as the standard of care

for this form of breast cancer. Some doctors give tamoxifen and also routinely use a drug or other means to slow or stop the production of estrogen by the ovaries (a procedure called ovarian suppression) in women who are still menstruating.

Stopping the release of estrogen from the ovaries prevents estrogen from reaching a hormone-sensitive tumor and stimulating its growth. Tamoxifen blocks the estrogen receptor on breast cancer cells, further preventing estrogen from fueling growth of the cancer. However, because the body can produce estrogen by converting other hormones into estrogen, an aromatase inhibitor like exemestane (Aromasin and others) often is given to women with hormone receptor-positive breast cancer to block this source of estrogen and prevent it from stimulating the tumor.

In the SOFT trial, a total of 3,066 women with hormone receptor-positive breast cancer were randomly assigned to treatment with (1) tamoxifen alone, (2) tamoxifen plus ovarian suppression, or (3) exemestane plus ovarian suppression. Ovarian suppression was accomplished medically with monthly injections of triptorelin (Trelstar) or by radiation or surgical removal of the ovaries.

At the end of five years, about the same percentage of women who received tamoxifen alone or tamoxifen plus ovarian suppression were free of cancer (84.7% versus 86.6%), a difference that could have been due to chance alone. However, women who received ovarian suppression were more likely to experience side effects, including hot flashes and other menopausal symptoms; muscle, joint and skeletal complaints; thinning of the bones; depression; hypertension; and diabetes.

The real benefit of adding ovarian suppression to tamoxifen was seen only among premenopausal women under age 40 with tumors that were at high enough risk to justify treatment

with chemotherapy. In this group, ovarian suppression added to tamoxifen resulted in a 22% reduction in the risk of cancer returning after chemotherapy, compared with tamoxifen alone. The combination of exemestane plus ovarian suppression was even better, reducing the risk of recurrence by 35% compared with tamoxifen alone.

What Patients Need to Know

Researchers are calling the SOFT trial one of the most important studies to be presented in recent years, especially for younger women with hormone receptor-positive breast cancer. The results of this study suggest that a woman's age may have a lot to do with selecting the most effective treatment.

For older women (over age 40) in this study, there did not seem to be a significant benefit to adding ovarian suppression to tamoxifen treatment—and certainly not enough to

outweigh the increased risk of side effects due to ovarian suppression. So for these women, tamoxifen alone may be sufficient treatment to reduce the chance of cancer returning. However, in younger premenopausal women, particularly those under age 35 with high-risk tumors who have received chemotherapy, the addition of ovarian suppression to treatment with tamoxifen or exemestane was beneficial in reducing the risk of their cancer returning after chemotherapy.

Many doctors believe that these study results may change how younger women with hormone receptor-positive breast cancer are treated in the future, but further study is still needed to be sure.

ASSESSING THE RISK OF CANCER RECURRENCE

Determining the Need for Additional Treatment in Early-Stage Breast Cancer

Four studies presented at the 2014 SABCS meeting show that a diagnostic test called Onco*type* DX increasingly is being relied upon to determine a woman's risk of cancer returning after treatment for early-stage breast cancer and whether she might benefit from additional (adjuvant) treatment.

Onco*type* DX analyzes the activity of a group of genes that affect how a cancer may respond to treatment. From these test results, it is possible to predict whether the risk of cancer returning is high, medium or low. The test is intended for use in women who have early-stage invasive breast cancer (that is, a tumor that has spread from the milk-producing glands or ducts to surrounding healthy tissues in the breast) or hormone receptor-positive breast cancer with no sign of cancer in the lymph nodes. It also is used to predict whether a woman is likely to have a return (recurrence) of ductal

carcinoma in situ (DCIS), the most common type of non-invasive breast cancer.

In the largest study so far of Onco*type* DX, researchers found that nearly 14 percent of 112,522 women under age 65 with early-stage breast cancer—including almost 72 percent of those with hormone receptor-positive tumors—had been tested between 2005 and 2011. More importantly, the results of Onco*type* DX testing led to a significant reduction in the use of adjuvant chemotherapy after surgery. However, in patients 66 years of age and older, Onco*type* DX testing was not associated with a significant reduction in the use of adjuvant chemotherapy.

The contrast in results between older and younger patients may be due to the fact that older women diagnosed with early-stage breast cancer tend to receive much less chemotherapy than younger women because of their age and because they may have other health conditions.

In the second study of Onco*type* DX, 83 of 160 women with early-stage breast cancer were tested. From the results of the test, the researchers were able to identify patients at low, intermediate or high risk for cancer recurrence. Since the use of Onco*type* DX testing at the researchers' institution, the use of adjuvant chemotherapy has decreased significantly.

In the third study, researchers found that Onco*type* DX testing was useful in aiding doctors to determine which patients with DCIS may need to receive radiation treatment after surgery and which do not. They discovered that 39 percent of women with DCIS were at low risk for cancer recurrence after surgery and so did not need to undergo further treatment with radiation.

Finally, in the fourth study, researchers in Ontario, Canada, confirmed the value of Onco*type* DX testing in predicting a

recurrence of DCIS or invasive cancer in the same breast following a lumpectomy. In all, 718 patients with DCIS were followed for nearly 10 years. The researchers found that the risk categories predicted by the Onco*type* DX test closely paralleled the actual local recurrence rates of both DCIS and invasive breast cancer in these women.

What Patients Need to Know

In November 2015, initial results from the TAILORx trial, a multinational study in more than 10,000 women with early-stage, hormone receptor-positive, HER2-negative breast cancer, were published in the *New England Journal of Medicine.* The study revealed that, five years after surgery, women with a low Onco*type* DX score (10 or less) who received hormonal therapy only, without chemotherapy, had less than a 1 percent chance of recurrence of breast cancer at a distant site and less than a 2 percent chance of recurrence either in the same breast or at a distant site.

Over the past few years, more and more doctors are using the Onco*type* DX test to determine whether a woman who has had surgery for early-stage breast cancer or DCIS is at risk of her cancer returning. It also helps doctors to decide whether additional treatment, such as chemotherapy or radiation, would be of benefit. Doctors are pleased to learn that women who are at low risk of cancer recurrence may safely be spared the expense, time lost from work or family and potential side effects of getting additional treatment to prevent their cancer from returning.

Treatment Side Effects

Sometimes, side effects from medications can make it challenging to cope with cancer. Side effects can even delay or stop treatment. A key to managing side effects is to be aware of them and report them to your health care team when they arise. Your health care team can help prevent and reduce the side effects of breast cancer treatment, which may include:

Nausea and vomiting. With proper care, your doctor can help manage this common side effect of chemotherapy. Talk with your doctor about anti-nausea medications to ease or prevent symptoms. There are also a number of things you can do on your own:

- Rinse your mouth often to get rid of any bad taste.
- Distract yourself with music, television or other activities you enjoy.
- Wear loose-fitting clothing that doesn't bind or add stress to your body.
- Avoid strongly scented foods, which can bring on nausea.
- An hour or so after vomiting, try taking small sips of fluid or sucking on ice chips to help settle your stomach.

Diarrhea is defined as two or more loose stools per day. It may be caused by some types of chemotherapy or targeted treatments. Be sure to:

- Drink plenty of fluids, including Gatorade or Pedialyte. Make sure your doctor or nurse knows about the problem you are having with diarrhea.
- Choose high-protein foods such as lean meat, fish or poultry instead of fatty foods. Eat vegetables cooked

instead of raw. Ask your doctor to refer you to a registered dietitian for more information on good nutrition.

- Use anti-diarrheal medicine only if you need it. Talk with your health care team before you use any over-the-counter or prescription medicines.

Constipation is defined as fewer than three bowel movements a week (although fewer than four or five may be a reduced number for some people). Prescription pain medicines may be the biggest cause of constipation for women with breast cancer. Talk with your doctor about using over-the-counter stool softeners or gentle stimulating laxatives. The best thing to do is to prevent constipation. Among the steps you can take yourself:

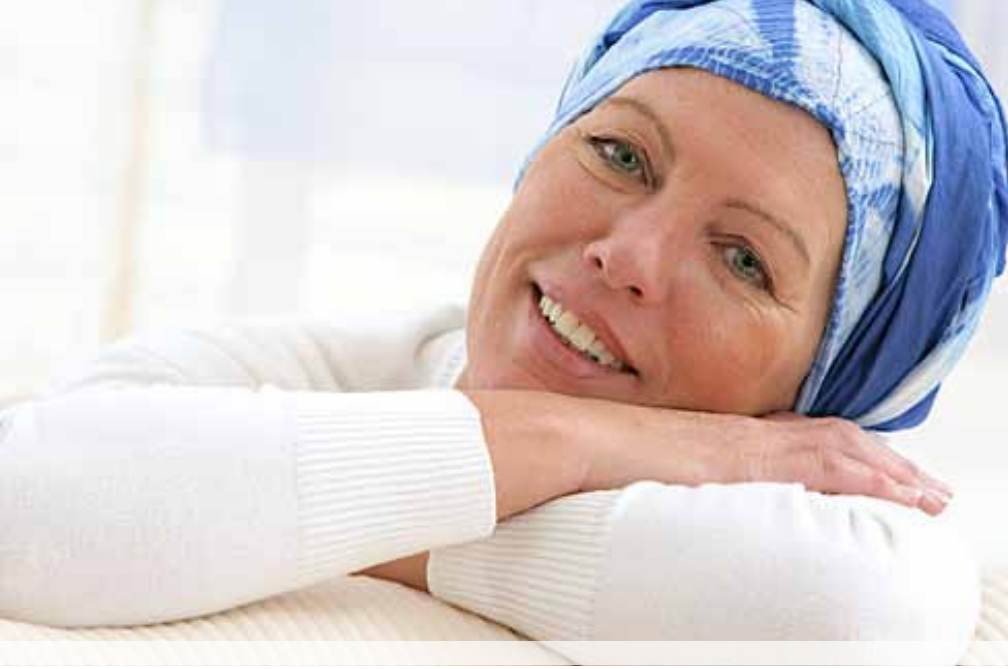
- Eat plenty of dietary fiber—grains, beans, fruits and vegetables such as cauliflower or broccoli.
- Drink plenty of fluids.
- Make light exercise a part of your everyday schedule.

Mouth sores inside the mouth and on the lining of the throat and digestive tract can result from radiation and some types of chemotherapy. Called mucositis, this side effect can be serious. Once treatment ends, the mouth sores do disappear. But before they fade, it's important that you work closely with your health care team to manage this side effect. A few things you can do on your own:

- Soothe mouth pain with ice chips or ice pops, over-the-counter pain relievers or Gelclair, a prescription oral gel designed to coat and protect sensitive tissues in the mouth.
- Take care of your mouth and keep it clean. If toothpaste irritates your mouth, use a mixture of one-half teaspoon of salt with four cups of water instead.
- Gargle with one quart of plain water, one-half teaspoon of salt and one-half teaspoon of baking soda.
- Drink plenty of fluids.

Fatigue. Feeling an extreme sense of tiredness that doesn't go away after rest can be the result of the cancer itself, treatment, anemia (low levels of red blood cells) or the emotional aspects of coping with cancer. If you are feeling fatigued:

- Seek help from your health care team. Your doctor can treat anemia with medication and, if they are needed, blood transfusions.
- Consult with a registered dietitian about changing your diet.
- Do light exercises, whenever possible. Moderate activity such as walking can help you feel better and increase your energy.



Hair loss is often one of the more frustrating aspects of chemotherapy. When hair falls out, it can affect a woman's self-image and quality of life. Depending on the treatment, hair loss may start anywhere from one to three weeks after the first chemotherapy session. Hair usually starts to grow back after you are finished with treatment. It may have a different texture or color, but these changes are normally temporary.

Many women who lose their hair after chemotherapy choose to wear some kind of head covering, whether it's a scarf, turban, hat or wig. Some insurance plans cover part of the cost of these head coverings. If you choose to wear a wig, consider buying one before all of your hair falls out. This way, you will have a good match to your own hair color. Having a wig ahead of time also will help you feel more prepared. You can have your wig professionally fitted and styled by a full-service wig salon. Some salons specialize in hair loss from chemotherapy.

Nerve damage. Some women on chemotherapy or targeted treatments experience numbness or tingling in their hands and feet—what doctors call peripheral neuropathy. Other symptoms of nerve damage include difficulty picking up objects or buttoning clothing, problems maintaining your balance, difficulty walking and hearing loss. These symptoms can become worse over time. It's important to tell your doctor as soon as possible if you experience these types of side effects. He or she may want to adjust some of your medicines or chemotherapy and may want to see if there is another reason for the problem that can be treated.

Often, nerve damage due to cancer treatment is temporary; it will usually get better, but it can take time. If you are coping with this side effect, take extra care when handling hot, sharp or dangerous objects. And use handrails on stairs and in the tub or shower.

Lymphedema. Women with breast cancer who have undergone lymph-node removal and/or radiation as part of their treatment are at risk for developing lymphedema. Lymphedema is a painful swelling that happens when your body's lymphatic fluid is unable to circulate properly and builds up in your soft tissues instead. It usually occurs in an arm or leg. Here are some things you can do:

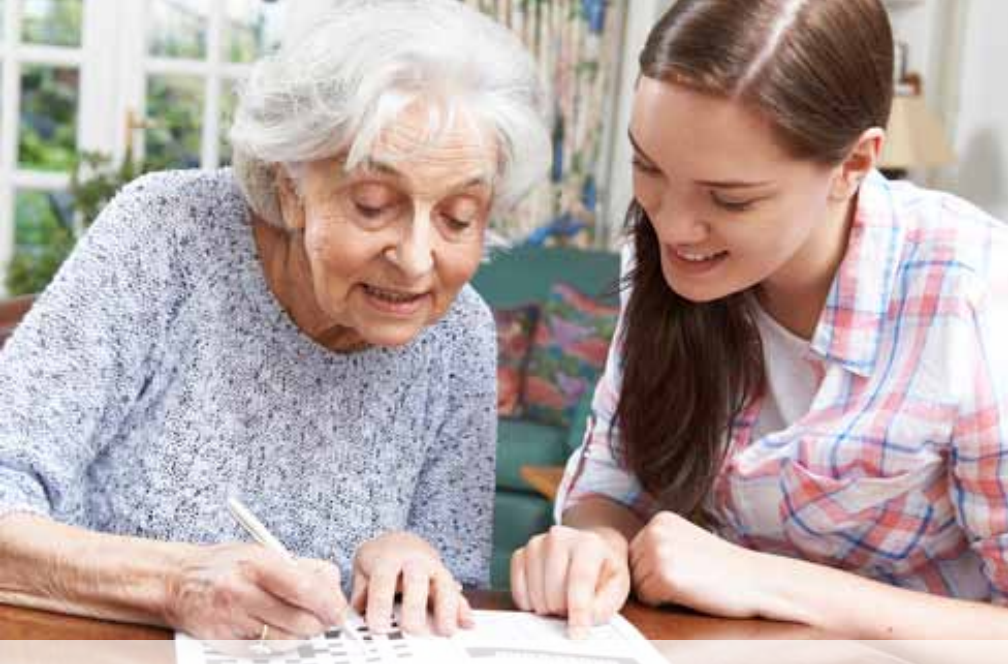
- Get help for your symptoms as soon as possible. In addition to swelling of the affected limb, the most common problems associated with lymphedema are pain, hardening of the skin and loss of mobility. If left untreated, the swelling can get worse and may cause permanent damage.
- Consider undergoing manual lymph drainage, or MLD. This type of massage helps move the fluid out from where it is settled. Afterward, the affected limb is wrapped in low-stretch bandages that are padded with foam or gauze.
- Learn exercises that can help prevent swelling due to fluid build-up. Your health care team can refer you to a program of special exercises that are taught and monitored by a physical therapist.
- Wear a compression sleeve. This can help drain the lymph fluid. It's important to wear a compression garment when flying, even on short flights.
- Always treat scratches, cuts, and insect bites by cleaning the area and applying an antibiotic ointment. If you notice swelling or redness, contact your health care team immediately. Bring your own nail-care supplies when you have a manicure, and ask them not to cut your cuticles.
- Wear gloves when gardening or removing hot items from the oven or stove.

- Be kind to your body. Carrying heavy packages, luggage or shoulder bags puts stress on your affected limb and could cause additional swelling and pain.

Low white blood cell counts. Chemotherapy may lead to low white blood cell counts, a condition called neutropenia. White blood cells play a key role in fighting infections. A reduced number of these cells increases your risk of infection. Your doctor can prescribe medication designed to help increase white blood cell counts. If you develop a fever, which is a sign of infection, let your health care team know immediately so you can get proper treatment.

Memory lapses. After chemotherapy, some people have difficulty concentrating or thinking clearly. If you experience what is often called chemobrain, speak with your health care team. Studies show that feeling tired or anxious even before treatment may make it more challenging to focus afterward. Treating such symptoms before chemotherapy may improve mental function during treatment. There are a number of things you can do to cope with these symptoms. Many of these techniques are used every day by people who want to increase the power of their aging brain:

- Keep a diary or a log to track how your memory lapses affect your daily routine.
- Make lists. Carry a pad with you and write down the things you need to do.
- Organize your environment. Keep things in familiar places so you'll remember where you put them. To help stay focused, work, read and do your thinking in an uncluttered, peaceful environment.
- Repeat information aloud after someone gives it to you. Spoken cues give your memory an extra boost.



- Keep your mind active. Do crossword puzzles and word games, or go to a lecture on a subject that interests you.
- Exercise, eat well and get plenty of rest and sleep to help keep your memory working at its best.

Bone loss. Both hormonal therapies and chemotherapy can cause bone loss, which increases a woman's risk for osteoporosis—thinning bones that are more likely to break. When cancer spreads to the bone, it can also weaken bone and lead to fractures. Talk with your health care team about how exercise and changes in your diet may help keep your bones healthy. It's also important to talk to your doctor about the medications available for bone health. There are three different classes of drugs, and each acts differently:

- Bisphosphonates such as zoledronic acid (Zometa and others) slow the process by which bone wears away and breaks down.

- RANK ligand inhibitors block a factor in bone development known as RANK ligand, which stimulates cells that break bone down. By blocking RANK ligand, these drugs increase bone density and strength. So far, the only drug approved in this class is denosumab (Xgeva), which has been shown to be less toxic and cause fewer kidney problems than zoledronic acid.
- SERMs (selective estrogen receptor modulators) are believed to slow the breakdown and removal of old bone. Examples of SERMs are raloxifene (Evista and others), tamoxifen and toremifene (Fareston).

Hot flashes. Breast cancer treatments can lead to menopausal symptoms such as hot flashes and night sweats. They also can lead to vaginal dryness and a lowered sex drive. If you are experiencing these side effects, speak with your health care team about ways to cope with them. There are a number of things you can do:

- Identify the triggers for hot flashes. For many women, stress, a hot shower, caffeine or spicy foods can set off a hot flash.
- Change your lifestyle habits to cope with the triggers. That may mean doing exercise, using relaxation techniques or changing your diet.
- Dress in layers and keep ice water handy to cool yourself off. Wear pajamas and use sheets made of cotton rather than synthetic material.
- Take a cool shower before going to bed.
- Try a mild medication such as acetaminophen (Tylenol and others).
- For vaginal dryness, try using a personal lubricant or moisturizer such as Astroglide, K-Y or Replens.

- If vaginal dryness persists, talk to your doctor about whether other prescription medicines are safe to use (such as hormone creams or suppositories—medicines inserted into the vagina). Your health care team also can advise you on regaining the desire for sex. (You may wish to ask for a referral to a health care professional who specializes in these issues.) It's important to keep an open dialogue with your intimate partner. Vaginal dryness can make sexual intercourse uncomfortable, but together you can find other ways to please one another.

Infertility. Young women with breast cancer generally receive treatments that include radiation and chemotherapy after lumpectomy. Many of these women may not have started or finished expanding their families, so preserving their fertility (ability to conceive a child) plays a large part in their treatment decisions. If you are concerned about your ability to have children after treatment, you can take these steps:

- Discuss treatment plans with all members of your health care team.
- Consider consulting with a specialist in reproductive medicine, who can help weigh the benefits and risks of a given treatment.
- Ask about newer options for preserving fertility such as oocyte cryopreservation, where a woman's eggs can be removed, frozen and stored for later use. Some fertility-preserving alternatives may be used before a woman starts chemotherapy.

Communicating With Your Health Care Team

In working with your team of doctors and nurses, it's important that you feel comfortable talking about any topic related to your diagnosis and treatment. Here are some tips:

Keep in mind that you are a consumer of health care. Seek out doctors who have experience treating breast cancer. Make sure that your doctors are available to you based on your schedule and location—and that the cost of seeing them is not prohibitive.

Think about how you prefer to communicate. Do you want the "big picture," or do you need to know all the details?

Your Support Team

When you are diagnosed with breast cancer, you're faced with a series of choices that will have a major effect on your life. Your health care team, family members and friends will likely be an invaluable source of support at this time. You also can turn to these resources:

Oncology social workers provide emotional support for people with breast cancer and their loved ones. These professionals can help you cope with the challenges of a breast cancer diagnosis and guide you to resources. Cancer*Care*® offers free counseling from professional oncology social workers who understand the challenges faced by people with cancer and their caregivers. Cancer*Care*'s professional oncology social workers work with you one-on-one to develop strategies for coping with treatment and its side effects.

Oncology social workers also can help you communicate with your doctor and other members of your medical care team about the health care issues that are important to you.

Support groups provide a caring environment in which you can share your concerns with others in similar circumstances. Support group members come together to help one another, providing insights and suggestions on ways to cope. At Cancer*Care,* people with cancer and their families can participate in support groups in person, online or on the telephone.

Financial help is offered by a number of organizations to help with cancer-related expenses such as transportation to treatment, child care or home care.

To learn more about how Cancer*Care* helps, call us at 800-813-HOPE (4673) or visit www.cancercare.org.

Do you want to be an equal partner with your doctors in making treatment decisions, or do you want to be well informed but leave the decisions to them? Tell your oncologist how much you want to know and your preferences.

Prioritize your questions and concerns. It may not be possible to get to every item on your list, so write down your questions before each visit and place them in order of their importance. Make sure whoever accompanies you agrees on which questions need to be answered.

Teach your oncologist to work with you. Oncologists may be experts in diagnosing and treating cancer, but they are not mind readers. However, they will listen and work with you in a way that best meets your needs if you let them know what they are.

Make the conversation about you, and share with your health care team what matters most to you. Increasingly, we are facing choices and trade-offs, where something has to go to achieve a more important goal. For example, if you are a young woman recently diagnosed with a hormone-sensitive breast cancer, your oncologist may recommend a treatment that blocks the function of your ovaries. This means you will spend at least five years managing the symptoms of early menopause. Though temporary, those symptoms will affect your quality of life. It's important to partner with your health care team to explore all of these options.

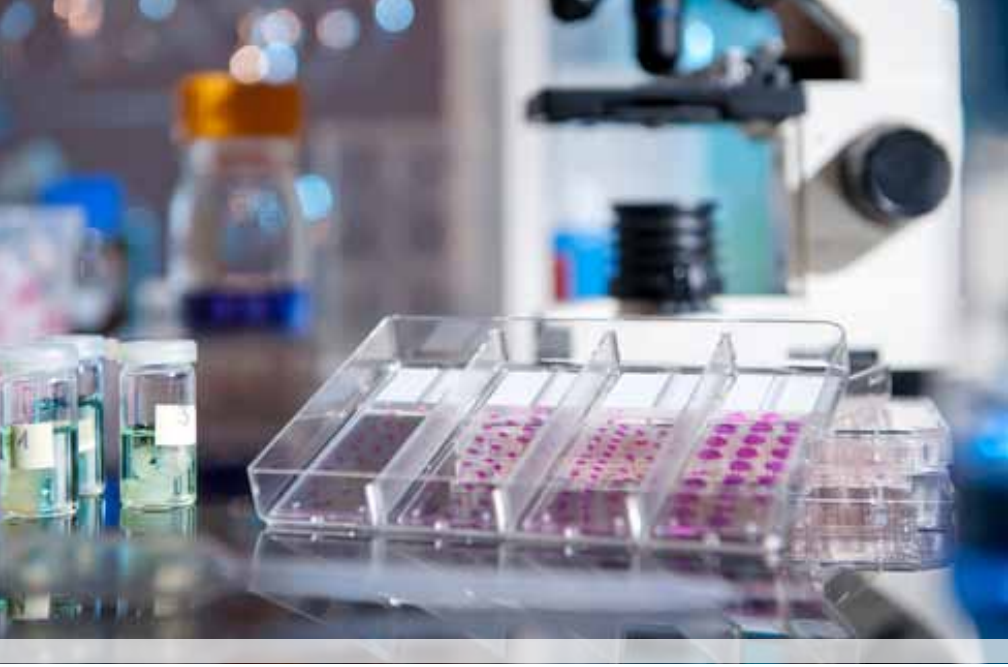
Tell your oncologist what you worry about. For instance, it could be the cost of your medicine, the difficulty of taking time off from work for treatment or the effect fatigue is having on your social life. Your health care team is there to help you. The most important thing is to try to establish a relationship that thrives on open communication.

Frequently Asked Questions

Q. Is there any new evidence regarding the advantage of taking tamoxifen for 10 years instead of five? What factors enter into the decision to lengthen treatment with tamoxifen for 10 years?

A. Long-term follow-up of the ATLAS trial, a worldwide study in nearly 13,000 women with early breast cancer originally reported in 2012, continues to show that 10 years of tamoxifen is superior to five years of tamoxifen. The benefits of extending tamoxifen treatment—a significant reduction in the risk of relapse and longer survival—appear to be across the board and unrelated to any particular type of patient.

What is interesting is that the benefits of extended treatment appear 10 to 15 years after starting tamoxifen and not necessarily during the first five years. Clearly, there are some women who are postmenopausal who might choose to take tamoxifen for five years plus an aromatase inhibitor for another five years, but does every premenopausal woman need to be treated with tamoxifen for 10 years? The size of her tumor and her lymph-node status will affect that decision, but so too will the increased risk of uterine cancer by taking tamoxifen for 10 years. Doctors take all of these things into account, as well as how well their patient is tolerating tamoxifen, before they prescribe it for another five years or switch her to an aromatase inhibitor. New diagnostic tests may help identify those patients who have a greater or lesser risk of their cancer returning, so we may have more data soon to help make a more informed decision about extending hormonal treatment.



Q. I had a molecular diagnostic test done four years ago and am in remission. Is there any advantage to requesting an updated molecular test?

A. Molecular or genomic tests like Onco*type* DX and MammaPrint are tools that help doctors determine whether chemotherapy is necessary and the chances of cancer returning after treatment. Once these tests are done, the results are final, and any further testing would have the same result.

Newer tests that can be used to determine whether longer or continued hormonal therapy would be beneficial are becoming available. But these tests normally are not used until the time comes (generally five years after starting hormonal treatment) to decide whether to continue treatment.

Resources

Cancer*Care*®
800-813-HOPE (4673)
www.cancercare.org

American Cancer Society
800-227-2345
www.cancer.org

Cancer.Net
888-651-3038
www.cancer.net

Cancer Support Community
888-793-9355
www.cancersupportcommunity.org

National Cancer Institute
800-422-6237
www.cancer.gov

National Comprehensive Cancer Network
215-690-0300
www.nccn.org/patients

BreastCancer.org
610-642-6550
www.breastcancer.org

Living Beyond Breast Cancer
855-807-6386
www.lbbc.org

Susan G. Komen for the Cure
877-465-6636
www.komen.org

Triple Negative Breast Cancer Foundation
877-880-8622
www.tnbcfoundation.org

CLINICAL TRIALS WEBSITES

Coalition of Cancer Cooperative Groups
215-789-3600
www.CancerTrialsHelp.org

EmergingMed
877-601-8601
www.emergingmed.com

National Cancer Institute
800-422-6237
www.cancer.gov/clinicaltrials

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