



## **Update from the 25th Annual San Antonio Breast Cancer Symposium December 11–14, 2002**

Nearly 5,000 physicians, oncologists, radiologists, epidemiologists, basic scientists, and breast cancer advocates from 76 countries converged in San Antonio, Texas, December 11–14, 2002, for the 25th Annual San Antonio Breast Cancer Symposium.

This year's meeting included 36 general presentations and 685 poster presentations. Below is a summary of some of the key presentations and findings and what they mean for women with breast cancer.

### **\*Arimidex or Tamoxifen: New Data, New FDA Approval**

The initial findings from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, the largest adjuvant trial ever conducted in postmenopausal women, were a key aspect of last year's Symposium. The ATAC trial enrolled 9,366 women and put tamoxifen (brand name Nolvadex) and the aromatase inhibitor anastrozole (brand name Arimidex) head-to-head. The researchers reported that after 2.5 years of treatment, the women on Arimidex appeared to have a small but statistically significant improvement in disease-free survival. These findings led the Food and Drug Administration (FDA) to approve Arimidex for the adjuvant treatment of hormone-sensitive early breast cancer in postmenopausal women in October 2002.

This year the updated ATAC data were presented. The researchers reported that after four years of treatment, 290 of 2,617 women on Arimidex had a relapse or died compared with 345 of 2,598 women on tamoxifen. (In 2001, the researchers reported that 217 women with hormone-sensitive tumors on Arimidex relapsed or died compared with 272 women with hormone-sensitive tumors on tamoxifen.) This means that since the last report an equal number of women (73) relapsed or died in each group.

The researchers also reported that they continued to find that women on tamoxifen were more likely to experience hot flashes, vaginal bleeding, and vaginal discharge, while women on Arimidex were more likely to experience fractures and musculoskeletal disorders, like arthritis.

*Susan says...*

*Does this mean that Arimidex is a better choice than tamoxifen for all postmenopausal women?*

*First some background:* Although both tamoxifen and Arimidex are estrogen blockers, they work in different ways. Tamoxifen keeps estrogen from getting into the cancer cells, whereas Arimidex blocks aromatase, the enzyme that converts androgens into estrogen. Although pre- and postmenopausal women can use tamoxifen as hormonal therapy, only postmenopausal women can use an aromatase inhibitor. That's because postmenopausal women get most of their estrogen from the conversion of androgens into estrogen by the aromatase enzyme, which the aromatase inhibitor blocks. In contrast, premenopausal women get most of their estrogen from their ovaries, and an aromatase inhibitor wouldn't block this.



In 1996 Arimidex was approved for women with advanced breast cancer whose disease progressed while on or following tamoxifen. Four years later it was approved for use as first-line treatment for metastatic disease. These findings in women with advanced cancer set the stage for the evaluation of Arimidex in the adjuvant (after surgery) setting and the ATAC trial.

*Where we are now:* We have a lot of data on tamoxifen. We know that it works best if women take it for five years (rather than ten or two), and we know that the effect tamoxifen has on cancer cells continues even after a woman stops treatment. We have less data on Arimidex. The ATAC trial was designed as a five-year trial because that's the length of treatment for tamoxifen. But we don't know if Arimidex should be taken for five years, ten, or just two. We don't know how long it will continue to keep cancer cells in check after treatment ends. And we don't know if it will keep women alive longer because it is too early in the ATAC trial to compare overall survival between the women on Arimidex and those on tamoxifen.

Side effects are an additional concern. While it's great that women on Arimidex had fewer side effects like hot flashes, weight gain, and vaginal dryness, the higher rate of bone fractures is cause for concern. Also, there may be other negative side effects from Arimidex that we aren't aware of because researchers have only been looking at and analyzing the side effects known to occur with tamoxifen.

*What this adds up to:* Choosing Arimidex or tamoxifen will ultimately be a personal decision. Some women will find the data from ATAC compelling and believe that Arimidex is a better choice for them. Others may feel better about being treated with tamoxifen. It's important when making this decision to discuss the pros and cons of each drug with your physicians; this conversation should include the results of your bone density tests and whether you have or are at high risk for developing osteoporosis. (If you are at high risk for osteoporosis, tamoxifen will probably be a better choice.) Lastly, women who choose Arimidex should be monitored carefully by their oncologist throughout their treatment, especially for early signs of osteoporosis.

### **\*Endocrine Therapy in Premenopausal Women**

Typically an aromatase inhibitor would not be given to a premenopausal woman. (This type of drug isn't effective in premenopausal women because their ovaries make large amounts of estrogen.) But because goserelin (brand name Zoladex) shuts down the ovaries and puts a woman into temporary menopause, it should, theoretically, allow the aromatase inhibitor anastrozole (brand name Arimidex) to be as effective in premenopausal women as it is in women who have become menopausal naturally—and a handful of trials now being conducted in Europe and the US are looking to see if this is true.

[Combined endocrine therapy—Zoladex and tamoxifen—is used more frequently in Europe than in the US as adjuvant treatment for hormone-sensitive breast cancer in premenopausal women. Austrian researchers are conducting a trial in 1,250 premenopausal women with hormone-sensitive disease that compares the use of Zoladex and tamoxifen with Zoladex and Arimidex.

Because aromatase inhibitors are known to increase the risk for bone fractures, a major concern has been the impact these drugs will have on bone mineral density in premenopausal women. To address this, the Austrian study is exploring whether adding a bisphosphonate (a



drug used to treat osteoporosis) to the hormone combination will decrease bone loss. [To date, some studies have suggested that bisphosphonates may decrease relapses from breast cancer while others have found this not to be the case. More studies are currently underway.]

The Austrian researchers designed a four-arm trial. One group of women is receiving tamoxifen and Zoladex. A second group is receiving tamoxifen, Zoladex, and the bisphosphonate zoledronate (brand name Zometa). A third group is receiving Arimidex and Zoladex. And the fourth group is receiving Arimidex, Zoladex, and Zometa. All of the women will receive treatment for three years.

The researchers reported that a preliminary analysis that looked specifically at bone loss after six months of treatment found that the women given Arimidex lost more bone density than did the women on tamoxifen. However, the women receiving Zometa had significantly better lumbar spine measurements than did those not receiving the bisphosphonate. The women will have to be followed longer to see if the effects on bone mineral density continue. And while there was a significant difference in bone loss between the two groups, it's important to point out that the amount of bone loss at six months was very small, and that none of the women developed osteoporosis.

A second presentation by researchers from Spain described a randomized trial of Zoladex and tamoxifen compared with Zoladex and Arimidex in pre-/perimenopausal women with hormone-dependent advanced breast cancer.

From January 1999 through December 2001, 119 women were enrolled in the trial. The researchers found that the women on Zoladex and Arimidex survived about four months longer than the women on Zoladex and tamoxifen—a statistically significant finding. This may lead to the Arimidex and Zoladex combination being considered as first-line therapy for premenopausal women with advanced disease.

*Susan says...*

*What does this mean for premenopausal women?*

Premenopausal women who have advanced disease may find Arimidex (or another aromatase inhibitor) and Zoladex to be a better choice than tamoxifen and Zoladex. Women may also want to take Zometa to help decrease bone loss. [Zometa is often recommended for women who have bone metastases as it can help decrease fractures and reduce bone pain.]

For premenopausal women with early stage disease, the choice may be more difficult. Based on the data showing Arimidex to be slightly more effective than tamoxifen in postmenopausal women, some US oncologists have already begun recommending that premenopausal women use an aromatase inhibitor with Zoladex as adjuvant therapy. Other oncologists are concerned about going ahead with this combination in premenopausal women because the trials are still underway and there is no data to support its use.

Premenopausal women who do decide to try Arimidex or another aromatase inhibitor as adjuvant therapy should have their bone density monitored. And while preliminary results from this study showed that a bisphosphonate did help decrease bone loss, there is concern about



what the long-term effects of bisphosphonates will be in women who take them before they have osteoporosis. The current recommendation is that women only begin taking bisphosphonates once they have osteoporosis.

While we wait for more data from these and other studies, some premenopausal women may decide to be treated with an aromatase inhibitor. Others may decide to be treated with tamoxifen. I would encourage any premenopausal woman who chooses to go on an aromatase inhibitor to enroll in a clinical trial. And I would encourage all women taking tamoxifen or an aromatase inhibitor to do weight-bearing exercise and to get adequate amounts of vitamin D and calcium in their diet, taking supplements if necessary.

### **\*Dose-Dense Chemo Improves Survival**

A study that found a clear survival benefit for dose-dense chemotherapy in women whose cancer has spread to their lymph nodes was the buzz at this year's conference.

The Cancer and Leukemia Group B (CALGB) 9741 trial compared dose-dense chemo (a regimen with a shortened interval between treatments) with regular dosing schedules in 1,973 women with primary breast cancer that had spread to the lymph nodes and with no other metastases. Because the trial was also designed to compare sequential versus combination adjuvant treatment, there were four treatment arms of doxorubicin (brand name Adriamycin) (A), paclitaxel (brand name Taxol) (T), and cyclophosphamide (brand name Cytoxan) (C):

A followed by T followed by C, every three weeks  
A followed by T followed by C, every two weeks  
AC followed by T, every three weeks  
AC followed by T every two weeks

Because frequent administration of chemotherapy can result in a serious condition called neutropenia—the decline in a number of certain white blood cells—the women on the dose-dense regimens received filgrastim (brand name Neupogen), also known as granulocyte-colony stimulating factor (G-CSF). Filgrastim stimulates the bone marrow to make more white blood cells (chemotherapy kills white blood cells) and thus reduces the risk for neutropenia.

After four years of follow-up, the researchers found that the dose-dense regimens, whether sequential or concurrent, were significantly better than the conventional three-week regimens in improving disease-free survival and overall survival. Among women on the dose-dense regimen, disease-free survival was 82 percent compared to 75 percent for those who received standard treatment. In terms of overall survival, after three years 92 percent of women on the dose-dense regimen were alive compared with 90 percent on the standard regimen. Additional follow-up is necessary to confirm this overall survival benefit.

The researchers also reported that the women on the dose-dense regimen did not have more side effects than those on the conventional regimen. Further, they experienced fewer cases of neutropenia.



*Susan says...*

*Should dose-dense chemotherapy now become the standard of care?*

It does appear that many women may benefit from this schedule, but it will be important to see whether additional follow-up finds that there truly is a survival benefit. The researchers did not look at whether the women on the dose-dense regimen were more likely to experience amenorrhea—having their periods stop—than were women on the conventional dosages. This could be a decision-making factor for women who hope to become pregnant following their treatment. It's also important to point out that filgastrim adds to the overall cost of treatment, and whether insurance companies will cover this drug is not yet known and may also be a factor for some women.

#### **\*Poster Sessions**

This year 685 posters were presented on topics ranging from tumor cell biology and breast cancer detection and treatment to epidemiology, outreach, and advocacy. Some of the highlights were:

#### **Ductal Cells, Hyperplasia, and Breast Cancer Risk: Results from a Long-Term Follow-Up Study of Lavage Patients**

Susan Love, MD, and Catherine Carpenter, PhD, presented this study, a follow-up of 414 women who had received ductal lavage in the 1970s and 1980s. [The Susan Love MD Breast Cancer Research Foundation funded the study.]

The researchers were able to contact 56 of the 414 women, and they found that the women who had had hyperplastic and atypical hyperplastic breast epithelium cells on ductal lavage were more likely to have developed breast cancer later in life. This data adds to the body of evidence supporting the use of ductal lavage in early breast cancer detection. [To learn more about ductal lavage, click here...](#)

#### **Quality of Life and Psychosocial Status at Diagnosis Are Not Associated with Disease-Free or Overall Survival**

It is often said that women who remain optimistic during their treatment will do better than women who become depressed or helpless. To see if this is indeed true, researchers at the University of Toronto gave 378 women who had early stage disease (no one had cancer that had metastasized) questionnaires to assess their mood and emotion, quality of life, and mental adjustment to cancer two months after their diagnosis.

This does not mean that if a woman is depressed, helpless, anxious, or angry she should not seek out counseling or even consider antidepressants—she should. But it does indicate that it would be wrong to say that a woman's depression or hopelessness was the reason that her cancer recurred.

#### **Incidence of Amenorrhea in Breast Cancer Patients 40 and Younger After Paclitaxel (Taxol)-Based Adjuvant Chemotherapy**

The type and duration of chemotherapy along with age are key factors in whether premenopausal women will experience chemotherapy-induced amenorrhea (having one's periods stop). This study, the first report on the effects of adjuvant paclitaxel (brand name Taxol) on premenopausal women, reviewed data on 102 women who had a treatment regimen



composed of doxorubicin (brand name Adriamycin) (A), Taxol (T), and cyclophosphamide (brand name Cytosan) (C). Approximately half of the women had hormone-sensitive tumors and continued on to tamoxifen; the other half had tumors not sensitive to hormones.

The researchers found that Taxol did not appear to increase the risk of amenorrhea over that of other chemotherapy regimens. This finding may influence chemotherapy choices in women who hope to become pregnant after their treatment.

#### **Updated Survival Results from the ZEBRA Trial**

The Zoladex Early Breast Cancer Research Association (ZEBRA) trial was designed to compare the endocrine treatment goserelin (brand name Zoladex) with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy in pre- and perimenopausal women with node-positive early breast cancer.

Endocrine therapies are treatments that block or alter the hormone levels of estrogen and progesterone, which fuel many breast cancers. Zoladex puts women into menopause, and thus decreases a woman's estrogen levels. In this study, 817 women received Zoladex for two years and 823 women received six cycles of CMF. The poster, an update of the initial results, reported what happened after the women had been followed for seven years.

The researchers found that in women with estrogen receptor (ER)-positive tumors, disease-free survival remained equivalent in the Zoladex and CMF groups. The groups remained equivalent in terms of overall survival as well. In the Zoladex group there were 148 deaths (25 percent of the women in that group); in the CMF group there were 154 deaths (25.8 percent). In women with ER-negative tumors, CMF was found to be superior to Zoladex in terms of disease-free and overall survival.

This is important because researchers were concerned that Zoladex was only effective as long as a woman was on it. Instead, it now appears that Zoladex seems to work more like tamoxifen, which puts cancer cells to sleep (or maybe even kills them) and then keeps them asleep even after treatment ends.

#### **Older Women, Chemotherapy, and Hormonal Therapy**

A number of posters presented studies that looked at how often elderly women (typically defined as women 70 and over) were being offered chemotherapy and hormonal therapy. And virtually all of them came to the same conclusion: There is often no reason, other than age, that elderly women are not offered these treatments.

The researchers hope that these studies will push doctors to question a common assumption that older women will not benefit from chemotherapy or hormonal therapy or that it is too "hard" for them. It is true that some older women with breast cancer may have other life-threatening diseases and that must be factored into decisions about adjuvant treatment. But all women, regardless of age, should be told about the risks and benefits of all treatment options.

#### **Vitamin E Supplements and Tamoxifen**

Like other cancer patients, women with breast cancer frequently take vitamin E supplements during their cancer treatment. To see if this could have a negative effect on treatment, the



researchers looked at the interaction between vitamin E and tamoxifen in mice and in laboratory cultures. The dose used was comparable to 400 IU/day. The researchers found that in both mice and in the cultures vitamin E appeared to decrease the effectiveness of tamoxifen.

Since this research was not done in humans, we can't yet say if vitamin E would have the same effect in women taking tamoxifen. Still, it would be wise to not use vitamin E while on tamoxifen until we learn more.

### **Zometa (Zoledronate) or Aredia (Pamidronate) for Women with Breast Cancer with Bone Metastases**

The majority of women with advanced breast cancer (65–75 percent) experience bone metastases, placing them at high risk for fracture. Intravenous bisphosphonates have been shown to inhibit bone loss and to help reduce fractures and bone pain. Since 1996 pamidronate (brand name Aredia) has been the standard of care for treating bone metastases in women with breast cancer. Zoledronate (brand name Zometa) is a newer more potent drug that was recently approved in the US for use in patients with bone metastases from solid tumors.

In this study 1,130 women with at least one bone metastasis were randomized to either Zometa or Aredia. All of the women also took vitamin D (400mg) and calcium (500mg) supplements. After 25 months of follow-up, the researchers reported that Zometa was more effective, that it reduced the need for radiation therapy to help alleviate bone pain, and that it reduced the annual incidence of bone-related problems. They also noted that the 15-minute infusion with 4mg of Zometa is more convenient than the two-hour infusion with 90mg of Aredia. This finding may lead to Zometa becoming the standard of care for women with bone metastases.

### **Flaxseed to Treat Hot Flashes**

A study by researchers in Manchester, England, looked at the effect of flaxseed on hot flashes. To be eligible for the six-month trial, women had to experience at least five hot flashes/night sweats each day. For the first three months the women were randomized to either 40 grams of flaxseed or a placebo. During the next three months they were given the opposite of what they had been on (women on flaxseed were now on the placebo, women on the placebo were now on flaxseed). The women didn't know whether they were on flaxseed during the first three months or the second three months. The study looked at women's hormone levels as well as the number of hot flashes they experienced.

The researchers found that the flaxseed had a statistically significant effect on reducing hot flashes. When the study began, the median number of hot flashes the women experienced was 206. The median number on the placebo was 146; on flaxseed it was 59. This indicates that the flaxseed did better than the placebo and that 40 grams of flaxseed per day may be a good option for women experiencing hot flashes.