Update from the 24th Annual San Antonio Breast Cancer Symposium

Every year hundreds of physicians, oncologists, radiologists, epidemiologists, basic scientists, and breast cancer advocates attend the San Antonio Breast Cancer Symposium, a forum for the discussion of new advances in breast cancer treatment.

The 2001 meeting, which was held December 10-13, included 30 general presentations and 500 poster presentations. Below is a summary of some of the key presentations and findings and what they mean for women now being treated for breast cancer.

**Arimidex or Tamoxifen: Which is Better for Postmenopausal Women with Early Stage Breast Cancer?**

That's the question many in San Antonio were waiting to hear the answer to when data from the Arimidex, Tamoxifen, Alone, or in Combination (ATAC) trial, the largest adjuvant trial ever conducted in postmenopausal women was presented on the first day of the conference. The ATAC trial enrolled 9366 women and put Tamoxifen (Nolvadex) and Arimidex (anastrozole), an aromatase inhibitor, head-to-head.

Both Tamoxifen and Arimidex are anti-estrogens, but they work in different ways. Tamoxifen keeps estrogen from getting into the cancer cells. Arimidex blocks aromatase, the enzyme that converts androgens into estrogen. Although pre-and post-menopausal women can use Tamoxifen as hormonal therapy, only postmenopausal women can use an aromatase inhibitor. These drugs are not effective in pre-menopausal women because their ovaries are still producing high levels of estrogen (and this wouldn't be blocked by an aromatase inhibitor) whereas post-menopausal women get most of their estrogen from the conversion of androgens into estrogen by the aromatase enzyme which the aromatase inhibitor blocks.

In 1996, Arimidex was approved for women with advanced breast cancer whose disease progressed while on or following Tamoxifen. Four years later, after a study put Tamoxifen and Arimidex head-to-head in women with metastatic breast cancer, Arimidex was approved for use as first-line treatment. 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.

Before the study began, many experts predicted that Arimidex would outperform Tamoxifen in the adjuvant setting. But the first results are not that strong. The data presented in San Antonio indicate that 317 of the 3,125 women in the Arimidex arm of the trial had a relapse of their breast cancer or died, compared with 379 of the 3,116 women in the Tamoxifen arm.

The third arm of the trial has women taking both Tamoxifen and Arimidex. Interestingly, taking both together did not prove to be more beneficial than taking Tamoxifen alone.

What does this mean? First, it's important to keep in mind that this is very early data, the trial has only followed women for 2.5 years. After five years, the difference may be greater, or it may not. Second, although the difference in the number of deaths was statistically significant, it was still a
small number, and it can be misleading. The number of deaths included non-breast cancer
deaths, and in both groups the vast majority of deaths were not due to breast cancer. Actually, to
date, only 5 women in the study have died of breast cancer.

What about side effects? Women on Arimidex had fewer of the side effects long associated with
Tamoxifen, like hot flashes, weight gain and vaginal dryness. What was unexpected, and
important, though, is that the women on Arimidex had a higher rate of bone fractures.

The bottom line: Tamoxifen is a known quantity. Much more remains to be learned about
Arimidex and its use in the adjuvant setting. It took many years and a number of research studies
to determine that women benefit most if they take Tamoxifen for five years. We don't know how
many years women should stay on Arimidex to gain the most benefit. We also don't know if there
will be any negative side effects if women stay on these drugs for a long time.

Because Arimidex out-performed Tamoxifen in the metastatic setting, some post-menopausal
women with early stage breast cancer and their physicians are choosing to go ahead and try it in
the adjuvant setting. Women who make this choice should be monitored carefully by their
physician, especially for early signs of osteoporosis.

**News on Herceptin**

Herceptin, a monoclonal antibody designed to fight tumors that are HER2/neu positive, is
currently only FDA-approved for use in women with metastatic disease. But research is underway
to evaluate the drug's safety and effectiveness in the adjuvant (after surgery) setting in women
with early stage breast cancer.

Herceptin alone can increase the risk of a woman developing heart toxicity. The risk is even
higher when Herceptin is used in conjunction with Adriamycin (Doxorubicin). This is significant
because Adriamycin is one of the most common forms of chemotherapy used for adjuvant
therapy.

It also raises questions about what the best treatment will be for women with early stage breast
cancer who have HER2/neu-positive tumors. For women with early stage breast cancer, the risk
of heart toxicity matters more because surgery alone may have cured their disease. For women
with metastatic disease, the heart toxicity matters less because the benefit of the drug outweighs
the risk.

The information presented in San Antonio on Herceptin in the adjuvant setting was a pilot trial
conducted by the Eastern Cooperative Oncology Group. The trial (E2198) looked at whether
giving Herceptin before giving Adriamycin (rather than giving it concurrently) would be a better
option.

All of the women in the pilot trial were lymph-node positive and had no prior history of heart
problems. They were divided into two treatment arms. In Arm A the women received Paclitaxel
(Taxol) and Herceptin for four cycles. After a three week break they received four cycles of
Adriamycin and Cyclophosphamide (Cytoxan), known as AC. The women in Arm B had the same
regimen but then went on to receive Herceptin for 52 weeks.
The short-term result: the researchers found that combining Taxol and Herceptin has rare but real effects on the heart. Although long-term effects are still to be determined, the pilot study underscores why researchers are right to tread cautiously.

The bottom line: We still don't know very much about Herceptin's use in the adjuvant setting. Women who are considering trying it should be fully aware of the risks and the benefits and may want to consider enrolling in one of clinical trials that are looking at Herceptin in the adjuvant setting.

It is also important that any woman considering Herceptin especially if she is using it in the adjuvant setting be certain that her tumor is indeed Her2/neu positive. The immunohistochemistry (IHC) test has been the mainstay of HER2/neu tumor testing. But as research presented at San Antonio underscored, the fluorescence in situ hybridization (FISH) test is more accurate than the IHC test and is the one that should be used.

**Technological Advances in Gene Profiling**

The discovery of BRCA1 and BRCA2, the genes that were found to place women at significantly higher risk of developing breast and ovarian cancer, were an important medical advance.

But this is only the beginning of the role that genes will play in breast cancer treatment. By analyzing the genetic components of breast tumors researchers may be able to glean information about the tumor that can help women and their physicians make treatment decisions.

Advances in this area of research were discussed in one of Symposium's general sessions and presented as posters. One of the more interesting presentations looked at using gene expression profiling to try to identify which cancers are most likely to recur in women with node-negative breast cancer. Using techniques known as microarray analysis and hybridization, the researchers compared gene expression patterns in women who had their cancers recur and women who did not. After looking at more than 100 genes they identified 20 that were about 84% accurate in predicting whether the outcome would be good or bad. Next, the researchers will continue to test these genes to see if they can replicate their results and determine which genes are the best markers.

Another group of researchers looked for specific genetic defects in ductal carcinoma in situ (DCIS), which is non-invasive, and then looked to see if these same genetic defects were seen in women with invasive breast cancer. The researchers found 114 genes that appeared in both the non-invasive DCIS and the invasive tumors. Now these researchers are going to try to determine a genetic evolutionary relationship between DCIS and invasive breast cancer. If so, this information could help clinicians fine tune treatment options for women with DCIS.

This research on genes and gene expression patterns may one day help us to find breast cancers very early, especially if we can find these markers in the breast fluid that can be obtained through ductal lavage.
Beyond Mammography?

Another Symposium general session focused on new techniques that can be used to look for cancer or monitor the effectiveness of a specific chemotherapy regimen. These techniques include optical mammography, PET scans, and magnetic resonance spectroscopy.

Optical mammography: This type of mammography, which uses a laser like that used in CD players, allows researchers to detect not only physical but chemical changes in breast tissue that are signs of cancer. Because it measures concentrations of hemoglobin, optical mammography may also allow a woman and her physician to know within five days of starting treatment if her tumor will respond to the chemotherapy regimen she is on. If this works, this test could be done prior to surgery, both to shrink the tumor and to determine treatment choices.

Positron Emission Tomography (PET) scans: Before this scan can be performed, a woman must be injected with a short-lived radiotracer combined with sugar. Because cancer cells grow faster than regular cells, they will attract and eat up the radiotracer's sugar. The scan will indicate if there is a lot of glucose in one area, a sign that a tumor is present.

PET scans are sometimes used to detect axillary lymph node involvement. They are also sometimes recommended for young women with dense breasts or for women with a family history of breast cancer following an inconclusive mammogram. Some hospitals now have machines that combine PET scans and computerized tomography (CT) scans, which allows both tests to be performed simultaneously. These body scans are also used when a cancer is first diagnosed to determine if metastasis has occurred. They are also used to monitor the effectiveness of chemotherapy or radiation. They are not completely reliable though. Unfortunately, tumors have to be at least 2 cm to show up on a PET scan.

Magnetic resonance spectroscopy (MRS): MRS works by measuring the biochemical composition and metabolic state of breast (or other) tissue. Unlike mammography, which indicates where a tumor is and how big it is, MRS provides information about the pathology of the tumor. The hope is that the MRS test will determine which types of chemotherapy regimens a woman's tumor is most likely to respond to, thereby aiding in treatment decisions.

Will any of these techniques impact the mammography debates now underway? Probably not. It's possible that one day optical mammography may provide an alternative to X-ray or digital mammography, but more research needs to be done. The other techniques may help in determining treatment choices and may reduce the length of time a woman is on a chemotherapy regimen that isn't working for her or keep her off of the regimen to begin with, and that's very important.