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The 2004 annual meeting of the American Society of Clinical Oncology (ASCO) was held June 5–8 in New Orleans, Louisiana. This conference is one of the most important meetings that oncologists attend each year.

Highlights included:

Update on Taxanes

- **Abraxane Effective in Women No Longer Responding to Taxanes**

Taxanes like paclitaxel (brand name Taxol) and docetaxel (brand name Taxotere) are strong cancer fighters. The problem with them is that they are harder to administer than other cancer drugs because they cannot be dissolved in water. Instead, they must be dissolved in a special type of solution, and these solutions have their own toxicities.

Taxol is dissolved in Cremophor. Cremophor's toxicity limits how much Taxol can be given. It is also the reason why every patient who gets Taxol must receive a steroid premedication, why Taxol has a long infusion time, and why Taxol is more likely to damage the bone marrow, making neutropenia (an infection that can occur when a person's white blood cell count is too low) and other infections more likely to occur.

Abraxane is a new delivery method for Taxol. This new preparation contains no toxic solvents. Instead, the Taxol is contained in tiny nanoparticles and coated in a shell of human albumin protein, the body's natural transport system. Abraxane was designed to bring the Taxol more directly to the tumor and to limit how much of the drug is absorbed by normal, healthy tissue.

At ASCO, researchers from the Baylor Charles A. Sammons Cancer Center in Dallas, Texas, discussed a Phase II study of weekly Abraxane in women with metastatic breast cancer that no longer responded to Taxol or Taxotere. The trial enrolled 106 women, all of whom received a weekly 30-minute treatment of Abraxane, without premedication. Treatment cycles consisted of weekly doses on days 1, 8, and 15 followed by one week off. This was repeated every 28 days until the cancer progressed or the toxicity became unacceptable.

The researchers reported that 15 percent (16) of the women had tumors that partially responded to Abraxane, while 30 percent (32) of the women had a partial response plus stable disease for more than 16 weeks.

In terms of long-term disease control, the women in the study had a 38 percent chance of being progression-free at four months, a 13 percent chance of being progression-free at 12 months, and a 38 percent chance of surviving 12 months. In addition, Abraxane appeared to be well tolerated, with few instances of neutropenia (which can lead to infection) or other problems such as vomiting, fatigue, or nausea.

Susan says:
The toxicities associated with Taxol and Taxotere have been a problem since these drugs first began to be used for cancer treatment. It is exciting that Abraxane doesn't have these toxicities and has been found to be effective in treating women whose tumors no longer respond to Taxol or Taxotere. These findings are significant, and will undoubtedly lead to greater use of Abraxane in the metastatic setting.

- **Weekly Paclitaxel (Taxol) More Effective Than Standard Treatment**

Andrew Seidman, an associate attending physician at Memorial Sloan-Kettering Cancer Center, in New York, discussed initial findings from the Cancer and Leukemia Group B (CALGB) 9840a study, a randomized Phase III trial that compared a weekly paclitaxel (brand name Taxol) treatment with the standard three-week Taxol treatment regimen.

The trial enrolled 735 women with metastatic disease who were using Taxol as a first- or second-line treatment. The researchers found that the weekly treatment was superior in women with HER2-positive cancers who were taking Herceptin and in women who were HER2-negative (HER2 is also sometimes referred to as HER-2 or Her-2/new or erb-b2). This analysis also included data from 120 women enrolled in the CALGB 9342 trial who received Taxol every three weeks.

A response was seen in 40 percent of the women receiving Taxol compared with 28 percent of the women receiving the standard three-week regimen. Time to disease progression was also better with the weekly therapy—nine months compared to five months for the standard three-week treatment. Although the weekly regimen was well tolerated and caused less Grade 3 neutropenia (a decrease in white blood cells that can lead to infection), it did cause more Grade 3 sensory/motor neuropathy (pain in the feet and legs).

Susan says:
This is another real treatment advance, and I would expect that we will see oncologists begin putting women on a weekly Taxol regimen. If your oncologist has talked about putting you on Taxol, this study is one you should definitely discuss with him/her before you start treatment.

New Data on Hormonal Therapy

- **Letrozole (Femara) and Quality of Life**

Timothy Joseph Whelan, an associate professor at McMaster University in Ontario, Canada, reported on a quality-of-life study done in conjunction with the MA-17 trial. MA-17 was the large, international Phase III placebo-controlled trial of 5,187 postmenopausal women who were assigned to receive either letrozole (brand name Femara) or a placebo for five years after having completed five years of tamoxifen. The trial received extensive media attention

when it was stopped early after a preliminary analysis found that Femara was superior to a placebo.

The quality-of-life study evaluated 3,605 of the women enrolled in the larger study. It followed the women until the study was stopped, with the average follow-up being 30 months.

The quality-of-life study found that, overall, Femara did not have a negative impact on quality of life. For example, hot flashes affected 58 percent of the women on Femara and 54 percent of the women on the placebo; arthritis affected 25 percent of the women on Femara and 21 percent of the women on placebo; and muscle pain affected 15 percent of the women on Femara and 12 percent of the women on placebo. In addition, vaginal bleeding was a problem for 6 percent of the women on Femara and 8 percent of the women on placebo, while osteoporosis was diagnosed in 8 percent of the women on Femara and 6 percent of the women on placebo.

Femara appeared to have no effect on depression, memory, or weight gain. Some problems, such as body aches and joint pain, appeared to be more of an issue as women aged, with women 70 and older having more problems than women in their 50s or 60s. However, the older women also reported fewer hot flashes and night sweats.

Susan says:
Quality-of-life questions have been a big concern regarding the use of Femara after tamoxifen. These findings will undoubtedly be interesting to women who are considering taking Femara after tamoxifen but are worried about how it will affect their quality of life.

But while these data may seem reassuring, it is important to keep in mind that the women who were studied were not on Femara for the full five years. It is possible that more problems will develop as women stay on the drug longer. In particular, I remain concerned about the effect Femara has on bone density, musculature, and joint pain as well as its cognitive effects. We need to follow women on Femara longer to know the full impact it will have.

- **Raloxifene (Evista) and Breast Cancer**

US researchers involved with the Continuing Outcomes Relevant to Evista (CORE) trial presented data on the ability of raloxifene (brand name Evista) to reduce breast cancer risk.

Evista, like tamoxifen, is a selective estrogen receptor modulator (SERM). It was specifically designed to provide the benefits that tamoxifen offers without also having the negative side effect of increasing a woman's risk for uterine cancer.

Evista's use for the prevention and treatment of postmenopausal osteoporosis was approved by the FDA in 1999. This approval followed findings from the MORE study (Multiple Outcomes of Raloxifene Evaluation). The MORE study enrolled 5,213 women in their 60s who had osteoporosis. The women were randomized to receive either Evista or a placebo for four years.

The MORE study found that Evista improved bone density by about 3 to 4 percent. This is not as good as alendronate sodium (brand name Fosamax), which improves bone density by 8 percent, but is better than a placebo. Further, Evista was found to only prevent fractures to the vertebrae, not hip fractures.

The MORE study also looked at whether Evista could prevent breast cancer in the low-risk women. The researchers found that 13 of the women on Evista developed invasive breast cancer after three years compared with 27 women on the placebo, a risk reduction of 76 percent.

The CORE trial was a double-blind four-year follow-up to the MORE study. All of the 5,213 women involved in the MORE study were eligible to enroll in the CORE study, and 3,996 chose to participate. The primary aim of the CORE study was to evaluate the effect of eight years of treatment with Evista on the incidence of invasive breast cancer.

During the eight years the women were in the CORE and MORE trials, there were 61 cases of breast cancer that developed, with 31 occurring in the Evista group and 30 in the placebo group. Of these, 52 were invasive breast cancer, with 24 occurring in the Evista group and 28 in the placebo group.

Estrogen receptor status was determined for 46 of the 52 invasive breast cancer cases, and the researchers found that the incidence of ER-positive disease was smaller in the Evista group. Based on these findings the researchers concluded that eight years of use of Evista in postmenopausal women with osteoporosis can reduce the incidence of invasive breast cancer, specifically ER-positive invasive breast cancer.

The only serious side effect of Evista after eight years was an increased risk of blood clots in veins and in the lungs. There was no increased risk of stroke or heart attack.

Susan says:
Lilly, which makes Evista, is clearly trying to find a home for the drug in breast cancer treatment. But there are a couple of things we need to take into consideration in evaluating the findings from the MORE and CORE studies.

First, it is important to note that all of the women enrolled in the MORE and CORE studies had osteoporosis, and women with osteoporosis have a very low incidence of breast cancer to begin with. That's because the fact that they have developed osteoporosis is an indicator that they have had less exposure to estrogen. (Women who have been exposed to more estrogen have both stronger bones and a higher incidence of breast cancer.) We don't know if the results would be the same in other women.

Secondly, the absolute number of breast cancers that Evista prevented is very small—four (24 compared to 28). Lilly will point out that this is a risk reduction of 62 percent, which sounds large. But whenever we talk about risk reduction we need to talk about absolute numbers as well. Risk reduction, as a percentage, doesn't tell the whole story. It is still premature for any woman to take Evista for breast cancer prevention.

Treatment for Young Women

- **Ovarian Ablation, Tamoxifen, and Chemotherapy in Premenopausal Women with Early Breast Cancer**

Researchers from the United Kingdom reported results from the National Cancer Research Institute Adjuvant Breast Cancer International trial. The trial was designed to evaluate whether ovarian ablation provided an additional benefit for premenopausal women with early stage (I–IIIa) breast cancer who were receiving tamoxifen or tamoxifen and chemotherapy.

The Phase III trial enrolled 2,144 women; 1,063 had ovarian ablation, 1,081 did not. Of the women who had ovarian ablation, 68 percent had radiation to stop the functioning of their ovaries, 23 percent had their ovaries surgically removed, and 8 percent took LHRH (luteinizing hormone-releasing hormone) agonist drugs, like goserelin (brand name Zoladex), that put a woman into temporary menopause.

All of the women received tamoxifen for five years, and 80 percent of the women had chemotherapy, with most receiving CMF (cyclophosphamide, methotrexate, and 5-fluorouracil).

During five years of follow-up, 565 women relapsed and 418 died. The researchers found that the likelihood of a woman relapsing or dying was not related to whether she had ovarian ablation. This was true regardless of age, nodal status, or hormonal status.

Susan says:
Many young women diagnosed with breast cancer are eager to learn more about whether ovarian ablation can improve their chances of survival. The problem with the data reported from the NCRI trial at ASCO is that it does not provide information about how many women developed amenorrhea (had their periods stop) as a result of having chemotherapy. This is a significant omission from the abstract, since 80 percent of the women in the study had chemotherapy, and we know that women whose periods permanently stop due to chemotherapy would not benefit from having their ovaries surgically removed and have a better prognosis than do those women who get their periods back.

Not knowing how many of the women who did not have ovarian ablation became permanently amenorrheic due to chemotherapy makes it difficult to assess the findings from this study.

- **Taxanes and Chemotherapy-Induced Amenorrhea**

Researchers from Pennsylvania Hospital in Philadelphia discussed their research that explored whether adding taxanes to standard adjuvant chemotherapy regimens affects whether a premenopausal woman will develop amenorrhea (have her periods stop).

Data for the study was collected from a retrospective chart review of 159 breast cancer patients 50 years or younger who were premenopausal when they began chemotherapy. Women were designated "postmenopausal" if their periods had not returned within one year of completing chemotherapy.

Of the 159 women, 73 received AC (doxorubicin, cyclophosphamide) or CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) without a taxane, and 53 received AC or CAF followed by 12 weeks of a taxane—either paclitaxel (brand name Taxol) or docetaxel (brand name Taxotere).

The median age of the AC/CAF patients was 42 years and the median age of the AC/CAF and taxane group was 45 years. Of the women who received AC/CAF, 54 percent received subsequent tamoxifen compared to 60 percent of those who received AC/CAF and a taxane.

After treatment, 48 percent (51/106) of the non-taxane-treated group retained menstrual function, compared with 57 percent (30/53) of those who received a taxane. Based on this finding the researchers concluded that adding a taxane to either an AC or CAF regimen does not increase the likelihood that a woman will develop chemotherapy-induced amenorrhea.

Susan says:
Many young women diagnosed with breast cancer find when making treatment choices that they must weigh their concerns about future fertility against fighting a disease that can be fatal.

We know that women whose periods permanently stop due to chemotherapy have a better prognosis than do those women who get their periods back. That said, there are young women who are hormone-negative and who are hoping to maintain their fertility, and who will not benefit from developing amenorrhea. For these women it should be reassuring to know that adding a taxane to their treatment will not increase their risk of developing amenorrhea.

- **Chemotherapy-Induced Amenorrhea and Menstrual Cycle Phase**

Researchers from Rome, Italy, discussed a study that explored whether the phase of a woman's menstrual cycle at the time she starts chemotherapy can affect her chance of developing chemotherapy-induced amenorrhea (having her periods stop).

The researchers studied 88 premenopausal women with early stage breast cancer. The menstrual cycle was divided into four phases: menstrual phase, days 1–6; follicular phase, days 7–14; luteal phase, days 15–20; and premenstrual phase, days 21–28.

Amenorrhea occurred in 45 percent of the women who received CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) and in 47 percent of the women who received FEC/EC (5-fluorouracil, epirubicin, and cyclophosphamide followed by epirubicin and cyclophosphamide).

The study found that there was no significant correlation between whether a woman developed amenorrhea and her age, tumor size, number of axillary nodes, stage of disease, or hormone receptor status. They also found that the duration of chemotherapy (more or less than six courses) did not affect whether amenorrhea developed.

When they looked at menstrual phase, the researchers found that the incidence of amenorrhea was higher for women whose treatment began in the follicular phase than it was for those whose treatment began in the other menstrual cycle phases. Specifically, 68 percent of the women who started treatment in the follicular phase (days 7–14) developed amenorrhea, compared with 43 percent of the women who began treatment during the other three phases.

Susan says:
Timing of treatment in premenopausal women has been a topic of a growing body of research. The first prospective study on timing of surgery, which followed women for 10 years, found that 45 percent of the women who were operated on during the follicular phase of the cycle were still alive, compared with 75 percent of those who had surgery during the luteal phase. The study reported at ASCO has not followed women for 10 years, so we cannot ascertain if the timing of the start of chemotherapy had any impact on survival. We do know from other studies, however, that women whose periods permanently stop due to chemotherapy have a better prognosis than do those women whose get their periods back or those whose periods do not stop at all.

After the first study was released, I suggested that premenopausal women try to schedule their surgery during the luteal phase, or second half, of their cycle. Based on this study, I'd recommend that premenopausal women start chemotherapy during the follicular phase (days 7–14) of their cycle. It is easy enough to do, and might make a difference. An exception, after extensive consultation with an oncologist, might be made for women who have a good prognosis (they benefit less from developing amenorrhea), who are hoping to maintain their fertility.

- **The Gail Model and African American Women**

The Gail model is one of the models that have been developed to estimate a woman's risk of developing breast cancer. The Gail model is often used in research studies to evaluate which women are at high risk for developing breast cancer. A woman's risk is considered low if she has a Gail model score of less than 1.66 percent; it is considered high if she scores above 1.66 percent.

Although the model only has been validated on white US women, it is used to predict the risk of breast cancer in women of all race/ethnic groups. Researchers from Howard University in Washington, D.C., and Boston University discussed a research study that has explored the utility of the Gail model as a diagnostic predictor in African American women.

This study used data from the Black Women's Health Study, which gave women a questionnaire about their breast cancer risk factors. Women provided updates every two years about whether they had developed breast cancer or their risk factors had changed.

The researchers then compared 75 women who developed breast cancer with 75 women who did not. The women who developed breast cancer had a Gail score of 0.3 to 2.7 while the women who did not develop breast cancer had a Gail score of 0.2 to 2.4. The sensitivity of the Gail model—the number of women who had breast cancer who were actually deemed high risk by the test—was 14.7 percent (11/75). The specificity of the Gail model—the number of women who did not have breast cancer and who the test found to be low risk—was 93.3 percent (70/75).

Based on these findings the researchers concluded that the Gail model underestimates the risk of developing breast cancer among African American women, and is not an appropriate model for this population.

Susan says:
The Gail model is an attempt to quantify which women are at high risk for developing breast cancer. Questions have been raised about the Gail model since it was first introduced, and, as this study indicates, there are real concerns about the Gail model's ability to predict risk in populations other than white US women (and even among these women it has accuracy problems). This is a real problem because it may keep women who are high risk from qualifying for certain prevention trials, and one that increased attention and research needs to be focused on.

- **Horse Chestnut Seed Extract for Lymphedema Treatment**

Researchers from the University of Wisconsin, Madison, presented data from their study on the use of horse chestnut seed extract for treating lymphedema. This treatment is currently widely used in Europe to treat lymphatic problems.

To date, the researchers have enrolled 25 women in their study. Half of the women were randomized to receive 50mg of horse chestnut seed extract two times a day; the other half took a placebo twice a day.

After three months of treatment with horse chestnut seed extract, no statistically significant differences were seen in the amount of lymphedema in the women on the horse chestnut seed extract compared with the women on the placebo. The researchers are continuing to accrue women into the study, and will conduct future analyses on this larger sample size.

Susan says:
Lymphedema is a frustrating chronic problem experienced by many breast cancer survivors whose treatment included extensive lymph node dissection or radiation.

More research on lymphedema is needed. It is encouraging that alternative treatments like horse chestnut seed extract are being studied, even if the treatment is not found to be effective. All too often alternative treatments become popular based on anecdotal evidence rather than actual research studies.