Dear Readers,

The American Society of Clinical Oncology meeting (ASCO) took place at the beginning of June. It is the single largest international clinical cancer meeting that takes place every year. The more important results from that meeting are first reported to the public by the media. Over the next few months, I will review major results for you and help you integrate them into your thinking.

Best regards,

Dr. Silvana Martino

The Angeles Clinic FOUNDATION

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Breast Cancer Advisor

BY DR. SILVANA MARTINO • June 2013

What's Inside

BIOLOGY BASICS

Breast Cancer in Men

In this issue, I will continue the theme of male breast cancer. The focus will be on adjuvant therapy decisions. Adjuvant therapy refers to drug therapy given after the initial breast cancer surgery. Its purpose is to eradicate any remaining tumor cells that might be left behind and which may then become the source of a recurrence. These therapies reduce recurrence rates and, also, improve survival rates.

As in women with breast cancer, the decision about the need for drug therapy as an additive to local therapy (surgery and radiation) is based on the probability of developing distant metastases. This assessment is based on (1) lymph node involvement, (2) tumor size, (3) hormone receptor status of the tumor, (4) HER2 status of the tumor,

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(5) the overall medical health of the patient and, (6) the preferences of the individual patient.

Our knowledge about specific adjuvant therapies for men with breast cancer is limited. The reason for this is because of the rarity of this diagnosis. The American Cancer Society estimates, that in 2013, there will be 2,240 men diagnosed with breast cancer in the U.S. This number is too small to be able to perform studies that include only men. We would have to find a method by which every man with breast cancer was included in a study in order to have sufficient numbers to achieve the necessary statistical power. This degree of national cooperation and coordination is difficult and has yet to be achieved. Consequently, adjuvant trials comparing various therapies generally either exclude men or, if they included them, will not contain enough men to be able to look at the outcome in men as a separate group. The bottom line is that how we treat men with breast cancer is primarily based on knowledge obtained from studies done on women. Generally speaking, male breast cancers respond in the same manner as breast cancers in women; therefore, the same basic principles are applied.

The basic principles are the following: (1) If a tumor is HER2 positive, treatment includes HER2 directed therapy, such as Herceptin for one year. Chemotherapy (usually Adriamycin, Cytoxan, and a taxane or taxotere and carboplatin) is given in conjunction with this, (2) If the tumor is hormone receptor positive, as are most breast cancers diagnosed in men, hormonal therapy is given for a minimum of 5 years. Tamoxifen is still the hormonal therapy most commonly used. There are limited data using the aromatase inhibitor family of hormones (Femara, Aromasin and Arimidex) in men with early breast cancer. Therefore, even though in postmenopausal women with breast cancer, the aromatase inhibitors have primarily replaced tamoxifen, this is not the case in men, (3) The decision to use chemotherapy and the choices of drugs used for men with early breast cancer is the same as in women. Chemotherapy is given in conjunction with Herceptin if the tumor is HER2 positive. It is administered if lymph nodes are involved. It is also used if the tumor is triple negative (hormone negative and HER2 negative). In node negative and hormone receptor positive tumors, chemotherapy is added if the risk of relapse is judged to be high in spite of treatment with hormonal therapy.

Commonly used chemotherapy choices are the same as in women and include the following:

- Adriamycin/Cytoxan-Taxane (AC-T)
- Taxotere/Cytoxan (TC)
- Taxotere/Adriamycin/Cytoxan (TAC)
- Adriamycin/Cytoxan (AC)
- Cytoxan/Methotrexate/5- Fluorouracil (CMF)

Previous Issues

You can review all previous issues of the Breast Cancer Advisor on our website at:

www.theangelesclinicfoundation.org

click on the NEWSLETTER tab

BIOGRAPHY

Dr. Silvana Martino

is the Director of Breast Cancer Research and Education at The Angeles Clinic Foundation in Santa Monica, California. She is board certified in internal medicine and medical oncology. Dr. Martino has specialized in the treatment and research of breast cancer for over three decades. She is a nationally recognized leader in the field of breast cancer. Her body of work has included research in breast cancer prevention, treatments for early breast cancer and metastatic disease. Dr. Martino has conducted and coordinated large national and international studies which have resulted in changing the standard of care worldwide.

Dr. Martino's Curriculum Vitae

WHAT'S NEW

Tamoxifen—Continued Benefits

For the past two decades, the recommended use of adjuvant tamoxifen for newly diagnosed breast cancer has been for a total of 5 years. The conclusion reached from data gathered in the 1980's and 1990's was that therapy with tamoxifen beyond 5 years resulted in more side effects but did not reduce recurrence from breast cancer. In fact, some believed that longer use would result in the development of new breast cancers that had a more aggressive biology. Though not all agreed with this conclusion, the majority prevailed and the 5 year time period became the standard.

Two additional studies were then organized to continue to look at this question. One of these studies, the ATLAS trial, was reported in December, 2012, at the San Antonio Breast Cancer Symposium. It compared tamoxifen use for 5 years versus 10 years. It reached the opposite conclusion. Specifically, the patients who were given tamoxifen for 10 years had fewer recurrences and had a better survival rate. Please review the January 2013, issue of the Breast Cancer Advisor for details.

The second study was presented at the recent Society of Clinical Oncology (ASCO) meeting. This study, called the aTTom trial, was presented by Dr. Richard Gray from the United Kingdom. In the aTTom trial, 6,953 women with early breast cancer who had been taking tamoxifen for five years and who had not had a recurrence were randomized (like the flip of a coin) to either continue taking tamoxifen for another 5 years (10 years total) or stop after 5 years. The group has now been followed for longer than 10 years. What has been observed, is that there were 580 recurrences among women who had taken tamoxifen for 10 years versus 672 recurrences in the group who had taken tamoxifen for only 5 years. More importantly, there were 392 deaths from breast cancer among those who had taken tamoxifen for 10 years and 443 deaths among women who only took it for 5 years.

> *"I think it is now clear that the conclusion that was reached 20 years ago suggesting that 5 years of tamoxifen was the optimal length of treatment was not correct."*

There were more side effects with longer use of tamoxifen. These include continued menopausal symptoms such as hot flashes, night sweats and poor sleep. The rare, yet more serious side effect of endometrial cancer, remains a problem with prolonged use. In the aTTom trial, there were 102 cases and 37 deaths (1.1%) from endometrial cancer (cancer of the uterus) in the 10-year group compared with 45 cases and 20 deaths (0.6%) in the 5-year group.

The results of the aTTom trial mimic the results of the ATLAS trial. Each trial included nearly 7,000 women. Taken together, I think it is now clear that the conclusion that was reached 20 years ago suggesting that 5 years of tamoxifen was the optimal length of treatment was not correct. There is now sufficient evidence that 10 year is better than five years. It is also clear that the side effects persist and those patients must be closely monitored for the entire period. This revised use of tamoxifen therapy should be applied to men with breast cancer as well.

Allow me again to remind you that for most women who are postmenopausal, tamoxifen is not the preferred hormonal therapy, but rather, it is the aromatase inhibitors.

QUESTIONS & ANSWERS

(Q) Dr. Martino, I had breast cancer diagnosed 12 years ago. It has now come back in my bones and my lungs. I am now on hormonal therapy, and I am also receiving radiation to one of the bones in my left leg. I feel well. My oncologist told me that he expected my tumor to go into remission. He said that I had a good chance of that happening. I have a neighbor who is a nurse and when I told her about my condition, she said that all I was receiving was palliative care for my cancer. She said that this will not cure me. I don't understand. If I have a remission, won't I be cured?

(A) It is important to understand the meaning of the word "remission" as it is commonly used in oncology. By classical definition, in solid tumors such as breast cancer, lung cancer, colon cancer, etc., the word remission is used when referring to a person whose disease has spread away from the organ of origin and is now apparent in other parts of the body. In your case, the cancer started in the breast and spread to your bones and lungs. All the therapies that are now available as treatment in this setting are used with intent to reduce or shrink the tumors. If enough shrinkage is accomplished, that person's tumor is said to have gone into a remission. Most of the time the tumors shrink partially and not completely and this is then called a partial remission. At times, the tumors shrink enough that all of the scans and x-rays and blood tests are back to normal. This is labeled a complete remission. In both of these situations, at some later point in time, the tumor will start to grow again. Given this pattern, all of the therapies that are given are appropriately referred to as "palliative". The term "curative therapy" is used in situations where the treatments are expected to prevent the tumor from ever coming back in any location. This is most often the case when a person is first diagnosed with breast cancer and the tumor appears to be limited to the breast and perhaps a few lymph nodes.

(Q) Dr. Martino, my mother has had advanced breast cancer for some years. She did well originally, but now her doctor has informed us that there is nothing more that he can do. He has advised hospice care to which my mother has agreed. She is now at home with me. The hospice people are all very nice and we like them. The problem is that we now have a new doctor who is managing her care and my mother misses her own oncologist. He appears to be no longer involved. Would it be wrong for us to call her original oncologist?

(A) No, I do not think it is wrong for you to call your mother's original oncologist. Though it sounds like he is no longer managing her day to day care, as that is being done by the hospice doctor and the hospice team, there is still a relationship between him and your mother. It is likely that the hospice team is keeping him up to date on how your mother is doing. Often, doctors have a choice of whether they wish to remain the primary doctor or they wish for the hospice doctor to take over when one of their patients is with hospice care. Increasingly, oncologists will allow the hospice doctor to take over, since they are experienced at managing this phase of care, and the nursing and other support staff of a hospice is accustomed to working with their own doctor. The problem of feeling distanced or abandoned by ones primary oncologist that your mother is now experiencing is sadly all too common in today's fractioned medical system. It is, in part, a consequence of overspecialization. Nevertheless, a good oncologist is trained with the knowledge that a patient is always their patient. Providing end of life care is always difficult, but most of us recognize it as our sacred duty. We prefer to believe that our attention and relationship remains important to our patients even when we have no further drugs to offer that patient. I believe that your mother's doctor would prefer to know that your mother still values their relationship. Yes, you should make the call.

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Breast Density—A New Law

On April 1, 2013, California Senate Bill 1538 (Health Care—Mammograms) became law. The bill requires that facilities performing mammograms notify women if they have "dense breasts," so they can consider discussing "further screening options" with their doctors. California became the fifth state to enact such a measure, following Connecticut, Texas, New York and Virginia. The bill was authored by Senator Jo Simitian (D-Palo Alto) after being suggested by Amy Colton of Soquel, California, who submitted the idea to the senator's "There Ought To Be a Law" contest in 2011. Ms. Colton, apparently, had found out that she had "dense breasts" only after completing treatment for breast cancer, which her mammograms reportedly had failed to detect.

What does "dense breasts" mean, anyway?

The breast is composed of four elements: (1) the lobules (the actual glands), (2) the ducts (that carry the milk), (3) the adipose tissue (fat) and (4) the fibrous connective tissue ("scaffolding" which holds everything together).

Density is measured on mammography and is determined by the amount of water-containing structures (lobules, ducts and fibrous connective tissue) present relative to the amount of fat. The water-containing structures appear white, while the fat appears dark on mammograms. The more fibroglandular structures that are present in a breast and are seen on a mammogram, the higher the density.

Why is breast density important?

There are two primary concerns regarding the amount of fibroglandular tissue present on mammograms. The first is that mammograms of breasts that are dense are more limited than mammograms of breasts that are not dense (i.e., "fatty"). Simply put, it is more likely that a cancer present in a dense breast will be obscured and, therefore, not recognized, than a cancer present in a fatty breast. The reason for this is that many cancers have the same x-ray attenuation as that of the dense, fibroglandular tissue. That is, both the cancer and the dense normal tissue appear white on mammography, and the margins of each may not be perceptible. In contrast, the white of the cancer may stand out against the dark appearance

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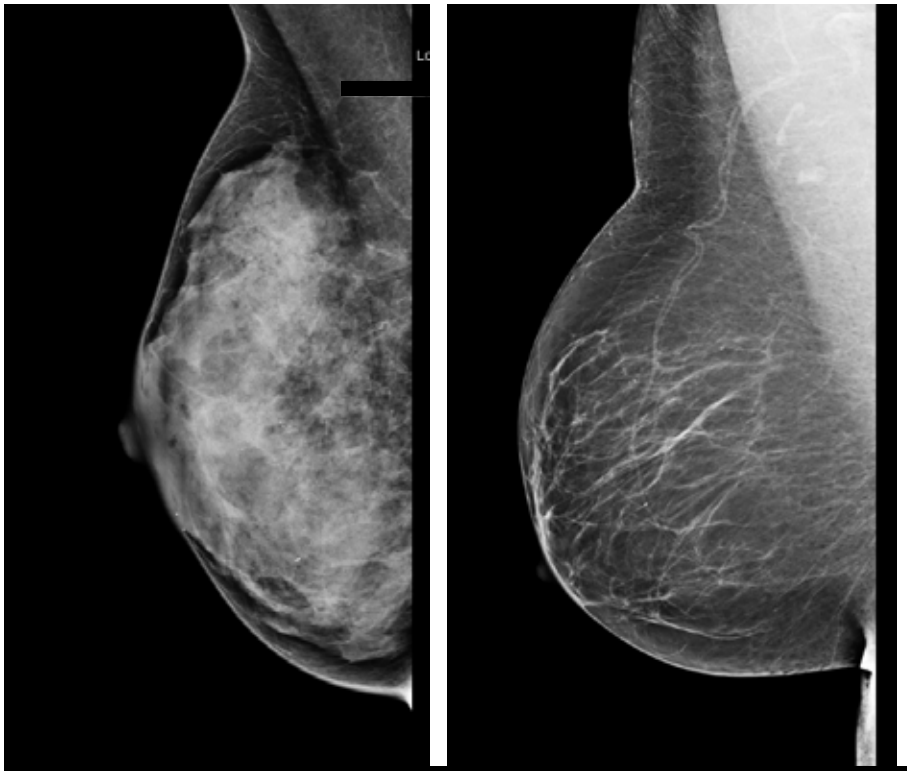

The mammographic spectrum of breast density:

(far left) right MLO view demonstrating density category 4, "extremely dense"

(left) right MLO view demonstrating density category 1, "almost entirely fatty"

Many cancers project white on mammograms, and can, therefore, be obscured by the also white fibroglandular tissue, which is more abundant in dense breasts.

of the fatty tissue, making it much more likely to be identified. To identify cancer in a dense breast, one must rely on secondary signs that reflect changes in the tissue surrounding the cancer, such as spiculations or distortion of the architecture, which are often subtle, if visible at all. This limitation of mammography in dense breasts is well known by radiologists that interpret mammograms and is noncontroversial. In contrast, ultrasound is not based upon these same x-ray attenuation principals, and, therefore, can detect some of these mammographically occult cancers. Breast MRI is even better at detecting them. This is one of the reasons why some have advocated "additional screening options" for women who have dense breasts. (There are other reasons, not discussed here, why neither ultrasound nor MRI can actually replace mammography for screening at this time).

The second concern is the possibility that having dense breasts in and of itself confers a higher risk of developing breast cancer; in other words, that there is an actual relationship between breast density and developing breast cancer. This notion is currently a hot topic, particularly in the lay media, and appears to be encouraged by companies who manufacture software designed to quantitatively measure breast density on a mammogram. Careful review of the pertinent studies and the actual data paints a much more ambiguous picture. It turns out, that it is deceptively difficult to determine what, in fact, constitutes a "dense breast." It does seem likely that there is a slightly increased risk of breast cancer in women whose breasts are subjectively considered to be dense. Most breast imagers believe that further study is necessary prior to incorporating breast density data into screening guidelines.

The decision of whether or not to pursue additional screening with breast ultrasound or MRI is complex. It should be remembered that mammography is the only modality that has actually been proven by studies to reduce mortality from breast cancer, and annual (or biannual) mammography after the age of 40 is recommended for screening by all medical organizations. Family history, results of any previous breast biopsies and other personal risk factors, as well as breast density, should all be taken into consideration when making this decision. This is a discussion that is best done with your breast care physician.

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The Angeles Clinic Foundation is a nonprofit organization whose purpose is to sponsor and support programs, services, education, advocacy, and research related to cancer. Our goal is to make a difference in all aspects of the lives of people touched by cancer. Your support is important in the fight against cancer and the journey towards a cure.

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