Breast Cancer Advisor

BY DR. SILVANA MARTINO

October 2014

Dear Readers,

October is Breast Cancer Awareness Month. It is a time to focus not only on the persistent need to stress the value of early detection, but also the time to appreciate the many advances that have been made in the field. In this issue, I will summarize some key points from the recent 2014 Breast Cancer Symposium.

Best regards,
Dr. Silvana Martino

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

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REPORT FROM THE 2014 BREAST CANCER SYMPOSIUM

This meeting is sponsored by several breast cancer organizations including the American Society of Clinical Oncology, the American Society of Breast Disease, The American Society of Breast Surgeons, the American Society for Radiation Oncology, the National Consortium of Breast Centers, Inc. and the Society of Surgical Oncology. The intent has been to create a truly multidisciplinary meeting, and this element is apparent throughout the meeting. Though some of the presentations are dedicated to new information, considerable time is given to in-depth discussion of topics that reflect the changing management of breast cancer.

I will summarize what I considered key points from this meeting.

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The Angeles Clinic FOUNDATION

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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SURGICAL MARGIN SIZE

As standard practice, when a portion of breast tissue containing a cancer is surgically removed, the tissue is covered with various colors of ink to designate the various edges such as right, left, etc. Margin size, as viewed under a microscope, is determined by the pathologist and is the distance between the tumor and the inked edges.

The issue of how much surrounding normal tissue should be removed along with a cancer has been a hotly debated and contentious issue. The prevailing opinion has been that if a surgeon removed a larger amount, the probability that a tumor would regrow at its initial site (a local recurrence) would be proportionately decreased. This approach was based on observations made years ago with mastectomy specimens demonstrating that with a 1 cm margin, remaining cancer was found in 40% of specimens, with a 2 cm margin, 17% of specimens had residual disease and even with a 4 cm margin, remaining cancer was found in 10% of specimens. Though these findings are concerning, the problem has been that as we evolved to treating most breast cancers with a lumpectomy rather than a mastectomy, obtaining large margins resulted in compromised cosmetic results. More recent observations have led to a new conclusion. It has become apparent that the addition of radiation to a lumpectomy greatly reduces the rate of local recurrence. The same is true for the use of systemic drug therapy. Both radiation and systemic therapy together are even more effective. These modalities have made the need for large margins less necessary. Equally as important has been the observation that it is the underlying biology of a tumor that determines both the probability of distant spread and the probability of local recurrence. Less aggressive lesions such as hormone positive cancers are less likely to recur locally than HER2 positive and triple negative cancers.

With this new knowledge, new guidelines for margin width when doing a lumpectomy have been promoted. The new recommendations are simply that there be no cancer cells at the very edge of what is removed and marked with ink. New data have demonstrated that a margin width of 1, 2 or 5 cm do not result in different local recurrence rates, and are not superior to no tumor at the inked edge.

These new guidelines only apply to a lumpectomy when performed as treatment for an invasive breast cancer. They do not apply to a lumpectomy when done for pure ductal carcinoma in situ (DCIS) or for patients treated in the neoadjuvant fashion. Similarly, they do not apply to those treated with a mastectomy.

I anticipate that it will take some time before all clinicians accept these guidelines. In part, this is due to the fact that most of us have been trained to change our behavior based on large randomized trials with long term outcomes. There are no such trials on this issue. Nevertheless, there is collectively a reasonable amount of data leading to a general consensus and the proposed national guidelines.

GENETIC TESTING

Dr. Kristie Bobolis from Capital Hematology Oncology Group provided an excellent update on genetic testing for the purpose of predicting breast cancer risk. The concept of inherited breast cancers is based on the principle that two errors must occur to our genetic material for cancer to occur. In hereditary breast cancers, one is born with one error in place and only one more needs to occur during an individual's lifetime for the cancer to manifest itself. The BRCA 1 and 2 mutations remain the mutations thus far identified that are most predictive of risk. The rate of these mutations in the Ashkenazi Jewish population is one in forty and one in five hundred in the general population. The BART mutation,

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where large parts of a gene have been rearranged, occurs less than five percent of the time. Several additional mutations have now been identified, but are much less common. These include P53, PTEN, STK11, CDH1 and PALB2. These are associated with very specific clinical syndromes. In general, younger age at diagnosis suggests an inherited genetic abnormality. However, in patients with triple negative breast cancer, age should be ignored and testing is advised.

Breast cancer screening is strongly encouraged for women who carry the BRCA 1 and 2 genes. The NCCCN has updated their recommendations in 2014 and now advises that yearly MRI screening begin at age 25 with mammography added at age 30. This level of intensive screening may be discontinued when a woman reaches the age of 70 to 75.

The degree of benefit derived from the use of tamoxifen as hormonal therapy for primary breast cancer prevention is questioned in women with a known BRCA 1 mutation, since most cancers seen in this population are hormone negative. It is advised in those with BRCA 2 and unknown mutations.

Genetic testing is now being offered by many companies, each of which has a "panel" of genes that they test. Clinicians remain uncertain as to what to do with some of the expanded gene testing that is now available, as there is limited outcome data with much of the added information. It may be best to have your own testing performed by a company that has been doing it for a while.

RISK FROM ATYPICAL HYPERPLASIA

An excellent presentation on atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH) was given by Dr. Lynn Hartmann from the Mayo Clinic. These two entities represent early changes that at times are seen in a breast biopsy. They are not cancer, but are tissue changes that are known to increase the risk of developing breast cancer. Their importance is at times unappreciated. I have seen occasions when patients have been told that their biopsy was benign, which in absolute terms is correct, yet appropriate follow up and education had not been provided. These lesions are twice as common as ductal carcinoma in situ (DCIS).

Both ALH and ADH carry the same risk for breast cancer. They each increase risk four fold. This risk is not affected by family history. It is affected by the number of foci of ALH and ADH found. Both types of lesions have been demonstrated to result in an incidence of breast cancer of 1% per year. Therefore, the risk is 10% by year ten and 30% by year thirty. The increased risk of cancer is shared by both breasts but is somewhat more prevalent in the breast where the atypical hyperplasia was identified.

Women with atypical hyperplasia have been included in breast cancer prevention trials with hormonal therapy such as tamoxifen and the aromatase inhibitors. These agents are effective in this setting and are reasonable therapeutic options.

DUCTAL CARCINOMA IN SITU

One of the dominant results of screening mammography has been an increase in the diagnosis of ductal carcinoma in situ. This has led to a major debate about whether this is a good or a bad thing. From one perspective, it is recognized that DCIS is a precursor of invasive breast cancer. From another perspective, the fact that not all patients with DCIS go on to develop an invasive breast cancer during their lifetime can be viewed as unnecessary and as over diagnosis. Presentations were given in support of both sides of this issue. A central question is whether we can identify patients in whom a diagnosis of DCIS is made on core biopsy who can be left without further treatment. It is believed that such patients do exist. The issue is how to identify them correctly. Data demonstrate that from 20% to 40% of patients who have a

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diagnosis of DCIS on core biopsy will be found to have invasive cancer when further surgical resection is done.

There is presently an international study ongoing that uses certain clinical and pathological parameters to define "low risk DCIS" and to then randomize patients to observation only versus further therapy. Whether such a trial could be performed in the U.S. is uncertain. Most believe that U.S. women with a biopsy result of DCIS would not allow themselves to be randomized to simply being observed. There is no resolution to this question at this point. As we further improve the diagnostic technology for screening, it is likely that DCIS will become an even bigger problem.

LOCAL AND REGIONAL RECURRENCE AFTER NEOADJUVANT CHEMOTHERAPY

The neoajuvant approach where, a portion or all of the drug therapy is given prior to surgery was originally suggested for two reasons: (1) to reduce tumor size so more patients could have a lumpectomy rather that a mastectomy and, (2) to determine if giving the drugs earlier would improve survival. Thus far, the first expectation has been met, but the second has not.

Another question has now evolved; if a lumpectomy is performed after neoadjuvant therapy, what determines the probability of recurrence in the breast and local lymph node area? Are the principles the same as when a lumpectomy is done prior to adjuvant therapy or are they different? This topic was addressed by Dr. Eleftherios Mamounas based on data pooled from the collaborative trials in neoadjuvant breast cancer (CTNeoBC). More than five thousand patients were included in this data-base, and were followed for 42 months. These are retrospective data. The conclusions were that, in patients treated in the neoadjuvant fashion, tumor subtype and achievement of a pathological complete response (no remaining invasive tumor in the breast or neighboring lymph nodes) affected local and regional recurrence rates. The rate of recurrence was highest in patients with hormone negative/HER2 positive and triple negative breast cancers. What we are learning, is that in all circumstances, the underlying nature of the individual's breast cancer remains very influential in determining outcome.

Dr. Gunter Von Minckwiz from the University Frankfurt added some interesting points to the discussion on neoadjuvant therapy. Some tumors respond very well to this approach and appear in essence to completely disappear from the breast (pCR). This has prompted some to speculate as to whether, in such patients, surgery is needed at all. In a group of 150 patients, who on biopsy of the breast post chemotherapy had achieved a pathological complete response, his group did further resection and found, that often, there was residual disease near the area of biopsy. He concluded that patients who achieve a pCR cannot avoid further surgery and radiation. He also reported on experience from the Royal Marsden hospital in the UK, where patients achieving a pCR received radiation without surgery experience a 30% rate of local recurrence. This suggests that surgery post adjuvant therapy cannot be avoided. This answer may change as our systemic therapies become more effective, but for now, all patients who undergo neoadjuvant therapy need to undergo surgery with a lumpectomy or mastectomy and also radiation when appropriate.

IMMUNE MODULATION AS A NOVEL STRATEGY IN BREAST CANCER

The idea of using the immune system to fight breast cancer is not new. Many years ago, skin lesions were injected with general immune stimulants with some success. More recently, vaccine therapies, both of a general anti-breast cancer nature or designed to be specific to individual patients, were developed and administered with limited success. It has only been with a clearer understanding of how the immune system works that

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DISCLOSURE

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a new wave of immune-based approaches have started to proliferate throughout the field of oncology. Other tumor types, especially melanoma, have led the way in this type of therapy. Breast cancer has been slower in making inroads in this arena. Nevertheless, clinical trials are now ongoing both in metastatic disease and in the adjuvant setting.

Several points have already been learned: (1) some tumors are infiltrated with lymphocytes which are a type of white blood cell with immune properties. Patients whose tumors have this characteristic are more likely to have a good response to therapy. This is especially true for HER2 positive and triple negative breast cancers where pathological complete responses are more frequent, (2) it has been observed in animal models that if a tumor is damaged by cold temperature (cryoablation), immune therapies appear to be more effective. This concept is now being studied in human breast cancer, (3) some immunotherapies have been studied in combination with hormonal therapy. Thus far, only stability of disease has been observed in early studies with this combination. Among the many fields of study in cancer biology, it is this field which at present is the most exciting.

SURVIVORSHIP ISSUES

One of the greatest accomplishments in the field of breast cancer is the fact that there are now many women and men who have been diagnosed with breast cancer in the past who remain alive and without recurrence. The field has had to think about how to observe this population during the rest of their lifetime and also to recognize that there are special issues that they and their families deal with even years after a diagnosis of breast cancer. Some of these issues are inherent in the diagnosis, some are results of our therapies, some are simply part of the aging process and of life itself.

SURVEILLANCE

One important issue discussed was how to follow patients once their initial therapy of surgery, radiation and chemotherapy is completed. The present recommendations are that patients be examined no more than every six months. There are no laboratory studies recommended, including no tumor markers, scans or x-rays, other than of the breasts. What is actually done varies greatly from country to country and among individual physicians, many of whom continue very "active" surveillance. It appears that we in the U.S. do the most "active" surveillance. It is also apparent that many medical oncologists in the U.S. function in part as primary care physicians and provide other services for their patients beyond cancer surveillance. Many U.S. patients are reluctant to separate from their medical oncologist and transfer their care to primary care physicians or physician extenders. This has certainly been true in my own practice. The problem with all of this is that of increased cost to an already overburdened medical system.

The basis for thinking that more intensive surveillance is not valuable is based on three old and underpowered studies. These studies demonstrated that survival was not improved with more intensive surveillance. Many of us recognize that this important question should be subjected to a modern and adequately powered trial. The national cooperative group, SWOG, has calculated that such a trial would require at least 10,000 patients followed long term. The cost of doing such a trial would be very high. In the U.S., there is tremendous reluctance among physicians to enroll their patients in such a trial. Consequently, it is unlikely to be done.

DEPRESSION AND ANXIETY

Depression and anxiety as persistent and chronic features were discussed. For many, the fear of relapse and death does not resolve. Some patients retain a feeling of aloneness. Some live with a feeling of hopelessness which increases their risk for suicide. To some degree, one can identify those who are at increased risk for long term negative feelings. They are patients with a prior history of depression and those who are unemployed.

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The nature of one's personal relationships is also important. It appears that distressed relationships tend to remain that way and are not improved with a diagnosis of breast cancer. Separation and divorce are more common.

It is recognized that the emotional effects of a diagnosis of breast cancer are not limited to the patient, but must be recognized as a family event. Emotional support must be extended to the adults and children that surround the patient as well. Support groups recognize this phenomenon and many provide programs that include family and friends.

OBESITY

Data have demonstrated that obese breast cancer patients have a higher rate of both distant recurrence and death. This relationship has been demonstrated for hormone positive and hormone negative disease and for both pre- and postmenopausal women. Physical activity and weight loss have been shown to decrease death rate from breast cancer. Several mechanisms are proposed and may explain these findings. Increased weight is associated with an increase in estrogen level, insulin level, glucose level and an increase in inflammation. Even a minimum weight loss of 5-7% has been shown to improve outcome. Physical activity is believed to be beneficial beyond simply aiding in weight loss. A minimum of 150 minutes of exercise per week is advised.

The relationship of diet and breast cancer recurrence is less clear. Whether it is specific foods that are critical or whether the issue is weight control is still not resolved.

PROGNOSIS OF SMALL INVASIVE LESIONS

The Oncotype DX assay was originally developed to assist oncologists and patients in deciding the benefit of adding adjuvant chemotherapy to hormonal therapy as treatment for hormone positive, node negative, HER2 negative breast cancers. It has proved very useful for this purpose and has resulted in many women avoiding chemotherapy. Dr. Christy Russell from the University of Southern California presented interesting data using the Oncotype DX assay in a group of about 600 patients with tumors that measured less than 1 cm. Performance of the assay demonstrated that 60% of these very small lesions had a low Oncotype DX score, 15% were intermediate and 15% had a high score, suggesting a more aggressive biology and a need for chemotherapy.

I found these results important because screening mammography has resulted in an increasing number of patients with very small lesions. We generally do not advise chemotherapy for such small lesions. This study points out that size alone is not adequate criteria to decide biology. Some small lesions can be very aggressive and need to be treated in a more aggressive manner. The Oncotype DX assay and other similar assays add knowledge beyond simple clinical criteria and can be useful in making treatment decisions.

BREAST CANCER SCREENING

No conference on breast cancer would be complete without a discussion on the value and pitfalls of breast cancer screening. As our readers know from prior issues of the Breast Cancer Advisor, what for many years appeared to be a widely accepted principle that screening the general female population starting at age 40 resulted in less deaths from breast cancer, has recently been challenged. The challenge is not restricted to the U.S. Other countries, have had various policies on what age group to screen, how often to screen and how many views of the breast to perform. A Canadian study, considered by some to have been flawed in design and conduct, has recently fueled this argument. The controversy has had consequences as, in the U.S., we have seen the rate of screening mammography decrease in recent years. In part, this controversy has led to creating a distinction between the concepts of over diagnosis versus over treatment. Each must be considered carefully.