

Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

This issue of the Breast Cancer Advisor begins our fourth year of publication. During the past three years, the number of subscribers has continued to expand throughout the country and abroad. About 40 percent of those who receive the Breast Cancer Advisor now are physicians and nurses. I am particularly pleased that the Breast Cancer Advisor accepts no pharmaceutical funding, allowing us to continue to bring you information free of commercial bias.

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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BIOLOGY BASICS

PREGNANCY ISSUES IN BREAST CANCER

The relationship between pregnancy and breast cancer is complex. Some aspects were noted long ago and some are more recent. Some aspects pertain to the risk of developing breast cancer and some relate to the effect of pregnancy following breast cancer.

Decades ago, it was observed that women who had many children appeared to be less likely to develop breast cancer. Though there may still be some relationship to total number of births, with time, this observation was refined, as it was appreciated that women who bore their children at a young age were less likely to develop breast cancer. There has been some controversy as to what the ideal "young age" is, but most studies suggest that the optimal age is before 18 or certainly

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BIOLOGY BASICS continued

before age 20. Perhaps the issue is less how many children a woman has, but rather how early she begins the process. This implies that some beneficial or preventive effect occurs as part of the biology of pregnancy. An observation made in a large group of women with breast cancer that were part of a large study conducted in Michigan was that women with three or more interrupted pregnancies had more breast cancer. This suggested that it was not simply being pregnant but rather carrying a pregnancy to completion that is protective.

These observations were further elucidated by work done by Drs. Jose and Irma Russo with whom I had the pleasure of working at the Michigan Cancer Foundation. They demonstrated that mice that became pregnant develop less breast cancer when exposed to a carcinogen compared to nulliparous mice. Further, once the animals became pregnant, if the pregnancy was terminated, there was a detrimental effect. The earlier their pregnancy was terminated, the higher the rate of breast cancer that could be induced in the mice. Drs. Jose and Irma Russo further demonstrated that if one studied the breast tissue of these animals, one could observe that the process of pregnancy changed the breast tissue. It became more differentiated; a state when tissue is known to be more resistant to carcinogens. This led to the hypothesis that perhaps if young women were given the pregnancy hormone HCG, which they suspected might be the key hormone in this process, and in so doing create an artificial state of pregnancy, the women might be made resistant to breast cancer. We never tested this hypothesis in humans, but I still ponder it periodically.

Many studies have also shown that women, who breast feed their children, especially if longer than a period of six months, have

a decreased susceptibility to breast cancer. This observation fits well with animal evidence suggesting that the differentiation that occurs in breast tissue in preparation for milk production is protective.

Several studies have demonstrated that women who have their first pregnancy later in life, in their late thirties or forties, have a higher rate of breast cancer compared to women who never bear children or who begin the process at a young age. An observation that has been made from many countries is that as the female population delays the age of child bearing, as often occurs when an increasing number of women acquire a higher education, the rate of breast cancer in the country increases.

Paradoxically, it has recently been noted that when a woman does have a pregnancy, for about five years thereafter, her risk of breast cancer is higher.

In a subsequent issue, I will discuss pregnancy during and after a diagnosis of breast cancer.

WHAT'S NEW**THE ALTO TRIAL: AN IMPORTANT LESSON?**

Within the past 10 years, nothing has caused more excitement within the field of breast cancer than the observation from several trials that the addition of trastuzumab (Herceptin) to chemotherapy greatly improved disease free and overall survival in HER2 positive breast cancer. This success led to the development of other anti-HER2 directed therapy. The agent lapatinib (Tykerb), with a mechanism different and complementary to trastuzumab was a welcomed addition. Its oral formulation was particularly appreciated.

A study in the neoadjuvant setting (the administration of drugs

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WHAT'S NEW continued

prior to definitive surgery), the NeoALTTO trial, where both anti-HER2 agents were administered together, demonstrated a doubling of the pathological complete response rate when compared to single agent therapy. The apparent synergy between these two drugs provided the impetus to test this combination in the adjuvant setting. The resulting ALTTO study was the combined effort of 946 participating sites from 44 countries. Beginning in June 2007, a total of 8,381 women with HER2-positive, early-breast cancer were randomized to receive one of four treatments: (1) trastuzumab alone, (2) lapatinib alone, (3) the sequential administration of trastuzumab followed by lapatinib, or (4) overlapping administration of trastuzumab plus lapatinib. All four regimens were administered for a one year period and were accompanied by chemotherapy which could be given either before or along with anti-HER2 therapy. The majority of patients, at least 95%, received an anthracycline-based (such as Adriamycin) chemotherapy program. The primary endpoints of the study were to compare the combination therapy of trastuzumab plus lapatinib to the standard arm of trastuzumab alone, and to demonstrate that the sequential therapy was not inferior to trastuzumab alone.

During the conduct of the trial, therapy with lapatinib alone was closed by the study's Monitoring Committee due to futility (mathematically, it was apparent that it would not be better). It was also noted at that time that, because of toxicity, many patients were not completing the prescribed course of lapatinib. To what degree this contributed to the lack of effectiveness of this agent is not clear at this time.

The results presented by Dr. Edith Perez at the 2014 ASCO meeting, demonstrated that the primary endpoint of disease free survival was not better with the combination of trastuzumab and lapatinib given concurrently, nor could non inferiority be

established for the sequential arm. In essence, ALTTO was a negative study.

It is important to recognize that the disappointment in the negative results have a much greater implication in the management of adjuvant breast cancer and are not confined to this study alone. I believe that it is for this reason that this presentation was included in the Plenary Session of the 2014 ASCO meeting. Adjuvant trials in breast cancer involve thousands of patients as can be seen from this trial. They are costly and time consuming. The field has sought a manner by which adjuvant studies could be avoided and obtain information on drug effectiveness in a simpler way. A solution was found in the neoadjuvant setting, with the measurement of a pathologic complete response at the time of surgery as an endpoint that could serve as a replacement for disease free survival and overall survival endpoints. The FDA has recently accepted this concept as a method for drug approval, and the national Cooperative Groups and others have pushed to adopt neoadjuvant trials as the new standard. Not all have been eager to accept this new approach. The results of the ALTTO study, which were based on results from the NeoALTTO trial, suggest that, at least for the combination of trastuzumab and lapatinib, an increased pathologic complete response rate did not predict a better outcome in a large, well-controlled adjuvant trial of over 8,000 patients. Perhaps this disparity is specific to this combination; perhaps it is not. Perhaps we need to reexamine our stand on replacing adjuvant trials with neoadjuvant studies.

ADJUVANT CHEMOTHEAPY FOR OLDER WOMEN WITH EARLY BREAST CANCER

Cancer in general and breast cancer in particular is a disease of aging. Though there are many young women with breast cancer, the incidence rises steeply as we age. Nearly one-half

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PREVIOUS ISSUES

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WHAT'S NEW continued

of all breast cancers are diagnosed in women age 65 or over. Yet, our knowledge of the benefit of chemotherapy in the older population is less well established. There are many reasons for this, but all reflect the fact that older women with breast cancer have not been enrolled in studies at the same rate as younger women. When the national Cooperative Groups began to study adjuvant breast cancer therapies in the 1970s, an upper age cut off was used for enrollment into clinical trials. That cut off was generally from age 65 to 70.

Why were older patients not included in our earliest clinical trials? Some of the reasons were physician-based and others were patient decisions. As physicians, we were fearful that older patients would not tolerate therapy as well; we anticipated more toxicity; we anticipated less compliance; we presumed that the multiple visits and procedures needed to participate in a clinical trial might be too burdensome for an older patient; and we expected less interest in participation. Older patients and their family members shared many of the same fears and concerns as their doctors. The result was that we failed to enroll adequate numbers of older patients in our original adjuvant trials, leading to the reality that we simply have less data in this age group and are less confident of our recommendations.

I recall when a group of senior citizens referred to as the "Gray Panthers," brought this issue to our attention. We were challenged to reconsider our rules for patient participation. We could no longer use age alone as a cut off. Since then things have changed. As our country has acknowledged that the greatest segment of our population is composed of men and women age 65 and over, the medical profession has had to reorient itself. The field of geriatrics was born, with physicians now specializing in the care of this population. This influence has also been felt within the field of oncology. There are now oncologists whose focus is the care of seniors. One of the leaders of this movement

in breast cancer is Dr. Hyman Muss from the University of North Carolina in Chapel Hill, NC. In the July 1, 2014 issue of the Journal of Clinical Oncology, he presented his views on how clinicians should approach the decision of adjuvant therapy in older women with breast cancer. His article begins by reminding us that mortality rates from breast cancer have greatly improved during the past 20 years, but this improvement is much more apparent in younger women. Older women have not gained equal benefit. He suggests that, in part, this may be from under treatment of older women. Most older women with breast cancer present with disease that is hormone receptor positive and HER2 negative. Hormonal therapy is commonly used for this population. The real question that we struggle with is when to use chemotherapy. Dr. Muss offers suggestions for considering this decision.

He emphasizes that chronological age alone is inadequate for making this decision. What must be considered is the functional status of the person, comorbidities, life expectancy for the specific individual, and the person's expectations and preferences. Studies have demonstrated that when younger women are questioned on how much improvement a therapy must provide for them to accept it, the answer has been that even a difference of 1% improvement in disease free survival and in overall survival is adequate for most young women to favor a therapy. Older women are less motivated by minimal differences in survival and more concerned with loss of function that might occur from a therapy. Loss of memory and cognitive function is of particular concern to them. Treatments that may cause peripheral neuropathy and interfere with manual dexterity as well as balance are also major concerns in the older population. The cost of treatment, both from a financial perspective as well as the logistics of obtaining care can be serious obstacles.

Dr. Muss proposes a logical approach to making a decision on the use of adjuvant chemotherapy in older patients. The first step is

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DISCLOSURE

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WHAT'S NEW continued

to estimate life expectancy for the individual. Online models such as www.epronosis.org can be utilized. The second step is to review the goals of treatment with each patient, keeping in mind their projected life expectancy. Next is to project the benefit of therapy. On-line models such as ADJUVANT! and PREDICT can be used to provide estimates of benefit from various therapies in the first 10 years from diagnosis. A gene expression assay, such as Oncotype Dx for hormone positive, HER2 negative patients can also provide guidance in estimating benefit from chemotherapy. Armed with these variables, if the patient's average survival is less than five years, chemotherapy is not advised and even hormonal therapy may be avoided. For those with an average life expectancy between 5-10 years, endocrine therapy is advised and chemotherapy should be considered if overall survival benefit is greater than 3%. For those with an estimated survival of more than 10 years, treatment decisions should be based on the same principles as in younger women with breast cancer.

Dr. Muss ends his article with a reminder that adjuvant trials in older populations must emphasize data not only on survival endpoints but on detailed endpoints of quality of life and patient function. A superficial assessment of these later endpoints is not adequate for this population.

I have known Dr. Hyman Muss for most of my professional years. I consider him an exceptional clinician and a fine gentleman. I have a deep respect for his interest in the care of older patients with breast cancer. I agree with his thoughtful and logical approach.

Reference: Hyman B. Muss, Adjuvant Chemotherapy in Older Women With Breast Cancer: Who and What? *Journal of Clinical Oncology*, 32(19): July 1, 2014, 1996-2000.

QUESTIONS & ANSWERS

(Q) Dr. Martino, I have been taking tamoxifen for the past 3 years. I recently heard that light in my bedroom at night time

interferes with how tamoxifen works. My husband likes to watch television in bed late into the night and he thinks this information is nonsense. Can you give me any advice?

(A) I recently also came across this same information in my reading and was intrigued by it. It is based on animal research done at Tulane University School of Medicine. These researchers are interested in trying to understand the effect of our biological clocks on drug resistance. By way of background, it is recognized that much of our biology is synchronized to the cycles of nature. We evolved in nature along with everything else in our known universe. We are not independent of the cycles of nature. An example of this is the menstrual cycle which appears to be in concert with the 28 day cycle of the moon's rotation around the earth. The day and night cycle is one that we observe every day. Studies have been done that suggest that even the time of day when certain therapies are administered has some influence on their effectiveness and the toxicities that occur. This recent report focused on the hormone melatonin which influences sleep. Its levels gradually increase as evening approaches, it continues to be secreted through the night and then levels gradually decrease as day time arrives. It is known that light has an influence on this hormone. These researches studied rats with breast cancer that were being treated with tamoxifen. One group was allowed to sleep in a completely dark cage and another group slept in cages that had dim light. They found that the animals that slept in dim light had lower levels of melatonin and had larger tumors that were more resistant to the effect of tamoxifen compared to the rats that slept in total darkness. Their preliminary conclusion from this experiment is that breast cancer patients taking tamoxifen should sleep in a dark room and should avoid even low light levels such as from our cell phones, clocks, televisions, etc. For those who cannot avoid these sources of light, they advise wearing an eye mask.

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QUESTIONS & ANSWERS continued

This is an interesting observation. Since this is work done in animals, we cannot be certain that it is also true in humans. I am sure that others will follow this lead and other work will be done to either confirm or refute this observation.

An interesting book on the topic of natural cycles and biological correlates that I read a few years ago and that I enjoyed tremendously is **LIGHTS OUT: SLEEP, SUGAR, AND SURVIVAL** by T.S. Wiley and Bent Formby.

(Q) Dr. Martino, I was recently diagnosed with DCIS. It was hormone receptor negative and HER2 positive. After a lumpectomy, I was treated with radiation. I know that there is a possibility that it will come back and that if it does, it could be more aggressive. I saw a medical oncologist to see if there is anything more that I could receive but I was told there is nothing since my tumor was hormone negative. Why can't they give me Herceptin since the tumor was HER2 positive?

(A) Just as it is true in invasive disease that some are HER2 positive, so it is with DCIS (ductal carcinoma in situ). In fact, the proportion of HER2 positive to HER2 negative is higher with DCIS than with invasive breast cancer. The full meaning of this is not yet clear. The value of Herceptin and similar agents in reducing recurrence from invasive breast cancer has been studied during the past decade and the benefits and toxicities are well known. However, the effect of these drugs in treating DCIS is not known. There is a study (NSABP B43) that is looking at this question, but there is no answer yet.

(Q) Dr. Martino, I recently heard that there is a new study that shows that if you are taking birth control pills, you have a much higher risk of getting breast cancer. I have not heard this before. Is it true?

(A) You are probably referring to information based on a recent

article published by Elizabeth Beaber of the Fred Hutchinson Cancer Research Center in Seattle, Washington. There have been many studies that have looked at the effect of birth control pill use and incidence of developing breast cancer. The results have been conflicting; meaning, that some have shown some relationship and other studies have not found a relationship. The recent publication from Dr. Beaber is an analysis of data from a large healthcare delivery system analyzing prescriptions for birth control pills and the diagnosis of breast cancer during the years 1990 and 2009. Within this data base, they identified 1,102 women with a diagnosis of invasive breast cancer and compared them to an age-matched group of 21,952 women without a diagnosis of cancer to identify what might be different between the two groups. Their analysis found that women age 20 to 49, who had a prescription for oral contraceptives during the previous year, were more likely to be in the breast cancer group than women who had no record of taking birth control pills, or who had a prescription dated more than a year prior. In addition, they found that prescriptions for contraceptives with a higher dose of estrogen or progestin were more strongly associated with an increased cancer risk than low dose prescriptions. Though these are interesting data, it is not clear what to make of them. There are many confounding variables in these data such as the fact that the cancer group also had a higher family history of cancer. Also, having a prescription does not mean that the drug was taken. So, we can add this to the mix of somewhat confusing data on this issue. I don't think that for me this report changes anything.

ASCO BREAST CANCER SYMPOSIUM

I will be attending this yearly conference, which is scheduled in San Francisco from September 4-6, 2014. I will summarize important presentations from the meeting in the next issue of the Breast Cancer Advisor.

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