Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

This month I will be attending the American Society of Clinical Oncology (ASCO) Breast Cancer Symposium in San Francisco. Though it is a relatively new annual event, an increasing number of international researchers are presenting new data at this meeting. I will summarize those presentations in the October issue of the Advisor.

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

BREAST CANCER AND PREGNANCY

Breast cancer is the malignancy most commonly diagnosed during pregnancy. However, a diagnosis of breast cancer during pregnancy or shortly thereafter is rare, with a rate of approximately 1 in every 3,000 pregnant women. Since women are delaying child bearing into later years, it is anticipated that this number will increase.

Diagnosing breast cancer during pregnancy or during lactation is difficult. The breasts experience many changes as part of these events that make an exam less reliable. The breasts enlarge and their texture becomes more dense and lumpy. Changes are often interpreted as normal variations of pregnancy, infection, blocked milk glands or trauma from breast feeding. Due to dangers to the fetus, mammography is often avoided. The result

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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.

BIOLOGY BASICS continued

is a general delay in diagnosis such that women diagnosed with breast cancer during this period tend to have more advanced disease. It is not entirely clear whether the more advanced stage of breast cancer encountered in pregnant women is completely due to delay in diagnosis or whether the pregnant state and the hormones and other biological processes that are part of pregnancy may actually result in a different growth rate for these breast cancers. The prognosis is generally believed to be worse; yet, several studies have suggested that when matched stage for stage, pregnant women do as well as non-pregnant women.

Diagnostic procedures are also more complicated during pregnancy because of the danger of radiation exposure to the fetus. Though the level of radiation from mammography is low, many physicians will not recommend a mammogram. Ultrasounds can be safely performed as can an MRI since these modalities do not use radiation. However, the contrast that is used for MRI is contraindicated, so these procedures become suboptimal. CT scans, bone scans, PET scans and standard X-rays are also contraindicated. A simple chest X-ray with proper abdominal shielding can probably be performed. The sum of all of this is a limited ability to diagnose and properly stage a pregnant patient.

Invariably, a biopsy must be performed to make a diagnosis with analysis of the tissue for hormone and HER2 receptor status. Once a diagnosis is confirmed, the challenge of choosing therapy begins. As in non-pregnant patients with breast cancer, the first decision to be made is whether one is dealing with a patient who already has distant metastases or whether the cancer appears limited to the breast and lymph node area only. Generally, this involves a series of scans which cannot be easily done in a pregnant patient. Fortunately, most women will be diagnosed with local disease and not demonstrate distant metastases; thus, the goal of therapy will be curative. The therapies that are to be considered are the same as for non-pregnant patients: the choice of surgery (mastectomy versus lumpectomy); the need for radiation; and selecting drug therapy (chemotherapy, hormonal therapy and HER2-directed therapy). These decisions are complex enough in a non-pregnant woman, but they are doubly so in a pregnant woman where one must factor in the potential effect and harm of these therapies to the unborn child.

Invariably, a discussion on whether to abort the pregnancy is considered. Though there are no randomized data on this question, the general consensus is that performing an abortion does not improve the outcome for the mother.

There is considerable experience in safely performing surgery on pregnant women and appropriate use of anesthesia. Worldwide, a mastectomy has been the preferred surgical choice for pregnant women; primarily, as this avoids the need for radiation. A lumpectomy procedure is accompanied by radiation and, therefore, is generally not favored. This approach is being reconsidered as radiation is now often advised for women with any nodal involvement even after mastectomy. Further, since chemotherapy is now given prior to radiation, one can perform a lumpectomy and delay radiation until after chemotherapy is completed as one does in non-pregnant women.

The most complex aspect of care for pregnant patients is the use of drug therapy (adjuvant therapy) as these are systemic therapies and the fetus cannot be spared their effects. The first trimester is the period during which organ development occurs and, therefore, the most dangerous. The risks to the fetus

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BIOLOGY BASICS continued

are numerous and include: malformation; organ dysfunction; retarded growth; abnormal mental development; premature birth; and the risk of miscarriage. It is expected that some of these abnormalities may not be completely apparent at birth but may manifest later in childhood or even in adulthood.

For many years it was believed that chemotherapy at any time during a pregnancy would harm the child and oncologists simply would not treat a pregnant woman unless she first had an abortion. Though many physicians are still reluctant, a new pattern has evolved, which is to withhold chemotherapy during the first trimester but treat during the second and third trimesters. Generally, in the third trimester, the oncologist coordinates care with the gynecologist and neonatologist and, if possible, delivery is induced as soon as they judge that the fetus is viable. They must also pay attention to the mother's blood counts so that a delivery is not planned when the blood counts are low and infection more likely to develop. If the diagnosis of breast cancer is made during the third trimester, at times the decision is made to delay drug therapy until after delivery.

The chemotherapy drugs with which there is the most experience as breast cancer therapy during pregnancy are Adriamycin, Cytoxan and 5-Fluorouracil. Methotrexate is avoided as it is well known to cause abnormalities especially in the first trimester. There is less information about the safety of newer agents such as the taxanes and carboplatin. There is limited data with the use of anti-HER2 therapies during pregnancy. Animal data suggests that they may be harmful to the fetus and are best postponed until after delivery. Similarly, experience with the use of growth factors such as used to elevate white blood cell count is limited and are best avoided during pregnancy. Hormonal therapy is known to cause fetal abnormalities, so agents such as tamoxifen are also avoided.

The complexity of each of these decisions should be obvious. Any decision to delay or reduce therapy may be detrimental to the pregnant woman. Simultaneously, the dangers to the unborn child from each therapy must be considered. In this setting, one cannot study therapies in a randomized fashion. The best that can be done is to gather information from animal studies, case reports, observational studies and occasional non-randomized prospective observations in humans. The decisions are generally agonizing for patients, their family, the gynecologist and the oncologist.

WHAT'S NEW

TREAMENT FOR VERY SMALL BREAST CANCERS

Breast cancer survival has steadily increased since the 1970s. The improvement has been primarily a function of two clinical developments: routine screening of the adult female population and the introduction of adjuvant drug therapy in the form of hormones, chemotherapy and HER2-directed therapy. The biological concept underlying both of these developments is that cancers change their behavior with the passage of time such that they become larger, more aggressive and more likely to spread. Therefore, if they can be found when they are small, they are less aggressive and more curable. This concept led to generalized screening with a desire to find disease when it is very small and to the aggressive use of drug therapy for almost all patients with invasive disease. Argument persists as to how much contribution has been made by each of these two parameters to the overall cure of breast cancer. Screening mammography is at present the most controversial, with some now concluding that we have gone too far and are screening too much; while others are simultaneously working to continue to improve screening modalities so that even smaller lesions can be found and less are missed. This is presently a contentious

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argument, with some European countries recently choosing to discontinue their screening programs.

Adjuvant chemotherapy was first introduced in the 1970s for node positive patients. Once its benefits were confirmed, node negative patients were also included. During the past twenty years, we have had to consider the question of when was a node negative tumor so small that it did not need systemic treatment. For some clinicians, the answer became one centimeter (cm). For others, any invasive size became an indication for some form of adjuvant treatment. For those who preferred a cut off of one centimeter, the question had to be re-addressed as we learned to distinguish HER2-positive and triple-negative breast cancers. Since these two subtypes of breast cancer are generally more aggressive, should half a centimeter size be the starting point or should it be even smaller? Should all invasive lesions be treated irrespective of size? It remains an unresolved question.

This should not be viewed as a purely philosophical question. The question is not "shall we deny anyone therapy even if their breast cancer is small?" The question is "for whom is the benefit of therapy sufficient that it outweighs the toxicity and cost?" Different drug therapies provide different levels of benefit, toxicity and cost. Consequently, the answer may not be the same for all therapies or all tumors.

It is important to recognize, that most prior adjuvant therapy trials have specifically chosen to exclude patients with small, node negative tumors as their prognosis was presumed to be good and, therefore, not need therapy. Consequently, there is very little data that provides guidance.

For patients with hormone-positive lesions, hormonal therapy has generally been given. Since hormonal therapy is considered to be relatively free of serious side effects and, because agents such a tamoxifen and the aromatase inhibitors have been shown to reduce the development of new second breast cancers in both breasts, most oncologists have chosen to prescribe hormonal therapy in all patients with hormone-positive breast cancer irrespective of size. The more critical issue is the use of chemotherapy and HER2-directed therapy, which are viewed as more toxic and costly.

So, how shall we approach the answer to this important question since the goal is to not under treat or over treat anyone? The ideal place to start would be to take many thousands of patients with node negative tumors measuring less than one centimeter, and to randomize them to treatment versus observation. One would want to observe them for many years, certainly no less than five, and preferably longer, to reach meaningful conclusions. These patients would need to be subdivided into several categories: hormone-positive/HER2-negative, hormone-positive/HER2-positive, hormone-negative/HER2-positive and triple-negative. At least two tumor sizes, less than 0.5 cm and from 0.5-1.0 cm, as presently used in the official staging system would have to be considered separately. The complexity of what ideally needs to be done should be apparent.

Some small, randomized, prospective studies are already in progress. It will take some time for answers to be available. In the meantime, what we have are a few limited observational studies that are attempting to provide some clues on how patients with such small lesions are being treated and their prognosis. Such a study was published in the July 10, 2014 issue of the Journal of Clinical Oncology by Dr. Ines Vaz-Luis and colleagues.

The study is from eight centers that are part of the National Cooperative Cancer Network (NCCN). It is a prospective cohort study. In essence, they collected information on how patients with tumors of one centimeter or less were treated between the years 2000 and 2009. This is an observational study, so the patients were treated by their own physicians in whatever

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DISCLOSURE

WHAT'S NEW continued

manner they considered best. The study itself did not influence treatment decisions. The data base included 4,113 women who were followed for a median of 5.5 years.

The authors found that over time, there were striking differences in the use of chemotherapy and anti-HER2 therapy for these small lesions. How these patients were treated clearly changed. For patients with hormone-positive/HER2-negative cancers, chemotherapy was rarely given during the entire period. Only eight percent of these patients received chemotherapy. This pattern did not change over time. In contrast, they found that there has been a clear change in how HER2-positive patients and triple-negative patients have been treated over this same time period. For HER2-positive patients, essentially all those with tumors of 0.5-1.0 cm are now being treated with chemotherapy and HER2-therapy. Even for those with hormone-positive/HER2-positive disease measuring less than 0.5 cm, in the more recent years, almost half received chemotherapy and HER2-therapy. The rate is about 70% for hormone-negative/HER2-positive tumors. For triple negative-disease, one half were given chemotherapy if the tumor was less than 0.5 cm and about 70% received chemotherapy if the tumor was over 0.5 cm

The authors concluded that all patients with tumors of 1.0 cm or less did well during the initial five year period of observation. The rate of distant recurrence for those with tumors less than 0.5 cm who did not receive chemotherapy ranged from 2-7%. For those with slightly larger lesions of from 0.5-1.0 cm, distant relapse rate when not treated with chemotherapy was from 4-10%. As expected, those with hormone-positive/HER2-negative disease did best and those with triple-negative disease had the higher relapse rate. For patients who were treated with chemotherapy with or without anti-HER2 therapy, none of those with tumors of 0.5 cm or less had a distant recurrence during this period. For patients with tumors measuring 0.5-1.0 cm, those with hormone-positive disease and those with triple-negative disease, each had a distant relapse rate of 4%. The highest rate of distant disease, 6%, was seen in hormone-negative/HER2-positive patients. Please keep in mind that this was not a randomized study, so one cannot make direct comparisons between the outcome of those treated with chemotherapy plus or minus anti-HER2-therapy and those who were not treated. Only generalizations can be made.

The overall good outcome seen in this study with or without treatment of these small breast cancers is generally superior to the results published by several other authors. Other series have also been relatively small and non-randomized. Consequently, we are left with interesting but inconclusive data.

A solution used by some clinicians when treating patients with tumors measuring 1.0 cm or less, is to rely on assays such as Oncotype DX or Mammaprint to help predict relapse rate and chemotherapy benefit. However, these assays were not developed with patients with such small lesions in mind and lack large numbers of such lesions in their data sets to give great confidence in their results. National guidelines also vary and provide limited assurance as to the real values of therapy in these patients. We cannot forget that all chemotherapy and HER2-directed therapies have not only short term but also long term toxicities that may outweigh a percent or two of benefit obtained from therapy.

The best that can be said at this time, is that our screening protocols identify a large number of patients who fall in this category; consequently, the opportunity to perform well designed clinical trials dedicated to subsets of these patients does exist. We must make use of these opportunities. The primary goal should be to identify patients with small cancers who do not gain sufficient benefit to warrant the administration of these therapies.

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QUESTIONS & ANSWERS

(Q) Dr. Martino, I am really upset. My oncologist who has taken care of me for the past five years and who I liked very much recently stopped practicing. He told me that he is going to teach at a medical school and will not be seeing patients anymore. When I asked him why he is leaving his patients, he said that he is feeling burned out and needs to do something else with his life. I don't understand why he is abandoning me.

(A) Since I do not know your doctor, I do not believe that I can give you an answer as to why he has chosen to retire from clinical practice. The answer that you were given that he is feeling burned out is likely to be the true answer. Feeling "burned out" is a fairly common problem among physicians. I am certain that you can appreciate that taking care of patients, especially in a specialty such as oncology, is very demanding. The demands are not only from patients, but also from a medical system that is becoming increasingly complex with new rules and regulations. Our own families also place demands on us, as they too have their own expectations. Burnout among physicians is not new, but it is an increasing problem. Physicians, like other people, experience personal and professional distress with feelings of physical and emotional exhaustion from long hours of work and sharing of our patient's experiences with their illness. We can become consumed by feelings of overwhelming responsibility. The doctors, who care about patients the most are, in my experience, the ones who are often the most affected.

(Q) Dr. Martino, I was recently diagnosed with two breast cancers in my right breast. I don't want to have a mastectomy. Why can't they do a lumpectomy instead?

(A) The answer to your question depends on several factors: the size of your breast; the size of the tumors; and the location of each tumor within the breast. In general, if the two lesions are close enough to each other that one lumpectomy can encompass them both while achieving clear margins around both of them, a lumpectomy is reasonable. If the two lesions are far apart such that two separate lumpectomy procedures would be needed, then a mastectomy is preferred. The size of the breast is also important. If the tumors are large, such that removing the entire area would leave you with a breast that is very deformed, then a lumpectomy may not be the best choice. Your doctors can also consider giving you drug therapy first with the intent of reducing the size of the tumors before they perform a lumpectomy. The details of your situation are important in deciding which surgical approach is best for you.

(Q) Dr. Martino, I am a 78 year old man and I have recently been diagnosed with breast cancer. I have been tested and found to be BRCA2 positive. I have made all four of my children aware of this. My three daughters are planning to be genetically tested, but my son refuses to believe that he, too, could carry the breast cancer gene that I have. I don't know why he is being so stubborn about this. What can I do to convince him that he should have this testing done?

(A) Thank you for reminding us that men also get breast cancer. This is especially true in families that have a genetic predisposition and a family history. It is common for various members of a family to have a different reaction to this information. Some welcome it, and others are not ready to deal with it. I don't think it is necessary for your son to be convinced that he should have genetic testing done immediately. He may need a little more time to emotionally deal with this information. Help him to understand that even though you have the BRCA2 gene, he may or may not have inherited it. That is true for each of your four children. Help him to understand that his information is also valuable for his own children. Please also remember that your own siblings need to know this information for themselves and their children.