BreastCancerAdvisor

BY DR. SILVANA MARTINO

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Dear Readers,

October is National Breast Cancer Awareness Month. It is a time to celebrate the many accomplishments that have taken place in the field as well as a time to realize how much more there is to be done. Research remains the primary weapon; and supporting it, either financially or when necessary as a participant, should be our mission.

Sincerely,
Dr. Silvana Martino

BIOGRAPHY

Dr. Silvana Martino

Dr. Martino is board certified in internal medicine and medical oncology. She has specialized in the treatment and research of breast cancer for over three decades. Dr. Martino is a nationally recognized leader and educator 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

A WAY TO THINK ABOUT CANCER

What is cancer? At a very basic level, cancer is a cell that behaves badly. Though a cancer cell can be distinguished from a normal cell by its appearance under the microscope and by biological changes within its internal structure, it is primarily its behavior that distinguishes a cancer cell from a normal cell. The human body is a collection of cells that form various cell groupings (organs and structures) and that are assigned certain specific functions to maintain the overall health of the collective (the body). Normal cells must cooperate and provide service for the benefit of the whole organism. It is an organized and highly coordinated system. It is not organized along the principle of survival of the fittest cell; but rather, organized along the principle of cellular cooperation.

The human body can be viewed as a society. Individuals

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BIOLOGY BASICS continued

perform work that is necessary for their own survival, but their work is also needed for the society to continue and function well. Though each individual has a certain degree of freedom, there are rules that must be followed for any society to function at an optimal level. If the society does not function successfully, the individual will ultimately also suffer. The body and its various cells follow these same principles. A society codifies the more basic rules of behavior into principles known as laws. Good citizens follow society's rules and its laws so that everything runs smoothly and a society thrives. Deviant members that do not follow the rules are considered criminals. They may look pretty much like the rest of us, but it is their behavior that creates problems. A cancer cell is a deviant that does not obey the laws of the body.

A primary rule of society is that each of us is limited in where we may be located. For example, we have a home where we live. We cannot change our home by deciding that we prefer another location and simply take possession of someone else's home. We cannot relocate at will. We also are not allowed to damage or destroy other individuals or what belongs to them. In a similar manner, cells have a place where they are to be and function. They may not move freely. They may not occupy another cell's location or damage another cell's environment.

It is primarily these basic rules that cancer cells violate. They relocate, stop serving the body as a whole and interfere and damage the location designated for other cells. They interfere with the function of other cells, alter the environment and cause the death of other cells. They demonstrate criminal behavior. For this reason, our body's immune system, which can be viewed as our policing and military system, has the function and authority to hunt cancer cells down by traveling throughout the body and destroying them. The health and skill of our immune system is critical to the body just as the police and military functions are critical to a society.

WHAT'S NEW

THE BOLERO-1 TRIAL RESULTS

With the identification of the HER2 receptor and the development of therapies targeted to this tumor growth mechanism, the natural course of disease for HER2-positive breast cancer has undergone major changes. What was once viewed as one of the most aggressive types of breast cancer has become one of the more treatable versions. Nevertheless, not all patients with HER2-positive disease respond to these agents and even those who do can develop resistance. For these reasons, agents such as everolimus (Afinitor), an mTOR inhibitor, have been of considerable interest because they held the promise of being able to inhibit or reverse tumor resistance to Herceptin. Initial studies using everolimus in HER2-positive metastatic patients appeared extremely promising. This led to larger randomized studies to verify preliminary observations.

One such study, the phase III BOLERO-1 trial was recently reported in The Lancet Oncology journal by Dr. Sara A. Hurvitz from the University of California, Los Angeles, on behalf of an international group of researchers. A group of 719 patients with metastatic breast cancer who had not had prior systemic therapy for their metastatic disease other than hormone therapy were randomized 2 to 1 to receive either everolimus or placebo along with a standard regimen of Herceptin and Taxol. In each group, 43% of participants had hormone receptor negative disease. Both groups were well balanced in terms of overall

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WHAT'S NEW continued

functional capacity, age, extent of bone metastases and visceral involvement with tumor. They were also well balanced in the type of prior therapy they had received in either the adjuvant or neoadjuvant setting.

The primary objective of the study was the measurement of progression-free survival (the time from start of therapy to the time of disease progression). During the course of the study, a second and similar objective was added, but was restricted to patients with hormone receptor-negative disease. At the time of this publication, median follow-up for the two groups was 41.3 months.

Objective response rate (decrease in tumor size) was 67.1% versus 69.0% in the two treatment groups. When looking only at the participants with hormone-negative disease, the response rate was 73.1% versus 70.9%. These differences are not sufficiently different to favor one therapy over the other.

Median progression-free survival in the entire population was 14.95 months in the everolimus group versus 14.49 months in the placebo group. This trivial degree of difference is neither statistically nor clinically meaningful. When looking only at patients with hormone receptor-negative disease, median progression-free survival was 20.27 months in those treated with everolimus and 13.08 months in the patients given placebo. This difference of seven months is not statistically significantly different. It is of some interest, as it may suggest but does not prove that in this population, everolimus may add some benefit. A second study or a larger number of patients will be needed to clarify whether these results can be reproduced and are biologically meaningful.

Dose reduction and interruption of therapy was common for both treatment groups (86% versus 74%), so that full planned doses of therapy could not be given. Side effects were also common and more pronounced in the group of patients receiving everolimus. The most common side effects noted were mouth sores (stomatitis), diarrhea and hair loss. Serious side effects occurred in 36% of everolimus treated patients versus 15% in the placebo group. These consisted of pneumonitis, pneumonia and fevers. Fifty-five percent of those in the everolimus group stopped therapy due to side effects versus 40% of those in the placebo group.

Deaths related to adverse events occurred in 17 patients (4%) in the everolimus group and no deaths due to side effects were experienced in the placebo group. Causes of death included respiratory problems, infections, cardiac disorder, cerebrovascular accident, injury and metabolic acidosis.

These results are disappointing. They are in keeping with the results from the BOLERO-3 trial, which evaluated the addition of everolimus to the combination of trastuzumab and vinorelbine (Navelbine) also in metastatic breast cancer. Both studies demonstrated no major benefit to the addition of everolimus to standard therapy. Each of these trials however, suggested that there may be a differential effect between hormone positive and hormone negative patients, with hormone negative patients experiencing a benefit and the hormone positive patients not demonstrating a benefit. If this is further substantiated, it may continue the present trend of dividing patients into various specific subgroups of breast cancer and tailoring treatment in a more specific manner.

MORE ON MALE BREAST CANCER

Breast cancer in men is relatively rare. Most often, it occurs as a primary diagnosis; but like in women, it can also be seen as a secondary event in patients who have previously been treated for another malignancy. Data presented by Dr. Deborah Farr, a breast surgery fellow at Feinberg School of Medicine at Northwestern University at the 2015 American Society of Clinical Oncology meeting, shed new insights on this clinical

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PREVIOUS ISSUES

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WHAT'S NEW continued

issue. She reported on 512 cases where breast cancer was a second cancer in men previously treated for various other malignancies. Her results demonstrated that this phenomenon was more apparent in men who had been previously treated for a hematological malignancy rather than those treated for solid tumors such as colorectal, prostate or urinary tract malignancies. This pattern is similar to what is seen in women.

The more serious observation in her data was that though the incidence of primary breast cancer in men was the same between the periods of 1973-1974 (1.15 per 100,000 men) and the period from 2010-2011 (1.11 per 100,000 men), the rate of breast cancer as a second malignancy when comparing these two time periods rose from 0.12 per 100,000 to 0.39 per 100,000 men. Dr. Farr concluded that men who have been treated for a hematological malignancy should be observed more closely for the development of subsequent breast cancer.

Whether this increased risk is due to genetics or is related to therapy such as radiation and drug agents used to treat the first malignancy is not clear from this work. The increased risk for breast cancer following radiation to the chest wall area is well recognized for both men and women. The relationship to chemotherapy is less clear.

PRECISION MEDICINE TRIALS, TAPUR and NCI-MATCH

The National Cancer Institute (NCI) and the American Society of Clinical Oncology (ASCO) have recently unveiled two new studies designed to expand our knowledge of the potential benefits from treating patients whose tumors have specific mutations with therapeutic agents that specifically target those mutations.

The basis to both trials is the concept of viewing every patient's cancer as unique with specific molecular characteristics rather than viewing a tumor based on the organ of origin or its appearance under the microscope. This concept is relatively well known to our breast cancer readers who are already familiar with the concept of treating hormone positive cancers with hormonal agents and HER2-positive cancers with HER2-targeted therapies. The ability to use targeted agents in breast cancer has proven to be of great benefit, resulting in a much higher probability of achieving a response and being able to influence the course of cancer. Many more specific mutations are now recognized; not only in breast cancer but in all cancers. Generally, 40% to 70% of tumors for which genomic profiling is done demonstrate a specific mutation that could be targeted. Drugs already available and others that are in development are designed to function specifically against cells that have specific mutations. This is the essence of "precision medicine".

ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) trial is scheduled to begin in early 2016. It will utilize more than 30 commercially available drugs that will be used in an off-label manner (not FDA approved for a particular tumor type such as breast cancer or lung cancer), matched to specific tumor molecular characteristics. Three health care systems, (1) the Michigan Cancer Research Consortium, (2) the Cancer Research Consortium of West Michigan, and (3) the Carolinas HealthCare System will participate. The study will enroll patients with advanced solid tumors, B-cell non-Hodgkin lymphoma, and multiple myeloma whose disease has progressed on standard therapies. Several pharmaceutical companies will supply the drugs which will be free to patients in the study. A group of experts will review the proposed drug-target match and guide the clinician on potential treatments for each patient. The primary objective of the study will be to measure response rate. Safety and side effects will also be recorded for each patient.

For more information on the TAPUR trial, visit www.asco.org/TAPUR.

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DISCLOSURE

WHAT'S NEW continued

The National Cancer Institute trial called NCI-MATCH is planned to be much larger than the TAPUR trial and will be available to many more clinicians. It will be conducted via the NCI-supported National Clinical Trials Network and is predicted to treat 1,000 patients. Initially, this study will focus on patients with 10 specific mutations and matching drugs. It is anticipated that it will then be extended to many more targets and matched drug therapies. Response rate and evaluation of side effects are the primary objectives of this trial as well.

For more information of the NCI-MATCH trial, visit www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match#1.

The results from these trials have the potential to revolutionize how we choose therapies for patients.

QUESTIONS AND ANSWERS

(Q) Dr. Martino, I have a five centimeter cancer in my left breast. It is a lobular cancer. My surgeon wants the medical oncologist to shrink it with chemotherapy before my surgery because he thinks he might then be able to do a lumpectomy instead of a mastectomy. The medical oncologist does not want to treat me in this way as in his experience lobular cancers do not shrink with chemotherapy. I am confused and don't know what to do. Can you help me?

(A) Dear Reader, perhaps the following concepts will assist you in understanding why there is a different opinion between the surgeon and the medical oncologist. In general, using various drugs such as chemotherapy, hormones or anti-HER2 therapy before a surgery will reduce the tumor size. Sometimes but not always, the size will be reduced enough that a lumpectomy can be performed instead of a mastectomy. This use of pre-operative drugs also serves the purpose of allowing your doctors to see if the drugs they have chosen have the ability to affect the tumor.

The primary issue with your tumor is that you have the less common type of breast cancer called a lobular cancer rather than an invasive ductal cancer. Lobular cancers generally are more diffuse, are often larger than expected from various imaging modalities such as mammograms, ultrasounds and MRI, are often in several separate pieces rather than just one tumor and generally have less aggressive features. All of these characteristics of invasive lobular cancer, generally result in less tumor shrinkage during the few cycles of chemotherapy that are commonly given prior to surgery. Therefore, the size may not be much smaller and complete responses (when all of the tumor disappears) rarely occur with lobular cancer. The bottom line is that lobular cancers are not often converted from a mastectomy to a lumpectomy. It may be that the details of your tumor were not available when your surgeon gave you his initial opinion but were available when you saw the medical oncologist. Ask your doctors to discuss this further between them and reach a consensus for you. They need to guide you. You should not have to "choose" between them.

(Q) Dr. Martino, I am 78 years old and have a four centimeter ductal cancer. I have been told that it should respond to hormones. In spite of my age, I do not want to have a mastectomy. My breasts are small and my doctors have advised that if I don't want a mastectomy they have to first treat me with chemotherapy to shrink the tumor before they try a lumpectomy. I don't want to have chemotherapy. Can they not do the same thing with hormones? I have read that they use this method in Europe and that it works well.

(A) Dear Reader, You are correct. If a tumor is hormone positive, hormonal therapy can be used before surgery for the purpose of reducing tumor size and increase the probability of doing a lumpectomy. One needs to allow a longer period of treatment

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QUESTIONS AND ANSWERS continued

time when hormones are used. Four to six months are typical time periods. You are also correct that the use of hormonal therapy for this purpose is more commonly used in Europe. In the U. S. we have primarily used chemotherapy preoperatively. Given your age, I agree with you that hormones alone may be adequate and chemotherapy is more optional.

PERSONAL REFLECTIONS

I was at the airport in Frankfurt, Germany, returning home to the U.S. from a holiday vacation. I was in my mid 30s then. My future was ahead of me. The flight was delayed for reasons that I no longer recall. After an additional four hours of waiting to get on board, I found myself seated next to an older gentlemen who appeared to be in his 60s. We were the only two people in our row, so we were each other's only source of company during the long flight back to the U.S. He had the window seat. I was next to him.

We greeted each other shortly after we sat down and spent the first few minutes complaining to each other about poor airline service and whether we would make our connections once we reached New York. I expected little conversation from him beyond that point as he seemed tired and I anticipated that he would sleep most of the way.

To my surprise, my fellow passenger began a conversation that did not end until we disembarked about six hours later. I contributed little to the conversation other than being the listener. Nothing seemed required of me other than my attention. The conversation had one central theme: it was a series of regrets that this gentlemen had about the events of his life. It was about things that he had done and things that he had not done, but all were regrets. I had misread his body language; he was not tired, he was sad. He did not need to sleep, he needed to talk and be listened to.

Since by nature and by training I am polite, especially towards those that are older than I, I did not stop him, though I wanted to. It was too much sadness for me to end my vacation with. However, I did what I always do when I find myself in a situation that I cannot escape. I ask myself, "What am I to learn from this experience? Can I find something of value?" I find that this helps me tolerate almost any event. As I pondered the question while continuing to listen to his conversation, I realized that I was being offered a valuable lesson. I decided that this man was positioned next to me purposefully to teach me not to live a life whose final summation would be filled with regrets. It was a long flight home and the message was monotonous, but it was simple and it was profound. I GOT IT! The question of course, is living the lesson.

I am now in my 60s, which is probably the age of my fellow passenger then. So, I have reached the same point in life that he had. Did I really learn the lesson that he taught me? I guess that is the real question. I am still pondering an honest answer.

CORRECTION

Dear readers, in the August/September issue I stated that the Breast Cancer Advisor newsletter would now be published every two months. After further discussions with our new sponsor, The Angeles Clinic and Research Institute, we have resolved to publish the newsletter on a quarterly basis. Therefore, the next issue that you will receive will be in January, 2016, and will be based on new research and information that will be presented at the annual San Antonio Breast Symposium.

As always, if you have questions for which you would like my opinion, you can reach me by email and I will respond to you directly.