

Dear Readers,

Another year is coming to a close. I want to thank each of you for allowing me to continue being a part of your life. The board members of The Angeles Clinic Foundation, the staff and I extend to you and your families our best wishes for the holiday season.



Dr. Silvana Martino

Breast Cancer Advisor

BY DR. SILVANA MARTINO • December 2012

BIOLOGY BASICS

In this issue, I will continue to discuss the management of metastatic breast cancer. Hormonal therapies and chemotherapeutic agents have been discussed in the two previous issues. The present focus will be on treatments for HER 2 positive tumors.

Approximately 25% of metastatic breast cancers will over express the human epidermal growth factor receptor 2, and are referred to as HER 2 positive tumors. This quality is generally associated with a more aggressive growth pattern (including a higher risk for spread to the brain), and an overall less favorable prognosis.

The development of the drug trastuzumab (Herceptin), which has the ability to identify and target HER 2 positive breast cancer cells, has changed the prognosis of this version of breast cancer. The initial studies demonstrated clear activity when Herceptin was given to HER 2 positive tumors. Further, when Herceptin was added to chemotherapy drugs, an additive effect was noted. This was particularly true with the drugs Taxotere, Taxol and Navelbine. It was also observed that when Herceptin

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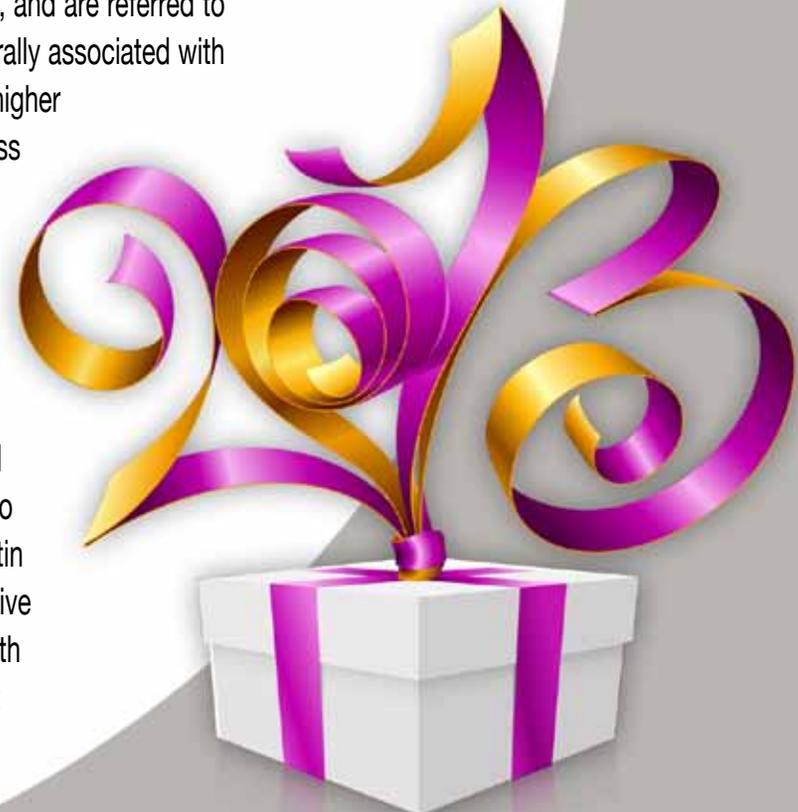
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was combined with Adriamycin, the rate of heart toxicity known to occur with this chemotherapy drug was increased. Consequently, these two agents are generally not given together. It was also recognized that Herceptin has a low level of reversible heart toxicity even when administered alone. In general, Herceptin has very little toxicity of its own and adds little toxicity when combined with other drugs.

The clinical success obtained with Herceptin led to the development of other targeted agents against HER 2 positive breast cancers. Lapatinib (Tykerb) was the second agent in this line. It is an oral drug and has some ability to penetrate into brain tissue. Both of these qualities were expected to provide an advantage over Herceptin. However, its anti-tumor effects do not appear to be superior to Herceptin. Additionally, it causes diarrhea which, if not properly controlled, can result in patients taking reduced doses which can compromise its effectiveness.

The third targeted drug against HER 2 positive breast cancer is pertuzumab (Perjeta), which is FDA approved in combination with Herceptin and Taxotere and superior to the use of Herceptin and Taxotere. This triple combination is considered by many clinicians as their first choice for patients with a new diagnosis of HER 2 positive metastatic breast cancer. Herceptin alone and Tykerb are now considered as second or third line drugs when given with either chemotherapy or when combined with each

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other excluding chemotherapy.

It is anticipated that the drug TDM-1, which is a combination of Herceptin and the chemotherapy drug emtansine into one agent, will be the fourth anti-HER 2 drug to become available. This combination was reviewed in the June 2012 issue of the Breast Cancer Advisor. It is superior and has fewer side effects than the combination of Tykerb plus Xeloda and will restructure the order in which these agents are administered.

Herceptin has also been combined with hormonal therapy and is used in tumors that are both HER 2 positive and hormone receptor positive. It is likely that all HER 2 directed drugs can be combined with hormonal agents if a tumor has both receptor properties. It is only a matter of time before all combinations are studied.

In summary, what was first identified as a bad quality of a tumor, specifically being HER 2 positive, has now been turned into an advantage because new drugs have been developed that are specific to this property and which are effective treatments. Anti-HER 2 drugs can be combined with both chemotherapy and hormonal therapy for more effective management.

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

1. Value of Screening Mammography Questioned

The New England Journal of Medicine published an article in the November 22, 2012 issue with the conclusion that “Despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with advanced cancer. Although it is not certain which women have been affected, the imbalance suggests that there has been substantial over diagnosis, accounting for nearly a third of all newly diagnosed breast cancers, and that screening is having, at best, only a small effect on the rate of death from breast cancer.”

This is not a new accusation against screening mammography, it is simply the latest. Is it completely unfounded? I think the answer is no.

The basic principle that underlies screening for any cancer is the assumption that cancers behave in a predictable manner starting from the time of their initial inception. We presume that they begin as small, not invasive lesions, and that with time they become invasive and larger. At some point in the invasive process they spread to the surrounding lymph nodes; and either at the same time or later, they spread to other parts of the body. If this is always true, than the earlier we identify them, the less likely they are to spread. Theoretically, all breast cancers could be found early enough that none would have the opportunity to spread. With this logic, if all cancers could be found when they are noninvasive, all cancers could be cured simply and require only local therapy.

year. At the same time, the number of advanced (node positive and metastatic) cancers has decreased by only 8%. Further, this small decrease has been primarily in node positive disease with almost no decrease in women presenting with metastatic disease. This suggests several things: (1) We are not preventing metastatic disease by this process, (2) We are modestly reducing node positive disease to node negative or DCIS, (3) We are probably identifying a number of women with DCIS and node negative disease that if not diagnosed might never develop symptoms of breast cancer at all. Presumably some of these women would be better off never knowing that they have an early breast cancer, avoiding treatment, anxiety and cost. This article further states that the improvement in survival that has been seen in breast cancer over the past decades is mostly due to improvement in systemic therapy and not from screening. Improvement in therapy makes screening increasingly less valuable.

The present report is based on data compiled from the Surveillance, Epidemiology, and End Results program. Breast cancer trends from 1976 through 2008 were used. These data suggest that the introduction of screening mammography over this period has been associated with a doubling of the number of early breast cancers (DCIS and node negative) diagnosed each

So where are we going with all of this? Clearly one of the goals is reducing the cost of medical care in the U.S. Screening the general population is not an inexpensive proposition. This controversy was preceded in 2009 by a report from the U.S. Preventive Services Task Force (USPSTF) recommending that screening mammography begin at age 50 and not at 40, and that mammograms be performed every other year rather than yearly. Since then, there has been a decrease in mammograms in women under 50 in spite of considerable public opposition to the recommendations. The present article serves to further



discourage screening mammography.

Other than a need to reduce medical expenditure, is there any other value to the present article? Truthfully, I am not certain. That we have not decreased the number of women who present with more advanced disease is disappointing. It may be that some breast cancers become metastatic so early in their course that we simply cannot find them “early enough.” One could argue that, perhaps, we are not screening often enough or we need to realize that mammography is simply not a “good enough” tool.

That we are diagnosing a lot of women with DCIS and early invasive breast cancer can be seen as both good and bad. Some women absolutely benefit by being diagnosed at an earlier stage than would happen otherwise. However, I do believe that there are women with early disease that if not diagnosed would be better off. These are women who would never go on to have any symptoms of breast cancer in their lifetime. Both the personal and financial cost could be avoided. If only we could identify these women, we could leave them alone. Is the key a better tool?

In summary, though many of us are deeply wedded to the concept of screening mammography, and I am suspicious that this issue is primarily about cost containment, we must be fair and critically analyze data that suggest that we have overestimated its biological value.

QUESTIONS & ANSWERS

(Q) Dr. Martino, my mother has been taking exemestane (Aromasin) and Afinitor for breast cancer. She developed some shortness of breath after two months and her doctor told us that she had a pneumonitis from the Afinitor. She was placed on some steroids, but has not been given any antibiotics. Should she not be receiving antibiotics?

(A) A pneumonitis is not the same as pneumonia, though the two can cause similar symptoms and clinically look the same. Pneumonia is generally caused by an infectious agent, such as a bacteria or a virus, and needs treatment appropriate to the specific cause. A pneumonitis is a noninfectious irritation or damage to the lungs. The drug Afinitor that your mother was taking is known to cause this problem. It is important for the doctor to be sure that it is not an infection causing the problem. If that has been verified, the correct treatment of the pneumonitis is steroids along with at least temporarily stopping the Afinitor.

(Q) Dr. Martino, my wife of 37 years is becoming more forgetful. She is aware of it and tells me that her doctor has told her that it is from the chemotherapy treatment that she received recently for her breast cancer. Is this possible? If it is from the chemotherapy, will it continue to get worse?

(A) Your wife and her doctor may be correct. There are many causes of “forgetfulness,” and chemotherapy is one of them. Generally, it is first noted during treatment and continues beyond the chemotherapy period. Many women complain that they do not remember as well as before, that they have a hard time recalling certain words, that their mind is foggy and that they cannot do several things at once (multi-tasking). This affects some women much more than others. Generally, it improves with time.

Please recognize that though this is a real phenomenon, it is hard to distinguish from other events that worsen our memory such as getting older, symptoms of the menopause, other medications, and early phases of various types of dementia. “Chemotherapy brain” is generally mild and gets better with time. If this is not the pattern that you are seeing with your wife, please have her doctors evaluate her further.

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The Role of Radiation Therapy After Mastectomy

More than 220,000 women are diagnosed with breast cancer each year in the United States. More than 2/3rds of them are treated with breast conservation therapy. This involves a breast conserving surgery, which consists of a lumpectomy accompanied by surgery to remove axillary lymph nodes, followed by a moderate dose of radiation therapy to the breast.

A significant number of women are not candidates for breast conservation therapy because they are not eligible for a breast conserving surgery. This situation arises in women with diffuse disease that cannot be surgically removed with a negative margin by lumpectomy or who have multiple tumors in different quadrants of the breast. In addition, women with large breast tumors relative to the size of their breast are unlikely to have acceptable cosmetic outcomes after lumpectomy. Such women are typically better served with a mastectomy with or without reconstruction as well as surgery to remove axillary lymph nodes. There are also women who elect to undergo a mastectomy because they are at an elevated risk of a second tumor in the breast, such as BRCA-1 or -2 carriers.



Although radiation therapy can be safely omitted in the care of many women who undergo mastectomy, post-mastectomy radiation therapy is a critical component of breast cancer treatment in certain scenarios. Typically, only women who are at a high risk of recurrence after mastectomy are offered radiation therapy. A recurrence along the chest wall or in the adjacent lymph node regions after mastectomy is a devastating event in that it necessitates further cancer therapy, can reduce patient quality of life, and is not always curable. The aim of post-mastectomy radiation therapy is to prevent such recurrences. Women with invasive cancers greater than 5 cm in size or with 4 or more lymph nodes containing tumor metastases are generally offered post-mastectomy radiation therapy. Without post-mastectomy radiation therapy, women with these high-risk features generally have a 30-40% risk of having a recurrence along the chest wall or in the adjacent lymph node regions. In modern clinical trials, post-mastectomy radiation therapy reduces this risk significantly to less than 10-15%. Modern clinical trials as well as a meta-analysis, or overview, of 46 clinical trials involving more than 23,000 patients have consistently shown that by reducing the risk of cancer recurrence after mastectomy in these high-risk scenarios, radiation therapy also significantly reduces the risk of death from breast cancer. Post-

Although radiation therapy can be safely omitted in the care of many women who undergo mastectomy, post-mastectomy radiation therapy is a critical component of breast cancer treatment in certain scenarios. Typically,

mastectomy radiation therapy is also typically offered in the setting of positive surgical margins along the chest wall or pectoralis muscles or in patients with lymphatic metastases that are so extensive that the lymph node capsule is ruptured (i.e., extracapsular extension). In some specific scenarios, radiation therapy may also be offered in patients with 1-3 positive lymph nodes.

In patients who require post-mastectomy radiation, this treatment usually begins 4-6 weeks after surgery to allow for adequate wound healing. If chemotherapy is needed, radiation therapy is typically delivered 3-4 weeks after the completion of chemotherapy. Post-mastectomy radiation therapy generally involves the delivery of a moderate dose of radiation to the chest wall or reconstructed breast, to the axillary lymphatics, and often to the infraclavicular and supraclavicular lymph node regions. In some cases, more extensive lymphatic irradiation to the internal mammary chain is necessary. Post-mastectomy radiation therapy is delivered in short daily treatments over the course of approximately 5-6 weeks. In some circumstances, this course of radiotherapy is followed by an additional “boost” of radiation dose delivered to the mastectomy scar over the course of an additional 1-2 weeks.

The radiation therapy process begins with a consultation with a radiation oncologist, who will review all relevant records, examine the patient, and determine if the woman is an appropriate candidate for post-mastectomy radiation therapy. The radiation oncologist develops

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a personalized radiation plan based on the anatomy of each woman. This process begins with a treatment planning CT scan. The radiation oncologist imports the images from this scan into a treatment planning computer and then generates a 3-dimensional model of the patient's chest. Using specialized treatment planning software, the radiation oncologist and physics team design multiple radiation beams that target the radiation dose to the chest wall (or reconstructed breast) and regional lymphatic chains while avoiding the adjacent normal tissues, such as the underlying heart and lungs. This treatment planning process typically takes several days. Once the treatment is approved by the radiation oncologist, the woman is ready to commence her course of post-mastectomy radiation therapy.

Post-mastectomy radiation therapy is a critical component of successful breast cancer treatment in women who are at an elevated risk of recurrence after mastectomy. The value of this therapy is supported by several modern clinical trials, a large meta-analysis, and the consensus statements of several professional societies, including the American Society of Clinical Oncology. For these reasons, post-mastectomy radiation therapy is an important and life-saving tool in the field of breast oncology and in our fight against breast cancer.

The Angeles Clinic

F O U N D A T I O N

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.

The San Antonio Breast Cancer Symposium

The yearly San Antonio Breast Cancer Symposium has concluded. A few, select, presentations have been covered by the public media. I have personally received many phone calls and e-mails regarding results from the meeting. I will discuss the key presentations in the January 2013 issue of the Breast Cancer Advisor.



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