Breast Cancer Advisor

BY DR. SILVANA MARTINO

May 2014

Dear Readers,

From May 30 through June 3, 2014, the American Society of Clinical Oncology (ASCO) will hold its annual convention in Chicago. This is a large international meeting where some of the most exciting and up-to-date information on cancer research will be presented. I will report on the major presentations from the ASCO meeting in the next few issues of the Breast Cancer 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

CONTENTS

BIOLOGY BASICS

In this issue I will continue to discuss rare sites of metastases from primary breast cancer. These will be a collection of uncommonly seen metastatic locations. I will describe them in descending order starting from the top of the body. These lesions are more likely to occur as part of a more generalized metastatic process; but in rare instances, they will be the first evidence of recurrence.

HEAD AND NECK REGION

On rare occasions, patients will present with lesions on the scalp. At times they are first noted by the patient and at times it is a hair dresser who identifies a lesion. There may be only one lesion or several lesions. A biopsy may be necessary to make the correct diagnosis. Such lesions are more common in hormone receptor positive breast cancers. Due to the proximity, patients often fear

continued next page

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

that these lesions will spread to involve the brain. This is generally not the case. I have seen direct extension from the scalp, through the skull bone and into the meningeal coverings of the brain in only one patient during the past 35 years of practice.

Though the skull is a fairly common bone for metastatic breast cancer, the facial bones are a rare location. These lesions can be painful but can also be a finding on X-rays in asymptomatic patients with other bone metastases.

Two glands in the head and neck region can at times be involved with breast cancer metastases. One is the parotid gland that is positioned in front of the ear. It generally presents as a mass or swelling. The facial nerve courses through this gland; compression of the nerve can cause paralysis of facial muscles. Involvement of the thyroid gland located in the neck also presents as a swelling or a mass. A biopsy is often needed to distinguish metastatic disease from a primary lesion of these glands since therapy would be quite different.

LOWER PORTIONS OF ARMS AND LEGS

It is common to see bone metastases from breast cancer, but rare to see the bones below the elbow (forearm and hands) affected, but it does occur. In a similar manner, it is infrequent for the bones below the knee (lower leg and feet) to be involved; nevertheless, it does happen. As in other locations, these lesions can produce pain or simply be noted on an X-ray.

OPPOSITE BREAST

Breast cancer rarely will metastasize to the opposite breast. It is more common to simply have a completely separate breast cancer originate in the other breast. I have seen what are truly metastatic deposits to the other breast occur in patients with widely metastatic disease. They are usually multiple discrete lesions. This pattern should not be confused with chest wall and skin involvement that simply spreads in a contiguous manner across the chest to encompass the area of the opposite breast. Inflammatory breast cancer is particularly prone to this latter pattern.

GYNECOLOGICAL ORGANS

Tumor involvement of the ovaries from breast cancer can occur (Kruckenberg tumors). It generally affects both ovaries. It can be an asymptomatic event or it can cause a variety of symptoms including abdominal or pelvic pain, bloating, increase in abdominal or pelvic fluid, hormonal changes, vaginal bleeding, painful intercourse, and increase in facial hair. It is more common that a woman with breast cancer will have a tumor that originates in the ovaries rather than metastatic disease from breast cancer to the ovaries. This is particularly true for women who carry the BRCA1 and BRCA2 genes or who have a family history of breast and or ovarian cancer. For this reason, a biopsy is generally necessary to make the correct diagnosis and prescribe therapy.

Other pelvic organs such as the uterus, tubes, cervix and vaginal canal can also be sites of metastatic breast cancer. Pain and bleeding are the more typical presentations.

At times, tumor may be positioned in the inner covering of the lower pelvic region called the peritoneum (Blumer's shelf). This location may manifest with symptoms of rectal obstruction. These lesions can often be felt while doing a pelvic or rectal examination.

ABDOMINAL ORGANS

By far the most commonly involved abdominal organ is the liver.

continued next page

BIOLOGY BASICS continued

However, other organs in this region can also become involved by breast cancer. These include the adrenal glands, kidney, spleen and pancreas. In my experience, these are areas that rarely cause symptoms but are more likely to simply be noted on various scans.

METASTASIS WITHIN ANOTHER METASTASIS

This is a truly rare event that I have seen only once. In a patient with both breast and kidney cancer, on biopsy, both tumors were found to be intermingled with each other.

WHAT'S NEW

RISK OF UTERINE CANCER REMAINING AFTER OOPHORECTOMY

It has been recognized for many years that women with breast cancer are at a higher risk of developing ovarian cancer and that women with ovarian cancer are more prone to breast cancer. These observations were apparent within individuals and also within families. This biological connection was clarified to a great degree when the BRCA1 and BRCA2 genes were identified. Though each of these genes predicts for the development of both cancers, it is now recognized that the risk is higher among women with the BRCA1 gene and somewhat lower in those who carry the BRCA2 gene. This recognized increased risk has led to a recommendation for surgical removal of both the ovaries and tubes (salpingo-oophorectomy) in women who carry these genes to be performed between the ages of 35 and 40, once child bearing is completed. Removal of the uterus has not been advised, as it appeared that gene carriers were not at increased risk for uterine cancer.

This practice has been called into question by new data from researchers at Memorial Sloan Kettering Cancer Center presented at the recent annual meeting of the Society of Gynecologic Oncology. Their results are based on 525 women with BRCA1 or BRCA2 gene mutations who had undergone preventive salpingo-oophorectomy without a hysterectomy and who were followed for a median of about six years during the period from 1995 through 2011. The women were followed using yearly questionnaires and a review of their medical records.

Their results indicate that among these women, there was no increase in the usual types of uterine cancers. In contrast, four women developed a high-risk uterine cancer, including two serous cancers, one carcinosarcoma and one leiomyosarcoma. All four events occurred in the 296 women in the study who had BRCA1 mutations. One woman had a prior history of breast cancer and the other three did not. Two of the women had also been on tamoxifen, which is also known to increase the risk of uterine cancer, and two had not been on tamoxifen. This translates into a 2.1%, ten year risk of uterine cancer following the removal of their ovaries and tubes. Based on age and race, the expected number of these events in this group of women would have been estimated to be about 0.28 rather than the observed number of four.

It must be recognized that this is a relatively modest sized study, and by itself is unlikely to change practice; nor do I think it should. Nevertheless, this observation is important and makes us aware that we must continue to think about and evaluate this risk. In fact, it may be even more important now, as we have recently changed our recommendations for the length of time that we prescribe adjuvant tamoxifen from five years to ten years. With prolonged use, we may see even more of an increase in uterine cancer.

PAROXETINE FOR MENOPAUSAL HOT FLASHES

Among the symptoms that accompany the menopause whether it occurs naturally or is medically induced, is the occurrence

continued next page

WHAT'S NEW continued

of hot flashes. Those who receive hormonal therapy for the treatment of breast cancer, as well as those who experience a decrease in ovarian function from chemotherapy, are also familiar with this unpleasant phenomenon. For some it is minor in degree, short in duration and simply an annoyance; for others, it is a very disruptive part of both their days and nights. Though some women are bothered for only a few years; for some, it may be a long term-event.

The most effective remedy for hot flashes is hormonal replacement therapy with estrogen and or progesterone. This form of therapy came into question about ten years ago based on results from the Women's Health Initiative. Reports from this large, randomized study demonstrated an increased risk for invasive breast cancer, coronary artery disease, stroke and blood clots when conjugated equine estrogen and progesterone were given together; and, an increased risk for strokes and blood clots when conjugated equine estrogens were given alone. These results greatly reduced the use of these hormones in the general population. For women with a diagnosis of breast cancer, estrogen therapy for this use has not been an option, though progesterone therapy has been used with caution in the past. Clearly, non-hormonal options are needed for both the general population as well as those with a background of breast cancer.

One form of non-hormonal therapy for the management of hot flashes has been the use of several drugs that are commonly used as anti-depressants. Studies and clinical use have demonstrated them to be of value for some but not all women. The drug paroxetine (Paxil) is one such example. Recently, a version of this drug (Brisdelle) has been approved by the FDA for use in the treatment of hot flashes. The efficacy of this product was demonstrated in two randomized, double-blind, placebo-controlled, multicenter clinical trials. Both studies demonstrated modest improvement in postmenopausal women with hot flashes compared to placebo. The approval has been controversial, since the FDA chose to approve the drug against the advice that it received from a panel of experts that it had convened to review these data. When approving drugs for general use, one must balance the benefits against the risks of side effects. One of the known side effects of this class of drugs is the increased risk of suicide that has been reported most notably in children and young adults. Another risk is interaction with other drugs.

For those who have a background of breast cancer, there is a particular drug interaction that must be considered; that is, the combined use of these drugs with tamoxifen. When tamoxifen is ingested, it is converted in the body into several biologically active forms. An important metabolite of tamoxifen called endoxifen is produced by the effects of an enzyme system called cytochrome P-450 CYP2D6. The co-administration of paroxetine containing drugs with tamoxifen reduces the ability of this enzyme to carry out this conversion, resulting in lower levels and possibly lower biological anticancer activity of tamoxifen. For this reason, I would not advise the use of this newly approved drug as a therapy for the control of hot flashes in women taking tamoxifen.

Reference: Orleans R J, et al, FDA Approval of Paroxetine for Menopausal Hot Flushes, New England Journal of Medicine, 370; 19, May 8, 2014, pg. 1777-79.

QUESTIONS & ANSWERS

(Q) Dr. Martino, I have a small invasive ductal cancer in my right breast which has gone to my lymph nodes. My scans do not show disease anywhere else. My tumor is hormone positive and HER2 positive. I have consulted with two surgeons that have given me different opinions. The first one wanted me to have

continued next page

DISCLOSURE

QUESTIONS & ANSWERS continued

a lumpectomy and removal of my nodes as soon as possible, but the second surgeon said that the best thing to do was to first give me chemotherapy. I am very confused and don't know which one to believe.

(A) From the information that you have given me, I expect that your treatment will include surgery to the breast and lymph nodes, probably radiation, chemotherapy, HER2 directed therapy and hormonal therapy. The fact that your tumor has features that make all of these therapies possible should be viewed as a good thing. In general, for small tumors, one can do either surgery or chemotherapy first; the data that are presently available suggest that it does not make a difference. For larger tumors, shrinking the tumors first with drugs and then doing surgery provides the advantage of allowing more women to undergo breast-sparing surgery rather than having to undergo a mastectomy. This approach can also increase the probability of obtaining clear margins at surgery. However, the more important piece of information about your tumor in this context is the fact that it is HER2 positive. If you receive drug therapy after surgery, at present you will be offered chemotherapy, the anti HER2 drug Herceptin, and hormonal therapy. In contrast and importantly, if you do the drugs first (neo-adjuvant therapy), your doctors will also be able to offer you one additional anti-HER2 therapy called pertuzumab. This drug is not yet FDA approved when given after surgery (adjuvant therapy). Clinical trials results done so far demonstrate that the addition of this drug to your program provides an advantage. I suspect that this is the reason why one of your surgeons has advised that you receive drugs first even though the size of your tumor is small and surgery could technically be done without trying to reduce its size prior to surgery. This is the approach I would favor.

(Q) Dr. Martino, I read in your last newsletter that continuing to smoke after a diagnosis of breast cancer is a bad thing. How about the use of electronic cigarettes? Is it OK to use them in place of regular cigarettes?

(A) I do not consider myself an expert on the use of electronic or e-cigarettes. My understanding of their design is that they consist of a lithium battery attached to a heating system that vaporizes a solution composed of either propylene glycol or vegetable glycerin and liquid nicotine. The process of vaporizing these substances allows them to be inhaled. It is not entirely clear to me why electronic cigarettes were originally created. Were they to be used as a way to stop smoking? Where they to be a way to reduce products that smokers spew into the air that others are exposed to? What has really occurred is that they have become an attraction onto their own and now we are dealing with an increasing number or teenagers and adults who use e-cigarettes as a new habit.

There is limited information on long term use of these products. Short term, they have been shown to irritate the pulmonary system. They are ultimately a way to introduce nicotine into the body. I doubt that they are good for you. At best, they may turn out to be less bad than other tobacco products. I would discourage their use.

(Q) Dr. Martino, I don't have a question about breast cancer, but I hope that you can still help me. My father has had lung cancer for the past two years. He has been on several drugs including experimental therapies, but he has now decided that he does not want any further treatments. We have discussed this with his oncologist who has suggested that my father consider hospice care. My father has agreed. The problem is that not all of my brothers and sisters are in agreement. Several want him to continue treatment.

continued next page

HOW TO RECEIVE FUTURE ISSUES

You may request future issues of this newsletter by e-mailing your request to:

smartino@theangelesclinicfoundation.org

QUESTIONS & ANSWERS continued

(A) The family dilemma that you describe is fairly common. In my experience, family members often disagree about when it is appropriate to stop active anticancer therapy. For some, there is never a right time as they feel one must fight to the very end. It is important that your father is made aware of all reasonable therapeutic options. Ultimately, the final decision to move to hospice care rests with him; and each of you, must respect his decision.

IMMUNE THERAPY TRIALS AVAILABLE FOR METASTATIC BREAST CANCER

CATHIE T. CHUNG MD, PHD

Director of the Breast Cancer Program
The Angeles Clinic and Research Institute

Our immune system is tightly regulated through a balance of stimulatory and inhibitory signals, which direct the function of a class of our immune cells, known as T lymphocytes. For instance, when faced with infection, our T cells become activated so that we can clear an offending pathogen. At the same time, however, we require the simultaneous activation of inhibitory immune checkpoints to dampen the immune response, in order to prevent the development of auto-immunity and collateral damage to our own normal tissues. One such checkpoint receptor protein is known as programmed cell death protein 1 (PD-1). When this receptor protein (akin to a lock) is engaged by binding with one its ligands (akin to a key) such as PD-L1, T cell function is inhibited.

Many cancers are able to proliferate due to their ability to take advantage of our innate inhibitory immune checkpoints, thereby escaping immune recognition. It was shown, for example, that PD-L1 can be upregulated on the cell surface of many human cancer types and that PD-1 expression can be enhanced among tumor infiltrating lymphocytes. The interaction between PD-L1 expression on tumor cells and PD-1 receptor expression on T cells, allows the cancer cells to proliferate because of inhibition of T cell function. In recognition of this immune escape mechanism, a promising approach to restore therapeutic antitumor immunity has been the development of drugs which block inhibitory immune checkpoints. This strategy has been successful in the treatment of melanoma and is expanding to other tumor types including lung, breast, head and neck, bladder, renal, gastric and other solid tumors.

At The Angeles Clinic and Research Institute, we have an active clinical cancer immunology program in which we are studying the safety and efficacy of antibodies to block PD-1 and PD-L1 in the treatment of patients with metastatic cancer. These are clinical trials of great interest because we think they may ultimately provide a novel approach toward the treatment of cancer by taking advantage of our own immune system. If you or someone you know is interested in participating in clinical trial that involve various ways to manipulate and exploit the functions of the immune system, please contact me directly at (310) 582-7900 or by email at **cchung@theangelesclinic.org**.

The Angeles Clinic FOUNDATION