

Dear Readers,

I have spent a week vacationing in Mexico. It was great. I realized, however, that though the sun, surroundings and food were wonderful, the best part was spending time with family and friends. Relationships are like plants. They require time and effort, otherwise they wither. They are our best investments.

Best regards,

Dr. Silvana Martino



Breast Cancer Advisor

BY DR. SILVANA MARTINO • March 2013

BIOLOGY BASICS

In this issue, I will discuss a version of breast cancer referred to as inflammatory breast cancer. This is a particularly aggressive form of breast cancer. Its name is derived from the fact that inflammatory breast cancer looks similar to a breast that is infected. It is often confused with conditions such as cellulitis, mastitis or infected cysts.

A common set of events are often described by a woman with this entity. Their breast became swollen, red and hot. They saw a physician who diagnosed an infection and started the patient on antibiotics. The antibiotics did not resolve the condition and a second antibiotic was tried. The breast may have improved somewhat but not completely. At this point, the doctor became concerned and a mammogram was done. At this point, the diagnosis was made. It was inflammatory breast cancer.

There are two aspects to making the diagnosis of inflammatory breast cancer; (1) the appearance of the breast and (2) the pathological features described from a skin

continued next page

WHAT'S INSIDE

BIOLOGY BASICS 1

WHAT'S NEW

LATE METASTASES IN HORMONE

POSITIVE BREAST CANCER 3

SCALP COOLING TO PREVENT HAIR

LOSS FROM CHEMOTHERAPY 4

PRECISION MEDICINE 5

QUESTIONS & ANSWERS 6

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Biology Basics continued

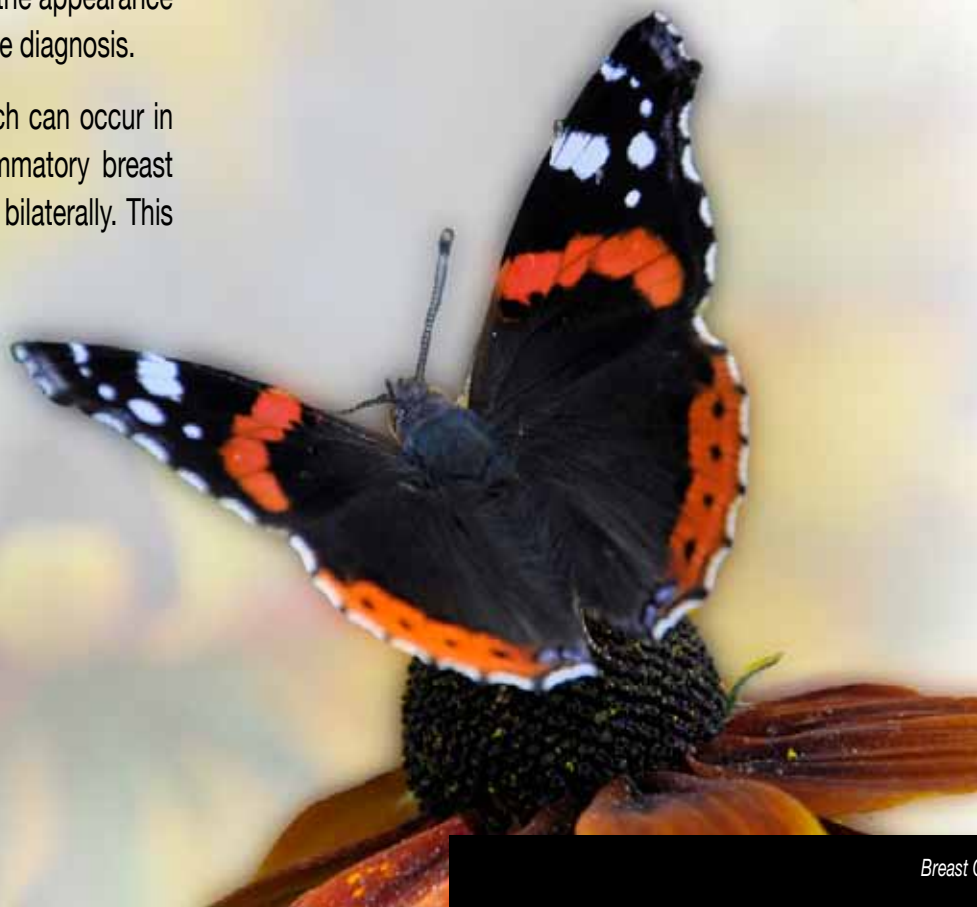
biopsy. The classical appearance of the breast includes a red rash on the skin of the breast. The rash may extend beyond the breast. The breast may look and feel swollen. At times, the patient feels that the breast has grown in size. There is not always a palpable mass within the breast. Often, but not always, the breast feels hot to the touch. To make the diagnosis, a breast biopsy is needed, along with a biopsy of the skin overlying the breast. Tumor cells within the lymphatic vessels of the skin confirm that it is inflammatory breast cancer. At times, the demonstration of this finding on skin biopsy by itself is confused and considered sufficient to make a diagnosis of inflammatory breast cancer. This is not correct. This type of skin involvement on skin biopsy can be seen in other forms of breast cancer. It is the clinical picture including the appearance of the breast which is most important in making the diagnosis.

Unlike most other versions of breast cancer, which can occur in both men and women, I have never seen inflammatory breast cancer in a man. Also, I have never seen it occur bilaterally. This

cancer can be both hormone positive or negative as well as HER2 positive or negative.

Because inflammatory breast cancer generally involves all or most of the breast, surgical treatment is generally a mastectomy.

There are occasions when typical breast cancer (non-inflammatory) recurs on the skin or chest wall and also looks like an inflammatory process. Some physicians will use the term “inflammatory” to describe this process, but this should not be confused with true inflammatory breast cancer.



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. Late Metastases in Hormone Positive Breast Cancer

It has been recognized for a long time that breast cancers that are hormone positive (estrogen and/or progesterone receptor positive) have a different recurrence pattern than those that are hormone negative. In general, hormone receptor positive disease takes longer to recur and is more likely to first recur in skin, soft tissues and bones. Hormone negative breast cancers recur more quickly, and are more likely to first recur in lung, liver and the brain. These patterns are known by oncologists and are useful in watching patients.

The highest risk of recurrence is in the first five years for all patients. This is particularly true for patients with hormone negative cancers. Patients with hormone positive breast cancers also demonstrate a pattern of “late recurrences,” meaning that they may recur many years after their diagnosis. The longest gap that I have ever personally seen is 33 years from the date of diagnosis. For this reason, there has always been an interest in trying to identify which patients within the hormone positive category might be at higher risk for late relapses. If we could identify them, our treatment and our follow-up of them would be structured differently.

Data using an assay that may help with this question were presented at the San Antonio Breast Cancer Symposium in December, 2012 by Dr. Peter C. Dubsy and colleagues from the Department of Surgery at the Medical University of Vienna, Austria. The study was conducted on tumor tissue from 1702 postmenopausal women with estrogen positive/HER2 negative breast cancers. One third of the women had node positive disease and two thirds had node negative disease. All of the women had received treatment with some form of hormonal therapy, but none had received any chemotherapy. Using a combination of clinical information (nodal status and tumor size) plus an assay performed on tumor tissue named EndoPredict, they were able to separate women into those with a low versus high risk of late recurrences. In this study, late recurrences were defined as years 5-10 following diagnosis. Importantly, they also observed that women with node positive disease had a higher rate of relapse during both the first 5 years and the second 5 years post diagnosis. The measurements of tumor grade and level of Ki67 were not predictive of late recurrence. Expanded studies are ongoing to confirm these observations.

The EndoPredict test is not yet available in the U.S., but is available in Austria and Switzerland.

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It is unclear at this point whether this test will become standard in helping us decide who is at high risk for late recurrences and, therefore, may need longer term adjuvant therapy versus women who may be at low risk for late recurrences and for whom shorter term therapy may be all that is needed. The fact that this study observed women for only 10 years is a limiting feature. Nevertheless, the fact that we are now starting to think about predicting late term recurrences is very important.

The EndoPredict test is designed to predict later term recurrences and should not be confused with tests such as Oncotype DX or MammaPrint which are used to predict benefit from chemotherapy at the time of diagnosis.

Reference: The EndoPredict score identifies late distant metastases in ER+/HER2- breast cancer patients, Dubsy P, Brase JC, Fisch K, et. al., abstract S4-3, Cancer Research, December 15, 2012, vol72 (24).

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2. Scalp Cooling to Prevent Hair Loss from Chemotherapy

Hair loss is one of the more emotionally significant side effects of many chemotherapies. Not only does it impact quality of life; but, for some patients, it is the basis for deciding which chemotherapy program they choose. For others, it results in the decision to not accept chemotherapy at all.

Trying to reduce hair loss by cooling the scalp is not a new idea. We attempted to do this about 30 years ago with the use of ice packs and various types of head coverings that we would simply put in a freezer and apply to the scalp during chemotherapy administration. The general experience was that this worked somewhat. It was helpful with some chemotherapies particularly when given in low doses. It did not appear to work with full dose Adriamycin, a commonly used drug. Also, there was a concern that by cooling the scalp and reducing the amount of chemotherapy that was delivered to the skin, we might subsequently see more metastases on the scalp since breast cancer is a tumor that tends to recur in skin. Both the concern for scalp metastases and the relative lack of hair protection resulted in many clinicians abandoning the concept of scalp cooling. However, our patients have not allowed us to completely forget the problem of hair loss and finding ways to prevent it.

Two presentations at the December, 2012 San Antonio Breast Symposium demonstrated a renewed interest in

preventing this common side effect. Preliminary results using two cold cap systems, the Penguin Cold Cap and the DigniCap, were presented. Each demonstrated encouraging results on a small number of women receiving chemotherapy for breast cancer. I am not aware of any data comparing the two systems to each other. Neither system reduces hair loss completely. They each appear to reduce hair loss in most patients sufficiently to avoid the use of a wig. They are both somewhat cumbersome and require training and assistance in their use.

Overall, it does appear to me that these systems are better than what we had used 30 years ago. More experience and studies are needed before this can be considered standard prevention of hair loss. It appears that Europe has had much more experience with these systems than physicians in the U.S. There is still concern among many oncologists about the possibility that, if we

use these systems, we may begin to see an increase in scalp metastases. Because this is such a rare place for metastases, it will be difficult to resolve this particular issue without doing studies that would involve many thousands of patients.

I anticipate that, as knowledge about these new cooling caps spreads, many more oncologists will be willing to have their patients try them. We have had a few patients in our office who have made arrangements to use them, so our experience is also limited. I expect that there will be much more to come on this topic in the near future.

References: Efficacy and safety of scalp cooling (SC) treatment for alopecia prevention in women receiving chemotherapy (CTX) for breast cancer (BC), Serrurier KM, Melisko ME, Glencer A, Esserman LJ, Rugo HS, abstract P2-12-12, Cancer Research, December 15, 2012, volume 72 (24).

Use of the DigniCap System to Prevent Hair Loss in Women Receiving Chemotherapy (CTX) for Stage I Breast Cancer (BC), Rugo HS, Serrurier KM, Melisko M, Glencer A, et.al., abstract P2-12-11, Cancer Research, December 15, 2012, volume 72 (24).



PRECISION MEDICINE

Many think that “precision medicine” is the future of oncology. So, what is it exactly? Primarily, it is the recognition that all cancers are different. They may look similar, but no two are exactly alike. Think of this like people. Though, superficially, we look very much the same in that we have one head, two eyes, two arms, two legs, etc., yet even identical twins can be distinguished from each other on many levels. The same diversity exists in cancer.

This diversity was first appreciated in breast cancer when it was recognized that some were hormone positive and others were hormone negative. This led to the development of hormonal therapies which have turned out to be excellent drugs for hormone positive breast cancer. In contrast, they are not of value in treating hormone negative breast cancers. More recently, the discovery of the HER2 mutation in about 25 % of breast cancers has led to the development of several effective drugs against HER2 positive breast cancer. Again, these drugs offer little for HER2 negative cancers.

Other similar examples exist in many other tumors. As new mutations are identified, we can separate tumors into those that carry the mutation and those that do not. These mutations then offer the opportunity to identify and develop drugs that are specific to that mutation. By treating a patient’s tumor with drugs based on the specific mutations of that tumor, we obtain better results. Additionally, it allows the avoidance of drugs that are unlikely to be effective because a tumor lacks the specific mutation needed for a specific drug to be effective. Not all mutations are equally as important in determining the biology of a tumor. This adds considerable complexity to interpreting the results.

This is an important concept. Targeted therapies are generally more effective, and with less side effects. This approach has been around for some time and has gone by several names. Originally we called it the use of targeted therapies. It then became known as personalized medicine or therapy based on tumor molecular profiling. Precision medicine is simply the most recent nomenclature.

What is required so that treatment decisions can be based on this degree of detail about a tumor is a biopsy

of the tumor. All patients have a biopsy at the time of original diagnosis, but, most often, what one needs is a biopsy of the tumor when it has recurred. One may actually do biopsies several times over the course of the disease process since tumors continue to evolve and change. The details of the tumor from a prior time point may not be the same at a second time point. There are times when a particular mutation is noted within a tumor, but as yet, there is no known therapy for that mutation. Another practical problem often encountered in this process is that one finds a mutation for which there is a known drug, but that drug is not FDA approved for the cancer in question, say lung cancer, or breast cancer. In this circumstance, insurance companies refuse to provide coverage for the drug as there is no FDA approval. The patient must then provide for the total cost of the drug. This is not always practical.

In summary, precision medicine is simply the latest terminology applied to an evolving concept. The idea has its roots in recognition that tumors are diverse in their biology. We can take advantage of this diversity allowing us to better predict which drugs will be most effective against a tumor. Many view this as the future direction of oncology.

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QUESTIONS & ANSWERS

(Q) Dr. Martino, I was confused by your article in last month's issue about tumor stem cells. Can you give me a better explanation of how they work within a cancer?

(A) I am sorry that I confused you. Perhaps a different way to think about tumor stem cells is to think of a bee hive where the queen bee is the mother to most, if not all, of the other bees. The vast majority of bees are workers; they have functions to perform, but it is the queen that has the job of giving birth to the members of the colony. For a new colony of bees to establish itself and survive, a queen bee must be present. This is similar to a new metastatic focus in a cancer. Ant colonies are also organized in a similar manner. Think of the cancer stem cells as the queen bee. It is a minority of the entire population, but it is necessary for the production of the vast number of other cells that make up a tumor. Again, please recognize that this is a conceptual model of cancer. There is evidence that tumors function based on this model, but there is not unanimous agreement that this is exactly how cancers function.

(Q) Dr. Martino, I have had triple-negative breast cancer and my oncologist wants me to have genetic testing. I thought this was only done if you had a family history of breast cancer, which I do not.

(A) In general, you are correct that we think of doing genetic testing (BRCA1 and BRCA2 testing) in those with a family history of breast cancer, but this is not the only group. This testing is also appropriate for those who are young at their diagnosis of breast cancer as well as those with bilateral disease and women with triple-negative breast cancer. Recent studies have reported that those with triple-negative breast cancer may be up to 5 times more likely to carry the breast cancer genes. The BRCA1 gene mutation is much more likely to be found in this situation, and rarely the BRCA2 mutation.

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