Breast Cancer Advisor

BY DR. SILVANA MARTINO

August 2013

Dear Readers,

This issue marks the beginning of the third year that we have published the Breast Cancer Advisor. We have decided that it was time to give it a new look. We hope the changes meet with your approval. The content will remain unchanged—my opinion and analysis of the field of breast cancer. Thank you for your continued support. Your comments and opinions are sincerely appreciated.

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
BRAIN METASTASES 1
WHAT'S NEW
POSSIBLE RELATIONSHIP BETWEEN OVARIAN CANCER AND POST-MENOPAUSAL HORMONE REPLACEMENT THERAPY 3
GENES CANNOT BE PATENTED 4
QUESTIONS & ANSWERS 5
THE HUMAN GENOME PROJECT 5

BIOLOGY BASICS

BRAIN METASTASES

The brain has long been recognized as a frequent location for breast cancer metastases. In fact, this distribution of disease has become more common. This increase was first observed in the early 1980's, a few years after adjuvant therapy was introduced in the management of early breast cancer. At the time, I was working at Wayne State University in Detroit. A junior faculty member made this observation and had written a paper that he planned to submit for publication. Several senior staff members, in reviewing his paper, became quite alarmed. They were reluctant to allow publication of the observation that brain metastases were becoming more prevalent, as it did not make sense to them, and they were fearful that it might derail the new movement of adjuvant therapy. Surely they reasoned, his observation must be wrong. Since adjuvant

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

therapy reduced overall recurrence from breast cancer, why would we simultaneously observe more brain metastases?

With time the phenomenon was confirmed and we came to understand that if you prevent systemic disease, patients will live longer and will manifest patterns of disease that you might not see otherwise. We also came to understand that our drugs were not able to penetrate into brain tissue in the same manner as in other parts of the body. The brain is protected by a system known as the blood-brain barrier, which functions to exclude toxic substances from entering into brain tissue. This mechanism, even if damaged by tumor, does not allow entry of most of our anticancer therapies in sufficient doses to protect the brain to the same degree to which other organs are protected.

In general, brain metastases occur more frequently in women who are younger, with larger tumors and with tumors that have a more aggressive nature, such as triple negative or HER2 positive. There are two types of involvement that are seen: metastasis to the brain itself, or metastasis to the coverings of the brain (meningeal carcinoma). The second pattern is less common, yet more serious.

The manner by which the tumor gets to these structures is the same as in any other part of the body. The tumor cells travel through the blood and lymphatic system. At times, patients will have tumor either on their scalp (skin) or in the skull (bone). They often presume that because these areas are physically close to the brain that their tumor will invade into the brain directly. This in not correct. Patients with scalp or skull metastases do not have a higher risk of brain metastases.

It is uncommon to screen patients with CT or MRI of the brain to look for these metastases. The usual manner in which both brain and meningeal metastases are found is by symptoms. The most common clinical clues that brain metastases may be present are; (1) new headaches, (2) focal numbness or weakness of a body part such as the face, arm or leg, (3) seizures, (4) new visual or hearing problems, (5) speech problems, (6) problems with balance and (7) changes in personality or behavior. Some years ago, an excellent Physician Assistant (PA) that worked with me, recognized this last clue in one of our elderly patients, who was noted on a clinic visit to be wearing bikini underwear. The PA realized this as a clear change in the patient's behavior pattern. On this basis, we performed a CT scan which demonstrated brain metastases.

Meningeal carcinomatosis or tumor involving the coverings of the brain can present with all of the signs described above, but, more often, will present with more severe headaches, often accompanied by a stiff neck and loss of function of the cranial nerves that govern the functions of the head and neck area. In my experience, the nerves that control movement of the eyes are most often involved.

When involvement of the brain or meninges is suspected, diagnosis and treatment must be done promptly. Clinical deterioration can occur quickly, with function becoming easily lost and no longer being reparable.

Though a CT scan can be useful, the best way to image the brain and the meninges is with an MRI. If meningeal cancinomatosis is suspected, analysis of the spinal fluid must also be performed. Tumor cells found in the spinal fluid confirm the diagnosis.

In patients who are symptomatic, treatment is often begun while the diagnostic procedures are in progress. Steroid drugs to reduce swelling caused by the tumor are started. Their discontinuation should be done gradually. If seizures have occurred, anti-seizure

continued next page

BIOLOGY BASICS continued

medications are begun and the blood level monitored. Since seizures are not common in patients with brain metastases from breast cancer, anti-seizure medications are not routine but prescribed only if seizures have occurred.

Treatment of brain metastases is accomplished primarily by surgical resection, stereotactic radiosurgery and whole brain radiation. If the lesions are limited in number and size, it is typical to target these lesions with either surgery or stereotactic radiosurgery. If the lesions cannot be technically treated with these more targeted modalities, then whole brain radiation is used. At times, some lesions are first treated with surgery or stereotactic radiosurgery and then whole brain radiation is added to treat the rest of the lesions or as a way to enhance the control of the treated lesions. Considerable judgment is required to choose the best way to control brain lesions and their symptoms. Brain metastases are often a recurring problem and decisions are needed at different time points.

Systemic drug therapy, such as chemotherapy, hormones and HER2 targeted drugs, can aid in the management of brain metastases. The issue of whether they can be used in place of surgery or radiation is still debated. Some reports have shown modest response rates. This may be particularly true when a patient has not already experienced a lot of prior therapy. However, most clinicians favor the use of local modalities with which there is much more experience.

Treatment of meningeal carcinoma is complex and of limited benefit. The process is rarely localized; consequently, whole brain radiation is generally given. In the past, some had advocated for radiation of the entire spinal column. This has not been found to improve survival. Surgery is indicated primarily for placement of catheters for drug administration. At times symptomatic metastases may be resected or catheters may be placed to reduce fluid buildup in the brain area (hydrocephalous). Various chemotherapy drugs are used and placed directly into the spinal fluid (methotrexate, thiotepa, and cytarabine). Studies that look at other chemotherapeutic agents and Herceptin for this process are ongoing. It is common for patients with meningeal disease to also have brain metastases; thus, requiring that treatment be directed at both sites simultaneously.

WHAT'S NEW

POSSIBLE RELATIONSHIP BETWEEN OVARIAN CANCER AND POST-MENOPAUSAL HORMONE REPLACEMENT THERAPY

For several decades, it was believed that giving postmenopausal women hormonal replacement therapy was not only a way to reduce their menopausal symptoms such as hot flashes, poor sleep and mood swings, but it was also a way to prevent heart disease, strokes, dementia, urine incontinence and probably cancer. Much of this thinking changed in 2002 when the results from the Women's Health Initiative (WHI) study demonstrated that the use of these hormones did not prevent heart disease and actually increased the incidence of breast cancer. This information resulted in a large number of women who had been taking HRT to promptly stop their use. It was subsequently demonstrated that, as this change in behavior occurred, the incidence of breast cancer in the U.S. population decreased.

An interesting report has recently been published by Dr. Hannah P. Yang and colleagues suggesting that the decrease in use of HRT has resulted in a reduction in the incidence of ovarian cancer as well. For their study they used the North American Association of Central Cancer Registries database and identified 171,142 cases of ovarian cancers diagnosed between 1995 and 2008. They found that among women aged 50 and over the incidence of

continued next page

DISCLOSURE

WHAT'S NEW continued

ovarian cancer was declining between the years 1995 and 2002 at a rate of 0.8% per year. However, after the publication of the WHI report in 2002, the incidence in this population decreased at a rate of 2.4% per year. The decrease was most pronounced among white women aged 50 to 69 and women who lived in areas with the highest rate of prescriptions for HRT.

Do these data prove that hormonal replacement therapy causes ovarian cancer? Not conclusively. The data indicate that the incidence of ovarian cancer was slowly decreasing even before the year 2002 when the WHI results were first published and we experienced a dramatic decline in the use of HRT. It is likely that other studies looking at this potential relationship between HRT use and ovarian cancer will follow. Those will either confirm or refute a relationship. Nevertheless, the results from this study provide further reasons to be cautious in the use of post-menopausal HRT.

Allow me to remind all readers that the use of HRT following a diagnosis of breast cancer is discouraged.

GENES CANNOT BE PATENTED

On June 13, 2013, an important legal decision was given by the U.S. Supreme Court that has far reaching consequences in the field of medicine. The question before the court was whether human genes are patentable. In the case of Association for Molecular Pathology versus Myriad Genetics, Inc., the court decided that patent protection cannot be extended to genes found in nature. The genes in question were the BRCA1 and BRCA2 that have been identified to carry mutations that predict for a higher incidence of both breast cancer and ovarian cancers. Justice Clarence Thomas stated, "To be sure, it (Myriad Genetics, Inc.) found an important and useful gene, but separating that gene from surrounding genetic materials is not an act of invention." Human genes are considered a natural product and may not be treated as private property. The result of this decision is that anyone is now free to do research on any part of naturally occurring human genes.

The reaction to this decision has been mixed. Many have seen this as the removal of a major barrier to researchers and anticipate that the field of medicine will greatly benefit from this step. Genetic testing for diseases is anticipated to become less expensive as multiple companies will offer similar services and create a competitive environment. Others are fearful that the Supreme Court's decision may slow research, as new ideas or tests based on genetic material will not receive patent protection and, therefore, there will not be a financial incentive for scientists to pursue research based on these materials.

To be clear, the court limited patent protection for "natural human DNA." It did not limit such protection to DNA that has been altered or modified. It is highly likely that this will be the path used by individuals and/or companies that want a patented product. I believe that the full impact of this legal decision is, as yet, unclear.

QUESTIONS & ANSWERS

(Q) Dr. Martino, I recently had a mastectomy for breast cancer and I am now taking hormones. I am 72 years old and I feel that I have had a good life. My surgeon and my oncologist have both suggested that I should have reconstruction. I don't feel that I need to have reconstruction and my husband does not care. He believes it is my decision. Is there something wrong with me for not wanting to do it?

(A) No, I don't think there is anything wrong with you for not choosing to have reconstruction after a mastectomy. Many women, in my experience, make the same decision. I have found this to be true in women of all ages, though perhaps a bit more in women who are older. It is completely a personal choice. Some

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

women simply feel that they have had enough surgery and do not want to have more. There are risks with all surgical procedures. For some, the cost of reconstruction is an issue, while others choose to wait or not reconstruct at all. My compliments to your husband. I respect his attitude that it is ultimately your decision to make.

THE HUMAN GENOME PROJECT

Our understanding of biology and disease underwent a dramatic shift in 1953 when James Watson and Francis Crick described the double helix structure of DNA (deoxyribonucleic acid). Our DNA contains the genetic instructions necessary for building, running and maintaining our bodies. In it are coded not only our gender, the color of our eyes and our basic temperament; but also many aspects of our health and the diseases that we are likely to experience in our lifetime.

In 1990, the National Institutes of Health (NIH) and the Department of Energy, along with other international bodies, joined together to plan and execute what was named the Human Genome Project. The goal of this project was to sequence all 3 billion base pairs in the human genome or DNA. This enormous international task was completed in 2003. The information obtained was made publically available and can be found on the Internet. By intent, this information is considered to belong to all people, and has become an invaluable human resource.

Perhaps a simplistic way to understand the nature of this project is to think of it as similar to identifying the letters of the alphabet. It is a place to start if you want to understand a language. Knowing the alphabet does not automatically mean that you can have a fluent, sophisticated, philosophical conversation. Different ways of combining the same letters and their sequence make an enormous difference in what word you end up with. Even when you are able to recognize and say certain words, it does not mean that you now know how to make a complete and correct sentence; even if it is only a simple sentence. These principles will be familiar to anyone who has tried to learn a new language. Commonly in a sentence, there are key words, and if you are able to recognize them, the meaning of the sentence can be understood. Other words in a sentence are important but not critical, or serve only as background or details. The same seems to be true of the genetic sequence. There are areas that are more important than others. Punctuations are key in knowing when a sentence has started and when it has ended. If you have ever tried to read material where the punctuations have intentionally been left out, or you did not recognize them, you know how confusing the material can be and how different readers will understand a different meaning. In essence, this is where we are in understanding the sequence of base-pairs in human DNA.

Even so, the information that we understand so far has already been put to many uses. Within the field of medicine, it has served as the basis for trying to understand, predict and treat diseases.

A more recent and related initiative has been the Cancer Genome Atlas. This is the same idea as in the Human Genome Project, but here the DNA of interest is that of cancer cells. Fifty major types of cancers will be outlined. Breast cancer is at the top of the list. It is hoped that this will lead not only to new detailed understanding about the genetic patterns of cancer but will lead to new therapies. Ultimately, the hope is that if they wish, each person will have their DNA sequenced, telling them what illness they are likely to develop in their life time. If they develop a cancer, the specific nature of their cancer can be sequenced and specific therapy can be administered. Finally, we can anticipate a time when we can actually change the genetic sequence and, in so doing, treat or prevent illness. Though these ideas are in the future, the basic groundwork to make these concepts a reality has been laid.