

Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

Thank you for continuing to allow the Breast Cancer Advisor newsletter to be a part of your education. Also, we sincerely thank you for your financial support. The newsletter, outreach and research programs cannot exist without your generosity. The

staff of The Angeles Clinic Foundation extends to each of you and your families best wishes for a happy and healthy holiday season.

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

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BIOLOGY BASICS

METASTASES TO THE LIVER

The liver is a common organ for metastases from breast cancer. It is usually involved as part of a more diffuse metastatic process that includes others organs as well. Liver metastases can be diagnosed in several ways. At times, they are diagnosed incidentally as part of doing a PET or CT scan. They can also present as abnormal liver function blood tests or elevated tumor markers. Often, they present with symptoms such as pain in the abdomen, abdominal fluid (ascites), leg swelling (edema), yellow coloring of the skin and eyes (jaundice) or an enlarged liver. Also, because the liver is responsible for producing substances necessary for the blood clotting system, excessive bruising or bleeding may also be a presenting sign.

The appearance of liver metastases on scans or ultrasound can

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BIOLOGY BASICS continued

vary. One may observe discrete round lesions or diffuse lesions. The liver may or may not be enlarged. Obstruction of the biliary (bile) system may or may not be present. Liver lesions from tumor must be differentiated from benign lesions that may look very similar such as fatty liver, hemangioma or cirrhosis. Even some infections including tuberculosis can appear similar to metastases. If the diagnosis cannot be made based on a clinical and/or radiological basis, a biopsy of a lesion in question can be performed to resolve the issue. The biopsy material should be analyzed for hormonal receptors and HER2 receptors, as these may aid in treatment decisions.

Since, most often, liver metastases are part of a generalized metastatic process, treatment is systemic in nature. That is, systemic therapy in the form of chemotherapy, HER2-directed therapy and hormonal therapy are used. In general, there is a tendency not to use hormonal therapy, as it is believed that liver metastases do not respond to hormones. This is not correct. Hormonal therapy can be used in patients with hormone positive breast cancer as long as one is not dealing with extensive or rapidly progressive disease.

There are situations when limited liver disease appears to be the first and only site of breast cancer recurrence. In such a situation, one can consider surgical resection of the liver metastases or some type of ablative procedure, such as freezing the lesions. This can be done either before or after giving systemic drug therapy. In highly selected patients, this can result in good long term control. This is not a manner of treatment that can be used for extensive disease or rapidly progressive disease. I do not advocate its use when other organs are also involved.

For some cancers that invade the liver, such as colon cancer,

chemotherapy can be infused using a catheter directly into the circulation of the liver. This is sometimes done for liver involvement from breast cancer but, in my experience, it is not particularly effective. It is best to give the chemotherapy intravenously.

Normal liver tissue does not tolerate radiation well. Liver metastases are usually multiple and diffuse. For these reasons, radiation of liver lesions is not a reasonable option.

There are no drugs that are specific for breast cancer that has spread to the liver. All of the systemic agents that are used for metastatic breast cancer in other locations are useful for metastatic disease to the liver. Liver metastases are rarely a localized process and it is this principle that dominates the overall management of this entity.

WHAT'S NEW**GUIDING THERAPY BASED ON TUMOR RESPONSE**

The concept underlying pre-operative or neoadjuvant therapy is that, rather than removing the tumor as the initial treatment, the tumor is left in place so that one can directly observe its size while chemotherapy is given. If, after a few doses of a chosen chemotherapy, one does not see reduction in the tumor size, one infers that the present chemotherapy is unlikely to work and the therapy can be changed. Surgery, in the form of either a lumpectomy or a mastectomy is performed after the chemotherapy is completed. An increasing number of patients, even those with small tumors, are now being treated in this manner. Generally, after two doses of a chemotherapy, the tumor is re-measured and a decision made as to whether it is smaller or not. If it is smaller, that is evidence of a beneficial effect and the

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WHAT'S NEW continued

same therapy is continued for several additional cycles. If instead the tumor remains the same size or is found to be enlarging, the therapy is judged to be ineffective and is discontinued and another chemotherapy program is substituted.

One must realize that even in tumors that appear to be responding after two doses, continuing the same therapy may or may not be optimal. For example, it is possible that changing to a different therapy might be better than continuing with the same program. Similarly, if it looks like a tumor is not responding after only two cycles, this does not automatically mean that if one gives a few more cycles the tumor might not respond. Changing therapy at this point is not necessarily optimal either. Each of these questions must be subjected to clinical trials.

An important trial dealing with these issues was recently published in the *Journal of Clinical Oncology* by Dr. Gunter von Minckwitz and colleagues from Europe. The trial, known as the GeparTrio study included 2,072 patients with early breast cancer all of whom were given two cycles of Taxotere/Adriamycin/Cytosan (TAC) therapy. After two cycles, they were divided into two groups based on whether there was a tumor response or not. Those who had a response were then randomized to receive either four or six additional cycles of the same therapy-TAC. Those whose tumor did not respond, were randomized to either receive four more cycles of TAC or were switched to Navelbine and Xeloda. All patients were subsequently treated with surgery. The patients have been followed for a median of 62 months to determine tumor recurrence and survival.

The results from this trial demonstrate that the responding group that received six additional doses of TAC (rather than only four additional cycles) and the non-responding group that switched to the combination of Navelbine and Xeloda experienced some modest improvement in the time it took to see a recurrence.

However, there was minimal, if any, survival benefit.

What can we learn from this study with results that were somewhat disappointing? Several things-let us start with these principles: First, we need to recognize that the results from one study cannot be taken as final evidence for or against a treatment approach. Second, we should appreciate that, in a tumor that is responding, giving a total of eight versus six cycles of the same therapy may not add much more benefit. Perhaps even here, changing to another therapy may be best. Third, in a tumor that is not responding, which drugs you switch to may be critical. Ideally, the new therapy must be very effective since three powerful drugs (TAC) have failed to affect the tumor. Tumor profiling, with specific matching of drugs to the tumor's own peculiarities, is likely to be what will be most successful.

Though the results of this study were disappointing, the lessons we have learned can be put to good use in how we design subsequent trials. Knowing what strategies are not optimal is important and valuable information that should not be underestimated.

Reference: Von Minckwitz G, *Journal of Clinical Oncology*, 2013;doi:10.1200/JCO.2013.51.0313

MARITAL STATUS AND CANCER SURVIVAL

An interesting observation noted in several prior studies is that married people with cancer tend to live longer than unmarried people with cancer. Some studies have shown that this is true for men but not for women. This relationship has not been consistent, however, with some studies failing to demonstrate any relationship between marital status and cancer survival. Such studies have generally been limited to specific tumor types. A new study addressing this issue was recently published by Dr. Ayal Aizer and colleagues.

The researchers used patient data from the Surveillance,

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PREVIOUS ISSUES

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WHAT'S NEW continued

Epidemiology and End Results (SEER) database which is sponsored and maintained by the National Cancer Institute and captures data from approximately 26 percent of the U.S. population. The study initially identified 1,260,898 patients diagnosed from 2004 through 2008 with one of 10 common cancers. The cancers included were (1) lung, (2) colorectal, (3) breast, (4) pancreatic, (5) prostate, (6) liver, (7) non-Hodgkin lymphoma, (8) head and neck, (9) ovarian and (10) esophageal cancer. Patients were excluded from the final analysis if they were less than age 18, had more than one cancer, their cancer was diagnosed at autopsy or their information was incomplete. This left 734,889 patients for the final analysis.

The question that the researcher wanted to address was whether a person's marital status at the time of diagnosis was related to the stage of presentation of the cancer, the type of therapy that they received and their survival. They were interested in this relationship both as it applied to the group as a whole, and, also as it applied to patients based on each of the 10 tumor types. Marital status was classified as married versus unmarried, which included those who were single, widowed, separated or divorced. The median follow-up for the patients analyzed for cancer-specific survival was 3.1 years.

The results of this study are that those who were married were less likely to present with metastatic cancer, were more likely to have definitive, curative therapy such as surgery or radiation and were less likely to die of their cancer than those who were unmarried. The difference for each of these parameters was more striking for men than it was for women. Further, when patients were separated based on the 10 different tumor types, the same results were found for patients in each tumor category.

This study is useful in that it contained a large number of patients and looked at different tumors. Consistent results were

observed, suggesting that the advantage of marriage is true for at least the majority of common tumors, implying a general underlying mechanism. Though several explanations are offered by the authors as to why being unmarried places a patient at a disadvantage, these data cannot provide an answer. Is this a biological phenomenon, a social phenomenon, an emotional phenomenon or is it financial? The difference in outcome between married and unmarried people is large enough to be comparable to the differences noted with the administration of many chemotherapy programs. Consequently, the authors suggest that unmarried patients be considered as being a higher risk category.

So, what do we do with this information? Do we encourage the American public to get married and stay married? Do we need to create support groups that are specific to the unmarried? Would that be enough? I don't have an answer. For me, what all of this comes down to is realizing that social contact is perhaps valuable in ways that we do not understand. Perhaps, deep and meaningful relationships are of greater influence than superficial encounters at the gym and neighbors whose names you do not know. Perhaps cultivating relationships with cell phones, computers and television sets are inadequate substitutes.

Reference: Ayal A. Aizer, *Journal of Clinical Oncology*, 31:3869-3876

QUESTIONS & ANSWERS

(Q) Dr. Martino, I was diagnosed with breast cancer 10 years ago. I had a large tumor with tumor in my lymph nodes as well. I was given chemotherapy for six months. During that time, I developed an anemia. My oncologist gave me a drug, I think it was called procrit several times for this problem. It helped with my anemia. Now I have developed a second breast cancer and I am on chemotherapy again. I have developed anemia as a side effect this time, too. But now, my oncologist who is not the same

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DISCLOSURE

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QUESTIONS & ANSWERS continued

one I had before has refused to give me anything for the anemia. He has treated me with blood transfusions. I don't like getting blood. It is time consuming and I know that you can have bad reactions to it. My doctor has told me that the procrit that I got before is bad for me. I don't understand why it's bad and why I cannot have it now. It was so much easier.

(A) It is not uncommon for people who are receiving chemotherapy to develop anemia. The manner in which we treat the anemia has changed. In the past, we had the option of either giving blood transfusions or of giving a drug such as procrit to help correct the anemia. These drugs are still available and are used for certain specific causes of anemia. Several years ago, it was recognized that in several types of cancers, patients who had their anemia treated with these agents actually did worse. In fact, their survival was worse if they received these agents. It is for this reason that their use was restricted in cancer patients. Your new oncologist is aware of this information. It is for this reason that you are now being treated with blood transfusions. I agree that blood transfusions are more cumbersome and time consuming. Reactions can occur and infections can be transmitted. Nevertheless, it is the option available at this time.

(Q) Dear readers, this is a question from me to you. A lady recently wrote to me about side effects that she experienced during her chemotherapy. I had not heard of these side effects before with her particular therapy, so I asked her if I might provide you with her description and see if any of you have had a similar experience.

The patient was diagnosed with breast cancer in March of 2012. Adjuvant therapy with Taxotere/Carboplatin/Herceptin was planned. During this therapy, she developed shaking of her whole body, especially her legs. This interfered with many activities including writing. Her legs felt like concrete, making it

difficult for her to walk, get in and out of her car and walk up and down stairs. The severity of this resulted in the need to stop her therapy. She has slowly improved during the past year-and-a-half, but is not back to normal.

These symptoms sound most like neuropathy, which is a known side effect of the drugs she received; but, the aspect of her entire body shaking is a side effect I have not heard described before. Have any of you had a similar experience? Please let me know. Perhaps we can all learn something from this.

OBESITY—A CHALLENGE FOR OUR TIMES

The past three months have been particularly busy for me. I have attended multiple meetings both in the U.S. and Europe. Though I enjoyed each meeting, the overall experience was exhausting and a bit overwhelming. I was anticipating a cruise to the Caribbean islands that we had planned with some friends. I was looking forward to a brief period of true relaxation during which I planned on not thinking about anything serious and certainly nothing related to my work. I had high hopes of accomplishing this state of mental and spiritual relaxation.

Alas, it was not to be. We boarded the ship on a Saturday afternoon. By breakfast time the next morning, healthcare thoughts began to encroach on my mind. The basis of the disturbance was my observation that at least 90% of the 4,000 passengers were markedly obese. Most of the remaining 10% were simply overweight. Only a few were thin or of normal weight. My first thought was that since this was a cruise and such excursions are known to provide abundant and frequent meals, that I was probably looking at a biased sample of the U.S. population. Perhaps, these were travelers who simply liked to eat more than most. This may have been true to some degree. However, I truly

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OBESITY continued

had to look hard to find the few who were not obese. Those who were merely overweight became the exception. I confess that I found this particularly disturbing. I knew that the U.S. population had an increasing proportion of both adults and children who were obese, but I truly had blinded myself to how much of a problem it had become. In spite of the warm weather and the beautiful natural surroundings, I could not get this reality out of my mind.

Please recognize that this is not just a social commentary on my part. This is the doctor in me realizing what a serious problem we have and the medical consequences that will follow from this pattern. The diet and beauty industries have done a good job of emphasizing the cosmetic aspects of weight control, but those of us in the medical profession have done a poor job of convincing our citizens of the serious health risks that accompany weight gain. This is an incomplete list of health problems that we already know are related to being overweight; (1) diabetes, (2) cardiovascular disease, (3) heart disease, (4) stroke, (5) cancer, (6) high blood pressure, (7) high cholesterol, (8) metabolic syndrome, (9) sleep apnea, (10) asthma, (11) arthritis, (12) gallbladder disease, (13) liver disease, (14) urinary incontinence and (16) depression. There probably are others, but these are the health issues we presently recognize.

So, who is to blame for this growing problem? I think we all are! We eat too much, we don't move enough and we want a simple and quick solution. We want magic—we want a pill. The fact is that there are lots of pills. Most of them are available without a prescription and there are many websites and health food stores that are more than willing to sell them to you. There are so many that you can spend a life time trying them.

To a reasonable degree, I think the fault lies with those of us in the medical profession. For many years, we chose to ignore

diet and nutrition. We thought of it as not really a serious part of our responsibility, other than in diabetics. We looked down on physicians who dealt with weight loss. We thought of them as doctors who ran “fat farms” and were primarily motivated by money and we did not view this as serious medical work. One of my own fellow residents, during my internal medicine training, was exactly such a physician. Right out of his training in 1977, he set up a weight loss clinic. We all thought he had abdicated his role as a true physician and that he was only interested in getting rich. Well, years later, many of us realized that perhaps he was the best of us. Perhaps, he understood even then, something that the rest of us failed to grasp.

Due to the medical profession entering late into the fields of nutrition and weight control, I believe that it has left the door open for others to dominate this arena. A visit to any book store, or a Google search, will demonstrate that there are hundreds, if not thousands, of gurus on weight management. Each has their own philosophy or fantasy to sell you. The variety is astounding. The options are confusing. Everything seems to work briefly and then you go back to your usual patterns.

I wish I knew the answer to this dilemma. I doubt that there will be a magical solution. I think we were meant to eat less food, not drink artificial beverages, reduce alcohol consumption, and eat food that does not come in a pre-cooked box or can and not sit for hours on end as we do now. I don't think it can be done for us. We each must do it ourselves and we must start now.



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Holidays!

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