Breast Cancer Advisor

BY DR. SILVANA MARTINO

September 2013

Dear Readers,

I wish to express my gratitude to those who have sent comments on the new look of the Breast Cancer Advisor. The general consensus appears to be that many of you find it easier to read; therefore, we shall continue the new format.

I recently attended the Breast Cancer Symposium 2013 in San Francisco. Some of the concepts presented at that meeting are summarized and discussed in this issue.

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 LUNGS

The lungs are a common site for breast cancer metastases. Metastases to this part of the body can demonstrate several patterns: (1) tumor spread to the lung tissue itself, (2) tumor spread to the pleura or covering of the lungs, (3) lymphangitic spread and (4) tumor in the bronchial tubes.

The primary function of the lungs is to exchange gases with the environment; the process of breathing. The lungs are designed like a bunch of grapes (similar to breast tissue actually). Bronchial tubes (similar to stems) carry air down to a network of small round structures, the alveoli, that are thin walled and elastic (the skin of grapes) and through these, the exchange of gases occurs. On the outside of these grape-like structures are small blood vessels

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BIOLOGY BASICS continued

(capillaries) that bring gases to and from the body and exchange gases with the lungs.

All patterns of lung metastasis share common symptoms that relate to lung function. The symptoms include cough, shortness of breath, a feeling of heaviness in the chest, a sound of gurgling in the chest and a feeling that one has no energy. Lung metastases, especially to the lung tissue itself (the parenchyma), can exist without any symptoms and found only on a scan or an x-ray.

Tumor spread directly to the lung parenchyma gives a typical picture on scan or x-ray. One or more round masses will be seen. This must be distinguished from a primary lung cancer, particularly if there is only one mass. It is not uncommon to see small nodules measuring less than one centimeter on routine CT scans. These are often too small to be certain whether they are malignant or benign. Even a PET scan may not help in answering this question because of the small size of these lesions. They are often too small to biopsy. In such cases, they are observed over time to see if they grow, which would then be a clue that they may be malignant.

When tumor has spread to the covering of the lungs, it often causes fluid to accumulate between the lungs and the chest wall. This fluid, called pleural fluid, will restrict the movement of the lungs and decrease their ability to expand during the process of breathing. Most often this will be a unilateral process. At times it will occur on both sides. This pattern of disease will often cause more symptoms of shortness of breath when a person is lying down rather than when upright. Depending on the amount of fluid that accumulates, your doctor may advise that this fluid be mechanically drained. This fluid often re-accumulates, so it may need to be drained more than once.

The most complex pattern of tumor involvement of the lungs is lymphangitic spread. In this pattern, tumor cells are positioned in the space between the alveoli of the lung and the capillaries of the circulatory (blood) system. This creates a mechanical barrier between the lung and blood system such that gases (air) cannot move between them. This creates a particular clinical picture that one must learn to recognize. The patient is often very short of breath, but the x-ray looks normal. Perhaps there may be a small amount of pleural fluid, but not enough to explain the severity of shortness of breath. A CT scan may be a bit more helpful but not always. It, too, may look normal. A patient may deteriorate quickly. Prompt treatment with steroids will improve symptoms.

Tumor positioned within the bronchial tubes is uncommon in breast cancer. If it occurs, it may obstruct and cause collapse of the alveolar system distal to the obstruction.

Clinically, it is important to recognize all of these patterns by which metastatic disease can manifest in the lung area. A biopsy may be necessary to prove the process and to clarify that it is breast cancer. Therapy may involve steroids for lymphangitic disease or fluid drainage for pleural effusion. Ultimately, one must control the underlying cancer process. This is best done with drug therapy based on the particular details of the tumor itself and includes hormones, chemotherapy, and HER 2 directed therapy. Please review prior issues of the Breast Cancer Advisor for details on the management of metastatic disease.

WHAT'S NEW

BREAST CANCER PREVENTION

A valid criticism of traditional "Western Medicine" is our focus on treating disease rather than viewing disease prevention as our primary focus. Most of us do not see a doctor unless we suspect

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WHAT'S NEW continued

that we have a problem. One of the goals of our new health care program (the Affordable Care Act/OBAMACARE) is to change this attitude and make preventive care a more serious aspect of medicine in the future. If we can prevent disease, not only will we be a healthier population, but, also, we may be able to reduce the overall cost of medical care. To move us in this direction, many medical societies are now increasing and fortifying their recommendations for therapies that have been shown to prevent certain diseases. The diseases that are most common in the U.S. population are the ones receiving the most attention. Among these recommendations, is a renewed emphasis on breast cancer prevention.

The original observation that breast cancer could be prevented (or more specifically its probability reduced) was made many years ago when it was noted that premenopausal women who had their ovaries removed were less likely to develop breast cancer. More recently, when the hormonal drug tamoxifen was introduced as adjuvant therapy for treatment of early breast cancer, it was observed that women who were taking this drug developed about half the breast cancers of the opposite breast as anticipated. This led to the question of whether tamoxifen was not only therapy for existing breast cancer, but if it was also a preventive agent. Studies have demonstrated that this conclusion was correct. In high risk women, those treated with tamoxifen developed about 50% less breast cancers than women given placebo. Similar results were obtained when the hormones raloxifene (EVISTA) and exemestane (AROMASIN) were compared to placebo. All of these studies confirmed the observation that had been made years previously in women who had their ovaries removed: namely; that by reducing the body's estrogen content, you can reduce the incidence of breast cancer by about one-half.

These studies also demonstrated that these various hormonal maneuvers were only effective in reducing hormone positive breast cancers (estrogen and progesterone receptor positive) and not hormone negative breast cancers. The number of hormone negative breast cancers were neither decreased nor increased in number. About 70% of all breast cancers are hormone positive, so even though these maneuvers do not affect all breast cancer types, they are effective against the most common type.

These are not recommendations for all women. They are recommendations for women age 35 or over and who are considered to be at high risk for developing breast cancer. There are several mathematical tools (models) that can be used to calculate an individual's risk of developing breast cancer. The GAIL model is a commonly used and simple tool that your doctor can find online to calculate your risk.

Though this knowledge has been available for at least 15 years, breast cancer prevention using these hormonal modalities has not become common practice. I believe that the reason for this is, in part, because these therapies use drugs more familiar to an oncologist than to physicians who practice primary care. It is my belief that prevention of cancer should not be "specialty care" but rather must be within the province of physicians who deal with healthy people. It should be part of primary care, internal medicine and gynecology. If we can educate these physicians to recognize disease prevention as their role, we will have a much better chance of moving our medical system and our nation to a preventive medical model and not continue our emphasis on care after disease detection. I do believe in the old adage that "an ounce of prevention is worth a pound of cure."

OPTIMAL SCHEDULE FOR TAXOL

The chemotherapy drug paclitaxel (Taxol) is one of the most commonly used drugs for both adjuvant and metastatic breast cancer. It can be administered once per week, every two weeks and at the original schedule of every three weeks. In both the adjuvant and metastatic setting, comparison of the weekly

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DISCLOSURE

WHAT'S NEW continued

versus the original three week schedule demonstrated that the weekly schedule was more effective and less toxic. The three week schedule has been essentially abandoned for the treatment of breast cancer.

What has provided complexity in the administration of this drug during the past several years has been a regimen studied in the adjuvant setting called "dose dense therapy." That study was a direct comparison of 4 cycles of Adriamycin/Cytoxan followed by 4 cycles of Taxol given either every 2 weeks or every 3 weeks. This comparison demonstrated that the more "dose dense" schedule of chemotherapy given every 2 weeks was superior. This was particularly true in patients with hormone negative breast cancer. What has been missing until recently was an answer to the question of whether weekly administration of Taxol was better than the dose dense two week schedule. I believe that we now have the answer.

The study addressing the question of weekly versus every two week administration of Taxol was conducted by the Southwest Oncology Group (SWOG), and the data were presented by Dr. G. Thomas Budd from the Cleveland Clinic's Taussig Cancer Institute at the recent American Society of Clinical Oncology meeting. The trial named S0221 included 3,294 women with both node negative and node positive breast cancer. All patients first received Adriamycin/ Cytoxan, followed by Taxol given either once per week at a dose of 80 mg/m2 for 12 weeks or at a dose of 175 mg/m2 every two weeks for a total of six doses. The growth factor pegfilgrastim (Neulasta) was given subsequent to each dose with the every two week schedule only. All patients were then followed to observe for tumor recurrence and survival. At about 5 years of follow up, the results (recurrence and survival) were identical between the two groups. There was no difference whether Taxol was given once per week or given every two weeks. There were, however, some differences in toxicities between the two schedules. Patients in the weekly schedule experienced lower white cell counts but without infections. Patients in the every two week schedule had more allergic reactions, musculoskeletal pain and peripheral neuropathy.

This was an important trial. It clarified that giving Taxol either once per week or every two weeks were equally effective. The weekly schedule can now be used even in the "dose dense" program. The advantage of this schedule is its lower toxicity and the fact that one does not need to add Neulasta to prevent infections. This reduced the side effects and cost of therapy. For patients who may wish to reduce the number of trips to the chemotherapy center, the two week schedule, which does require Neulasta, can be chosen. Though it is true that in this trial there was more toxicity with the two week schedule, the level of toxicity may have been a bit exaggerated since the typical number of cycles given when we use the two week schedule is 4 and in this trial as a way of giving therapy for the same number of weeks in both treatments schedules they actually gave 6 cycles. We now have two equally effective schedules when giving Taxol. Each patient and their doctor can choose which is more convenient for them.

MEETING REVIEW

THE BREAST CANCER SYMPOSIUM 2013

This yearly breast cancer meeting was co-sponsored by several national breast cancer organizations including the American Society of Clinical Oncology, the Society of Surgical Oncology, the American Society of Breast Disease and others. Its focus is to provide a multidisciplinary perspective on the clinical management of breast cancer. This year's meeting was primarily structured to provide discussion on management topics that remain controversial. Several major themes were debated. I admit that what I found most meaningful were not the same topics as I have seen reported in the public media. I will outline the main themes here and discuss them more fully is subsequent issues.

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MEETING REVIEW continued

OVER DIAGNOSIS

The concept of over diagnosis has become a major issue in the field of oncology. In part this is a true medical issue. In part, it is a financial issue and reflects the high cost of medical care in the U.S. and the financial burden of medical care on our economy and government. It is in light of this medical and economic background that the prior recommendations for screening tests such as mammography, PSA, and frequency of colonoscopy have been reviewed and revised. Within the field of breast cancer, the value of screening mammography has been challenged. This is particularly true in the diagnosis of ductal carcinoma in situ. There are those who feel that this entity does not necessarily need to be diagnosed and that its name should be changed. Specifically, the term carcinoma should be removed. Others feel that it should be diagnosed and, perhaps, only observed rather than routinely treated. Even if surgically removed, radiation should not always follow.

The attitude that we have had towards cancer in the past 30 years has been to champion early detection and early diagnosis. This has been based on the premise that if you can identify disease as early as possible, you can prevent metastases and death. Yet, if we find disease too early, we then have the problem of finding changes that may not really be disease. We may identify tissue changes that will never go on to become a problem at all. This is even more of an issue in older women for whom survival based on age and other medical conditions make the diagnosis of breast changes at an early point even less valuable, since with advancing age it becomes increasingly likely that an abnormality may not cause a problem within that person's life time. These are not simple issues either ethically or medically. Perhaps the real issue is not over diagnosis but rather overtreatment.

REDUCING TREATMENT

The concept of using systemic drug therapy (adjuvant therapy) in early invasive breast cancer for the purpose of increasing cure rate began in the 1970's. As these therapies have improved, not only have we seen less systemic recurrences, but local control in the breast and chest wall area has also improved. This has called into question the extent of both surgical and radiation therapy that is necessary to achieve local control. Questions about margin size, number of lymph nodes that need to be removed and when and how much radiation is needed are being re-considered. The theme is again that of whether we are "over treating" some patients with each of these modalities. It is important to note that while the medical profession is struggling with issues of over treatment, there has been a clear increase in mastectomy and double mastectomy rates in the U.S. during the past decade. This trend has been driven in part by patients choosing these more aggressive surgical procedures. There is substantial evidence that patients overestimate their risk of local recurrence and of contralateral disease and, thus, choose more aggressive surgical treatment often in spite of recommendations from their physicians.

NEO-ADJUVANT CHEMOTHERAPY

One of the dominant controversies at the present time is whether we should restructure the manner in which we investigate new drugs for early breast cancer. At the center of this issue is the concern that it takes too long to get a drug approved for common use and that our studies take too long to complete and are too expensive. Is there a better way to do studies that would solve these issues?

The treatment pattern for the past 30 years has been to first do surgery, and then use the information obtained from surgery to determine what drug therapy to prescribe. If one is doing a study and a new therapy is to be compared to an existing therapy, two groups of patients are needed, one treated by each of the two therapies. All patients are then followed for years to observe for recurrence and survival rates. Based on which treatment group does best, a winning therapy is declared. The number of patients needed in this trial design is two to four thousand. Since one is waiting to count

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PREVIOUS ISSUES

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MEETING REVIEW continued

the number of recurrences and deaths that occur, follow up time is a minimum of about 3 years and more often in the range of 5 years. The present question is whether we should change this study design and adopt a design that is more time and cost efficient.

The new proposed design is based on the principle of neoadjuvant chemotherapy. In this model, drug therapy would be given at an earlier time point and surgery would then follow rather than the other way around as we have been doing. Specifically, a biopsy would be done, a drug therapy would be administered (presumably a new therapy) for a number of cycles, one would observe whether the tumor in the breast was changing in size, and at a specified time point the patient would be taken to surgery. Surgery would yield a pathology report describing how much tumor, if any, was left in the breast and lymph nodes. Based on this pathological information, a decision would be made as to whether the therapy had been sufficiently effective or not. The specific measurement of interest would be whether any tumor had been found in the breast or lymph nodes. If none is found, this is called a pathological complete response (pCR). Remaining non-invasive breast cancer (DCIS) is allowed under this designation. The study would be considered completed at this point. There would be no specific goal to follow patients further as part of the study. A therapy would be declared a winner or loser based on the number of patients that achieved a pathological complete response. A new therapy or new drug would be approved on this basis.

Inherent in this model is the assumption that achieving a pCR correlates with a decrease in recurrence and a prolonged survival. There is some evidence that supports this assumption. Such a trial design requires only hundreds of patients and not thousands. Rather than waiting years to see a difference in outcome as in our present design of adjuvant therapy, this neoadjuvant design takes only a few months. It is quicker and more cost effective. It sounds like a great solution.

Are there reasons to question whether this will really be a step forward? There are several. Not all drugs work well in this short time period. This is particularly true of hormonal agents. It is likely that many of the existing drugs, such as tamoxifen and the aromatase inhibitors, would not have passed the test in this new setting and would not have been approved. Yet, they are very good therapies for most breast cancers. How will we identify long term toxicities in this new model since patients will be followed for a much shorter time period? Will we recognize rare side effects since we will study a much smaller number of patients? Are we certain that achieving a pCR will always translate into fewer recurrences and less deaths? If we are comparing two therapies, how much difference must be shown between the two to be certain one therapy is better than the other? Will expediency serve us well? It remains to be seen. I am cautiously optimistic on this new study design.

QUESTIONS & ANSWERS

(Q) Dr. Martino, I have heard about something called an electronic nose that can diagnose cancer anywhere in the body. Can I get this test done?

(A) I confess this is not a topic on which I am an expert. I am aware of some preliminary research data where the sense of smell is used to make a diagnosis. I believe that, in part, the basis of this is the observation that some animals, such as dogs, have demonstrated the ability to smell disease in some people. This suggests that certain disease processes give off chemicals that are carried into the air. Given a sensitive enough sense of smell, these compounds might be detectable. I know that several research groups have been pursuing this line of work. The diseases that are being most actively studied are those that primarily affect the lungs such as lung cancer, tuberculosis and asthma. Attempts are being made to analyze a person's breath and make a diagnosis. It is interesting work. It is logical. Whether it will turn out to work or not remains to be seen.

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