BreastCancerAdvisor

BY DR. SILVANA MARTINO

March 2014

Dear Readers,

In this issue, I wish to introduce to you a new program being established by THE ANGELES CLINIC FOUNDATION. We believe it represents an important step forward in how patients with cancer are treated. We are very excited to be able to offer this new approach to our community.

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

A NEW STRATEGY AGAINST CANCER

The management of patients with metastatic disease remains the biggest challenge to a medical oncologist. The goals are to improve symptoms caused by the cancer process, to maintain function and quality of life for each patient and to prolong survival. Systemic drug therapy is the primary method by which these goals are achieved. Choosing the drugs and their sequence is based on understanding which drugs are most likely to work against an individual's tumor.

There is considerable literature based on human clinical trials that provides a list of which drugs are more likely to work based on the type of tumor with which one is dealing (breast cancer, lung cancer, etc.). Whether a selected drug will actually work for a particular patient then becomes a process of trial and error.

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.

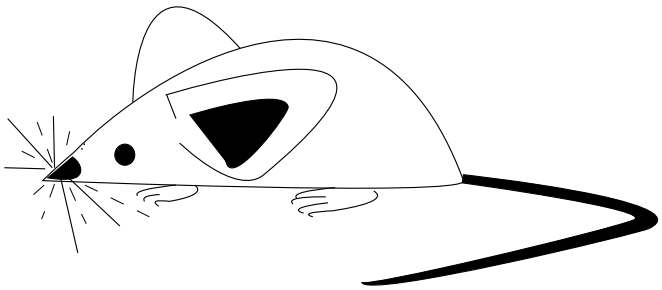
A NEW STRATEGY continued

We do not know beforehand whether the chosen therapy will be successful or not.

The question of interest is whether there is a way to reduce the level of uncertainty in this process. Is there a way to predict that a drug is unlikely to work and, therefore, should not be given and that another drug is much more likely to work in a particular patient? These questions are not new. What is now available, are new answers to these questions. Answers that we expect are superior to prior answers.

THE ANGELES CLINIC FOUNDATION is proud to announce the establishment of a collaboration with CHAMPIONS ONCOLOGY, a recognized leader in providing personalized oncology clinical testing services. Headquartered in New Jersey, and with facilities in Europe, Israel and China, our relationship with CHAMPIONS ONCOLOGY will allow us to offer patients, and our community a unique system for choosing optimal drug therapy through the creation of personalized TumorGrafts™.

The process begins with the acquisition of fresh tumor tissue obtained from a biopsy (FNA, core, or surgical) which is then engrafted (implanted) in its entirety (including its surrounding stromal compartment) into a specialized mouse host. This process is different from many other systems where tumor cells from a biopsy are separated from their surrounding and supporting structures. By implanting the tumor, plus its surrounding microenvironment, the animal tumor grafts continue to closely resemble the patient's own tumor with high genetic correlation. Engraftment into a specialized mouse is successful from 70% to 80% of biopsies, including from solid tumors, lymphomas and many leukemias. Tumor engraftment and growth occurs over a 12-20 week time period. Some tumors grow more quickly than others. At that point, molecular analysis of the tumor and drug testing can be performed on multiple mice bearing the engrafted tumor. The mice serve as surrogates for the patient. The drugs to be tested are based on the patient's clinical history and the results from tumor analysis and are selected by the treating physician in consultation with the scientific staff of CHAMPIONS ONCOLOGY and the patient. Multiple drugs (standard, experimental, targeted biological agents, antiangiogenics and combinations) can be



tested simultaneously on colonies of tumor bearing mice, thus avoiding the trial and error process that patients are exposed to in treating their disease. Data from CHAMPIONS ONCOLOGY suggest that concordance between patient clinical response and the response observed in tumor bearing mice has been about 90% in patients that have been treated using this system. We believe that this level of predictability is superior to other screening systems and is the motive for wanting to offer this service to patients.

Are there patients whose disease is most suited to this type of drug testing? In reality, any person can choose to have their tumor processed in this manner. However, I believe that there are clinical circumstances when this information is most useful and others where the information is less valuable. It is most useful

continued next page

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A NEW STRATEGY continued

for a patient with metastatic disease where long term therapy is being planned. It is less useful for patients with an early cancer where the probability of cure with well-known adjuvant chemotherapy programs is high and the likelihood of recurrence and need for further therapy is low. Since this process takes several months, it is not useful for someone who must start therapy quickly. In that situation, the next therapy should be chosen based on usual parameters and the information from the TumorGrafts™can be reserved and used for subsequent decision making. A report of the drug testing results is provided to the referring physician for discussion with their patient and for clinical decision making.

I wish to emphasize to our readers that this process is not limited to those who have a diagnosis of breast cancer. This innovative and optimal strategy for drug selection is equally successful for other cancers.

The development of TumorGrafts™ not only has implication for selecting drug therapy for individual patients but, also, has implications for how CLINICAL TRIALS are done. This is best understood in concert with recent developments in the field of cancer biology.

For decades, clinical trials have been based on the assumption that cancers originating in an organ, such as the breast, were essentially all the same. Therefore, when a new drug therapy was to be tested, the patients included in the study would be selected exclusively based on the parameter of organ site. With time, in breast cancer, the estrogen and progesterone receptors were recognized; and, thereafter, for some therapies, receptor status further refined patient selection. The recent discovery of HER2 receptors on some breast cancers resulted in a further point of refinement. With each of these tumor characteristics, our ability to study patients who were likely to benefit from specific drugs has improved considerably. This has had a direct relationship to improving outcome for patients. We are much more accurate in knowing which patients will benefit from hormonal therapy and which will need chemotherapy. Likewise, we know who is likely to benefit from agents such as Herceptin, and who will not.

Techniques are now available that allow us to study tumors in increasingly greater biological detail. We anticipate that our deeper understanding of tumor biology will soon revolutionize the process of drug development which until now has closely mirrored the historical, organ based, homogenous view of cancer. Further, we anticipate that tumors will be reclassified based on molecular characteristics and grouped for therapeutic trials based on their molecular profiles and no longer on organ of origin or histologic type. Thus, tumors that express a common mutation(s) will populate a study irrespective of organ site. For example, HER2 receptors are not only found on some breast cancers, but, are also found on some lung cancers, stomach cancers and other tumors. These cancers are collectively more likely to respond to drugs that target the HER2 receptor and should be studied together.

The creation of TumorGrafts™ as is done by CHAMPIONS ONCOLOGY, also offers the opportunity to further expedite the drug development process. By providing a large bank of mice bearing well characterized tumors, therapeutic trials can first be conducted using these animals. We view such a tumor bank as distinctively different from traditional tumor banks that maintain tissue in a frozen or otherwise preserved state. TumorGrafts™ from CHAMPIONS ONCOLOGY maintain tumors in live and functional animals, thus, preserving more of the natural and evolving properties of the tumor. Additionally, the host animal's own biological systems will interact with the tumor, providing an environment similar to the patient. These properties provide a

continued next page

PREVIOUS ISSUES

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A NEW STRATEGY continued

biological system that more closely mimics the natural human experience. This approach will be safer, quicker and more cost effective, thus, considerably expediting what is now a cumbersome drug development process.

I believe that we are in an era of great scientific discovery. I have practiced medical oncology for over thirty years and have never been more hopeful about our progress. It is clear to me that the pace at which new knowledge is being acquired has greatly increased. We have more and better therapeutic agents with which to fight cancer. I am excited and very optimistic about the future of medicine.

WHAT'S NEW

CANADIAN MAMMOGRAPHY TRIAL — LONG TERM RESULTS

This is another study adding confusion to the already controversial issue about the value of screening mammography. The history of screening mammography dates back to randomized trials conducted in the 1960s to 1980s. Meta-analyses of these trials showed a relative reduction in breast cancer death rate for women aged 50-69. However, the Canadian trial which was conducted in women aged 40-59, did not show a reduction in breast cancer death rate. So, from the beginning, this study reached a different conclusion. The most recent update from this study, titled "Twenty five Year Follow-up for Breast Cancer Incidence and Mortality of the Canadian National Breast Screening Study: Randomized Screening Trial" was published in the February issue of the British Medical Journal. It reached two main conclusions: (1) that annual screening mammography in women aged 40-59 does not reduce breast cancer mortality when compared to physical examination or usual care, and (2) screening mammography results in over diagnosis of breast cancers. Over diagnosis is not the same as false positives. It is best to view it as cancers that would not be expected to cause death if left undiagnosed and untreated.

The study began in 1980 and was conducted in 15 screening centers in six Canadian provinces. It included a total of 89,835 women aged 40-59 who were divided into two groups. Those aged 40-49 were randomized to five yearly mammograms plus a yearly physical breast exam or to usual care in the community. The age group 50-59 was randomized to five yearly mammograms plus a yearly physical breast exam versus a yearly physical breast exam. After the completion of the five year period of the study, the women were returned to the usual community standard of care and follow-up. Data has been collected on these women for the past 25 years, including diagnosis of breast cancers, death from breast cancer and death from other causes.

This publication has re-ignited the battle. There is a deep division on this issue already. As is usual, one can predict who will be on each side of this divide. Those who pay for this service are generally on one side and those who perform this service are generally on the opposite side. Those who question the value of screening mammography are quick to point out that this is a large trial with long term follow-up in a country with socialized medicine, where record keeping is efficient and cause of death is accurately recorded. Those who strongly believe in the value of mammography, argue that the mammography performed was of poor quality, that there was little difference in size between tumors found on mammography versus those found by physical exam, that too many women were diagnosed at a stage where they had lymph node involvement, that educating these women to do breast self-exam is not the usual community care and that having medical personnel perform a yearly clinical breast exam is not standard practice. In essence they argue that this was

continued next page

DISCLOSURE

WHAT'S NEW continued

simply not a good study and that the mammography performed was not of good quality.

We need to recognize that the concept of screening is based on the principle that tumors grow and behave in a simple and progressive manner; that they start small and get gradually bigger; that they only spread once they get to a certain size; that if you can find them early, they can all be cured. These assumptions do not always hold true. With a better understanding of biology, we now know that breast cancers are not all the same. This is true from their very beginning. Some grow slowly and some grow more quickly. Some spread early and others may not spread at all. Growth is probably not orderly and steady. The process of screening cannot accommodate all of these patterns equally as well.

I am reminded of the bell shaped curve, which I find describes much of biology. Most events fall in the middle, but there are two extremes that must also be dealt with. At one end of the spectrum of breast cancer, there are tumors that are so aggressive that finding them earlier when their size is smaller probably makes no real difference. Mammography screening is probably irrelevant for these. At the other end of the spectrum, there are breast cancers that grow so slowly that making an early diagnosis probably makes no real difference either as they are unlikely to result in death.

I am reminded of another principle. No single study - no matter how well conducted it appears to have been, should by itself guide policy. There are always flaws and there is always bias. Perhaps more importantly, no population of study patients is truly representative of the entire population of those affected or at risk. It is the sum of data that provides a more reliable conclusion.

HIGHER BAR FOR CANCER TRIALS

The American Society of Clinical Oncology (ASCO) has published the resulting opinion from a working group of experts on the topic of what both clinicians and patients should expect from clinical trials. One of the group's main conclusions was that oncology clinical trials that compare different therapies should be designed so that the primary endpoint of overall survival benefit is a more meaningful one. This implies two ideas: First, that overall survival should be the primary goal of most studies that compare therapies. Second, that when comparing several therapies, the difference in the lengths of survival should be meaningful. That is, it should be at least in the range of 2.5 to 6 months and not less. There have been studies where the difference has been in the range of only a few weeks. Most of us would not accept that as a particularly "meaningful" difference, even though mathematically these small time differences reached "statistical" significance.

The working group further concluded that for a secondary endpoints of 1-year survival rates, an absolute difference of 8% to 15% should be demonstrated. If progression-free survival (no apparent growth in tumor measurements) is used as a secondary endpoint, an improvement of 3 to 5 months should be required.

On the surface, it may seem that convening a panel of experts to reach and publish such conclusions should be unnecessary. Their conclusions appear self-evident and even modest. However, I believe that this exercise and especially publishing these conclusions is actually very important. Studies are generally designed based on statistical principles that will demonstrate statistical differences, which are not the same as differences that are clinically meaningful. The word "significant" when describing clinical trial results is often misused and misunderstood by many physicians, most patients and the lay press. I am reminded of an old adage in this context---"not all that shines is gold." Yes, we all must demand more from therapies!

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smartino@theangelesclinicfoundation.org

QUESTIONS & ANSWERS

(Q) Dr. Martino, I know that there is a vaccine to prevent cervical cancer. Why is there not a similar vaccine for breast cancer?

(A) Research to develop vaccines to prevent cancer has been ongoing for some years. Most results have not been particularly successful. The most successful vaccine strategies available in medicine are therapies directed at diseases that have a virus or bacteria as their cause. This is the basis of the vaccines that you reference relative to cervical cancer. There are currently two cervical cancer vaccines available in the United States - one targets the human papillomavirus (HPV) types 6, 11, 16 and 18 and the other targets HPV types 16 and 18. Viruses and bacteria have qualities that distinguish them from a human cell and this allows the immune system to react to them more successfully. Cancer cells originate from normal human cells and are not generally appreciated by the immune system as foreign or abnormal. Most human cancers do not appear to have an infectious agent as an underlying cause and so, developing vaccines to prevent them, has thus far not been particularly successful. Nevertheless, there is great interest in this approach, particularly as we now have a better understanding of the immune system. Serious research efforts continue in this arena.

At least two types of breast cancer vaccines are being developed; vaccines that would be given to healthy women to prevent breast cancer, and vaccines that could be given once breast cancer has developed. I expect that we will see considerable progress in this field within the next ten years.

(Q) Dr. Martino, I have smoked for many years. My family has always encouraged me to stop smoking, but since I developed breast cancer one year ago, they have become more emphatic and at times nasty about it. I know they mean well, but I don't believe that my smoking caused my breast cancer so it is not clear to me why I should stop.

(A) You are correct that there is no clear evidence that smoking causes breast cancer. There is, however, a fair amount of evidence that once there has been a diagnosis of breast cancer, those who continue to smoke have a worse prognosis. This relationship has also been observed with many other tumors that do not appear to be caused by smoking. It is not clear why this is so. Perhaps, it is a reflection of what smoking does to the immune system. It may also be due to weakening of other organ functions by continued tobacco use. I suspect you know that smoking has many negative consequences on the human body. I like to remind my own patients, who smoke, that it seems foolish to me to do so much work to prevent a recurrence of breast cancer including undergoing surgery, radiation, and chemotherapy, while continuing to engage in behaviors that are toxic to the body such as smoking or consuming too much alcohol.

Also, please remember that second-hand smoke is harmful to those around you. Smoking is not just a personal event. Though it is not easy to stop smoking, I agree with your family that it is worth doing.

(Q) Dr. Martino, I was diagnosed with LCIS and I have been taking tamoxifen for three years. My oncologist has told me that tamoxifen will also help my bones since I have osteoporosis. I went to a meeting of breast cancer patients at my church recently and someone told me that tamoxifen is actually bad for my bones and that it will worsen my osteoporosis. I am concerned with this since I have poor vision and I tend to trip easily.

(A) The effect that tamoxifen has on bones is different pending on whether you are pre- or postmenopausal. For women who are postmenopausal, it has been shown to improve bone density and reduce osteoporosis. It has the opposite effect on women who are premenopausal. For them, it reduces bone density. I suspect that this may be the basis to the contradictory information that you have been given.