Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

As we approach the end of another year, the staff of The Angeles Clinic Foundation and the staff of The Angeles Clinic and Research Institute extend to you and your families our best wishes for a healthy and happy new year. We look forward to bringing you another year of commercial free news and information.

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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WHAT'S NEW

This issue of the Breast Cancer Advisor will deviate from the usual format so that I may bring you an update of information presented at the 37th San Antonio Breast Cancer Symposium. This is one of the most comprehensive breast cancer meetings worldwide. It is my personal favorite. Nearly eight thousand participants were in attendance from one hundred different countries. Some highlights have been reported by the public media.

In this issue, I will summarize topics and presentation that I consider most important and influential. The meeting was dominated by presentations on new understandings of cancer biology rather than results of new clinical data with immediate application. This is necessary, as it is a better understanding of biological principles which leads to the development of new drugs and new treatment strategies. Some aspects of the meeting will also be discussed in the January issue.

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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.

WHAT'S NEW continued

IMMUNOTHERAPY

Dr. Mary L. (Nora) Disis from the University of Washington in Seattle, Washington, and Dr. Jeffrey S. Weber, from Moffitt Cancer Center in Tampa, Florida, summarized the advancements that have been made in the field of immunotherapy.

The primary function of the immune system is to identify all that is "individually you" from all that is not you. Because of this key driving principle, the immune system has the ability to fight off invading agents such as viruses and bacteria. It is a complex system, very much like a military organization, with many divisions designed for both general defense and defense against specific targets. The immune system is kept under exquisite control by a series of checks and balances, some of which we are now beginning to understand and use in the treatment of diseases such as cancer.

It has generally been believed, that breast cancer was not a cancer where the immune system played a major defensive role. However, that understanding is undergoing revision. Researchers have recognized that some breast cancers, especially the more aggressive versions such as triple negative and Her2 positive cancers, appear to be more immunogenic. It is likely that the increased number of mutations in these cancers makes it easier for the immune system to categorize them as abnormal and not as "self," and therefore, something to be eliminated. Several researchers have reported that in some patients, tumor infiltrating lymphocytes (TILs) have been identified in these cancers. Patients where this pattern is identified appear to do better that patients where this is not seen. Perhaps, at least in these more aggressive forms of breast cancer, the immune system is more active. If that is correct, then it is likely that manipulating the immune system through its check and balance system can be effective.

There are now several drugs that have been very successful in treating more immunogenic cancers such as melanoma, kidney cancer, lung cancer and others that are now being studied in breast cancer. An interesting concept proposed by Dr. Disis is that perhaps we should not anticipate that the best place to use these agents is the metastatic setting where the tumor burden is higher, but rather in earlier disease including DCIS, where there is less tumor for the immune system to deal with.

Many scientists anticipate that the field of immunology will result in major breakthroughs in the treatment and cure of cancer.

TUMOR HETEROGENEITY

The concept of tumor heterogeneity was the single most dominant theme at this year's meeting. Innumerable presentations were giving on this topic. The importance of this topic relates to the belief that it is through this mechanism that drug resistance and treatment failure occurs.

Heterogeneity refers to the fact that within a tumor, the cancer cells are not identical. Further, this diversity increases, changes and expands over the life of the tumor and the course of disease. Cancer is best conceptualized not as the expansion of a single "bad" cell, but rather as a community of cells that we choose to collectively recognize as a single entity. It is perhaps more like a large family where the members have some common features but actually each member is an individual. Each individual is capable of reproduction, but its progeny also has some shared features that are like its parent and prior generations, but it too is an individual. Just like in a family, this process continues over time, giving rise to considerable diversity or heterogeneity. Because of

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WHAT'S NEW continued

this diversity, one mode of killing (one therapy) does not kill all members. It eliminates only those that have certain properties. The others survive to continue the process of growth and diversity.

It has generally been assumed that within a cancer, its diverse members are in competition for survival. We are now beginning to recognize that though to some degree this is probably true, we also need to consider that cells cooperate with each other to assist in each other's growth and survival. Think of this as a dysfunctional family unit. The concept of a family or a group either within its place of origin (the breast) or in a new environment (the process of metastasis) is a good model for understanding the dynamics and adaptability of cancer cells. This understanding is necessary for the development of treatment strategies.

PHARMACOGENOMICS

Dr. James N. Ingle from the Mayo Clinic in Rochester, Minnesota, delivered the William L. McGuire Memorial Lecture. His presentation was on the topic of pharmacogenomics, which he believes has been generally undervalued. This field deals with the fact that not only is a tumor heterogeneous, but so are the persons who have the cancer. He emphasized the differences in how drugs are handled by the body. This is a complex biology, but one that must be recognized. How we digest, absorb, metabolize, distribute through the body, neutralize and eliminate drugs varies from person to person. Yet, these differences are rarely recognized or measured. We have functioned for the most part as if one size fits all. An example of this are the various hormonal therapies that are used in treating hormone positive breast cancer. Even in the use of an old drug such as tamoxifen, we have yet to resolve whether measurement of the metabolizing system CYP2D6 should be part of the decision to use this agent. Both efficacy and side effects are related to how the body handles drugs, and deserve study.

CIRCULATING TUMOR CELLS

In many but not all cancer patients, one can isolate and identify cells circulating in the blood which have properties of cancer cells (CTCs). There are now several techniques by which these cells are identified. It is not clear whether all of the methods used identify the same cells, nor which method of detection is best. It is a relatively new field, so much still needs to be done in this respect. Some systems identify few of these cells, and others identify many cells. This adds to the uncertainty.

In spite of these unresolved technical issues, several uses are being made of these cells. The first use was to simply measure the number of CTCs found in the blood of patients with metastatic disease and from this infer prognosis. Patients with higher numbers had a poorer prognosis as those with few or no cells identified. The next step was to use the number of cells found in a sample of blood at the time one starts a therapy for metastatic disease as a comparison to the number found 3 to 4 weeks after the first dose of therapy. If the number of cells decrease sufficiently, one can anticipate that the therapy will likely lead to a tumor response.

In patients where the number of cells do not decrease, determining whether a change in therapy is better than continuing the same therapy became the next question. Studies done thus far have not demonstrated that a change in therapy is best. Clearly this has been a disappointment. Additional studies are anticipated to confirm or refute this conclusion.

At the San Antonio meeting, several presentations described additional uses of CTCs. The present interest is to investigate circulating tumor cells, both as a way to study the development of mutations during the metastatic process, and also as a way to use information about these mutations to tailor drugs which are most likely to work against a tumor. It is perhaps from this

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perspective that circulating tumor cells will be of greatest benefit.

Some researchers have observed that some of these cells do not travel in blood as single cells but rather as small clusters. These appear to be most correlated with the metastatic process.

A further extension of this work is the study of circulating, cell free DNA. Some researchers believe that this will be even more useful than the study of circulating whole cells. This remains to be seen.

PATIENT DERIVED XENOGRAFTS

Dr. Alana L. Welm from Oklahoma Medical Research Foundation in Oklahoma City, Oklahoma, presented a plenary lecture on the use of xenografts. The idea is to take a fragment of tumor from a patient and implant it in specialized, immune deficient mice. Once the tumor has grown in these animals, it can then be used for various purposes. It appears, that the tumors grown in mice, retain most of the properties of the original tumor from the patient, preserving much of the same biology and making it a reliable source of information. Dr. Welm and colleagues are primarily using this system to study the biology of the metastatic process. They and others have made the observation that tumors with more aggressive features appear to grow best in these animals, leading to the possibility that this system can be used to predict prognosis. They have planned a clinical study to verify this potential use.

Many researchers are interested in using this animal system to study the effect of various drug therapies. This has applications both for the pharmaceutical industry and for use in individual patients. The pharmaceutical industry is using this system to test new drugs in groups of animals bearing tumors derived from patients with certain common mutations thus avoiding the need for similar studies in humans. Physicians and patients are beginning to use this system to study therapies that are being considered as treatment, so that a more informed choice can be made. Thus far, excellent concordance is being reported between treatment results obtained in the xenografts and the corresponding patient.

SCREENING FOR BRCA 1 AND 2

Dr. Mary-Claire King from the University of Washington in Seattle, Washington, discussed the issue of screening for genetic mutations such as the BRCA 1 and 2 genes. She reported that 50% of BRCA 1 and 2 carriers have no family history of breast or ovarian cancer. In part she explained, this is due to the fact that families are now small, and also because there is an underestimation of the frequency of inheriting genetic mutations from the father's side. She predicts that in the general U.S. population, 5% of breast cancers are in women who are positive for the BRCA 1 and 2 genes.

Presently, which men and women are screened for these mutations is based on personal and family history. Dr. King believes this to be inadequate. In fact, most women are screened once there is a personal diagnosis of breast cancer. She believes these to be cancers that could have been prevented if screening had already been done. Dr. King proposed what at first may appear to be a radical idea: that every woman have complete gene sequencing at age 30 to identify gene carriers and calculate risk. She anticipates that in the near future, the cost of such testing will be in the range of 300 dollars, making it financially feasible for the general population. She ended her lecture by reminding the audience that all of this may be moot, as there are already commercial companies available via the internet that provide genetic analysis to individuals without the intervention of a medical provider. This may soon become personal routine practice.

QUESTIONS IN NEOADJUVANT THERAPY

Dr. Eric Winer from the Dana-Farber Cancer Institute in Boston, Massachusetts, presented a summary of where we are in both

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DISCLOSURE

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adjuvant and neoadjuvant therapy as treatments for early disease. One of the unresolved issues at present, is the use of platinum compounds especially for triple negative disease. Though there are some data suggesting that platinum agents may provide some benefit in the triple negative setting, he believes there are not enough data to make this standard practice. The patients for whom there are the most data, are those who are BRCA 1 and 2 positive. In this sub category, the addition of platinum to standard chemotherapy can be considered.

The recent move by the FDA to accept pathologic complete response (no remaining invasive disease in the breast or nodes) after neoadjuvant chemotherapy remains controversial. This approach has practical advantages; it reduces tumor size allowing more breast conserving surgery, and decreases the number of patients and observation time needed to reach a conclusion about initial treatment benefit, but it has created certain other uncertainties. Does it correlate with time to recurrence and survival? The answer may be yes for some drugs, but not all. When comparing two or more treatment regimens, how much difference in pathologic complete response is necessary to demonstrate that one therapy is superior to another? To what degree is it applicable to tumors that grow slowly such as hormone positive/Her2 negative tumors? These important questions remain unanswered.

The neoadjuvant approach has opened up another area of research; identifying the best treatment for patients who do not achieve a pathologic complete response. Should they be treated further and in what manner? Should they have more surgery, more radiation, more drugs, or different drugs? These questions need further study.

MAMMOGRAPHIC DENSITY

Dr. Jean Weigert, a radiologist, discussed the issue of mammographic density. Forty to fifty percent of women in the U.S. have "dense breasts" on mammography. Not only are dense breasts at increased risk for breast cancer, but breast density can also mask certain lesions, reducing the diagnostic ability of mammography. In 2009, the state of Connecticut was the first to mandate that radiologists inform patients that they have dense breasts and that additional studies are advised. Eighteen additional states have adopted this mandate, with 5 requiring that insurance companies pay for these additional tests.

Dr. Weigert presented data collected from 5 practice sites in Connecticut where ultrasounds have been advised as an additional test in women with mammographically dense breasts. She reported that only 30% or such women had an ultrasound performed. Cost and lack of education were suggested as reasons why the other women did not have the recommended exam. During a 4 year period, the incremental cancer detection rate was 3.2 per 1,000 women. These cancers were generally small, node negative and of low grade. She stated that they observed an improvement in detection over the four years, suggesting that there is a learning curve. She concluded that there is overall benefit to this law for the general population, as it ultimately identifies more cancers than mammography alone.

It is clear that not all agree with her conclusion. The recommendations for additional testing adds not only to more cancers being diagnosed, but also to more women having biopsies and further follow-up testing that adds to stress, inconvenience and cost. Further, since the additional cancers found are small and typically not aggressive, it is likely that they would simply be found on the next screening mammogram and would not affect survival. I believe that both sides have valid points.

It should be recognized that this discussion on breast density applies to the general population. Women who have a higher risk of breast cancer because of a family history, genetic

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predisposition or a history of personal breast cancer, should be managed based on those principles.

HORMONE THERAPY FOR PREMENOPAUSAL WOMEN (THE SOFT TRIAL)

Selecting the optimal hormonal therapy for premenopausal women with hormone positive breast cancer has been an ongoing issue for many years. Tamoxifen emerged as the standard of care especially in the U.S. many years ago. However, the question of whether turning off ovarian function was also necessary for optimal management has remained. Results of prior studies on this important issue have been inconclusive. Most have been criticized on the bases of how and when, in the course of therapy, menopausal status was determined.

A modern study to resolve this question was designed. Its execution, which would involve several thousand women, required international cooperation. The result was the SOFT trial, results of which were presented by Dr. Prudence Francis on behalf of many colleagues, myself included, at the San Antonio meeting and simultaneously published in the New England Journal of Medicine.

The trial design was to enroll a large group of premenopausal women with early breast cancer into three treatment groups. Randomization was to: (1) tamoxifen alone, (2) tamoxifen plus ovarian suppression or (3) ovarian suppression plus an aromatase inhibitor. All treatments were administered for 5 years.

Premenopausal status was determined by estrogen blood level. If patients were to receive chemotherapy, which by itself may cause temporary or permanent menopause in some, they had to remain premenopausal as measured by blood estrogen levels after they completed chemotherapy. They could be randomized up to eight months from the end of chemotherapy.

At this meeting, the results of the primary comparison of tamoxifen alone versus the combination of tamoxifen and ovarian suppression were presented. The results were interesting if a bit perplexing. In the entire population of about 2,000 women, no significant difference was noted in disease free survival. However, in women who were at higher risk of recurrence, such as those age 35 or younger and those women who were judged by their own clinicians to be at higher risk of recurrence and therefore, were also given chemotherapy, treatment with ovarian suppression plus tamoxifen was superior to tamoxifen alone. The data are not sufficiently mature to provide survival results at this time point.

The portion of the study that compared ovarian suppression with either tamoxifen or an aromatase inhibitor was combined with a similar group of patients treated with these same treatments in the TEXT trial and were presented and published earlier this year. That important comparison demonstrated that in premenopausal women with hormone positive early breast cancer, therapy with ovarian suppression and an aromatase inhibitor was superior to therapy with ovarian suppression plus tamoxifen.

Though these results may appear a bit confusing, when taken together, the combined results of the SOFT and TEXT trials lead to important conclusions: (1) The underlying biology of the tumor provides the basis for choosing among hormonal treatments in premenopausal women. (2) Clinicians appear to be good at deciding which of their premenopausal patients with hormone positive breast cancer need to also receive chemotherapy. (3) Those at low risk of recurrence do well with hormonal therapy with tamoxifen only. (4) Those at high risk either because of young age (35 or younger) or high risk features of their tumor, benefit from the addition of ovarian suppression. (5) If at high risk and ovarian suppression is done, the addition of an aromatase inhibitor is better than tamoxifen.