BreastCancerAdvisor

BY DR. SILVANA MARTINO

July 2014

Dear Readers,

The 2014 meeting of the American Society of Clinical Oncology (ASCO) has concluded. As expected, the conference was dominated by presentations about therapies that are based on new understandings of the immune system. Many see this as the future of oncology wherein the use of chemotherapy drugs to treat cancer will soon be replaced with alternative therapies. I will review presentations from the meeting in this and the next several issues.

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

A NEW BREAST CANCER CLASSIFICATION

For many decades, breast cancer has been classified based on clinical presentation (early, locally advanced, inflammatory), extent of disease both locally and throughout the body (stage), and how it looks under the microscope (histology). From these parameters, clinicians have made judgments about prognosis and treatment. The past few decades have seen the introduction of measurements of hormone receptors such as estrogen and progesterone and more recently the discovery of the HER2 family of proteins found in some breast cancers. These distinctions further informed us on prognosis and which treatments could be most effective. More recently, a new classification system has been introduced called molecular subtyping. At present, molecular subtypes are being used as a way to classify breast cancers in research settings

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

and are not yet routinely included as part of a pathology report. However, the system is proving useful, and I anticipate that it will soon become part of common usage.

Molecular subtyping evolved from the ability to compare the gene expression of cancer cells versus normal cells and from this distinction, one can create microarrays or comparative maps. In this process, it has been found that not only are there differences in the gene patterns of cancers when compared to normal, but also that these differences often occur in clusters or groupings that are seen repetitively. It has been observed that these gene clusters tend to coincide with previously identified parameters such as hormonal status and HER2 status. As a result, this has led to a new classification that is already proving useful. Four subtypes have been described: (1) luminal A, (2) luminal B, (3) triple negative or basal-like, and (4) HER2 type. Each subtype has particular characteristics.

The most common subtype of breast cancer is luminal A, which is estrogen and /or progesterone positive, HER2 negative and has a low Ki67, which is a marker of how rapid the tumor cells divide and grow. About 40% of all breast cancers fall into this category. Luminal A cancers are the least aggressive. Approximately 20% of breast cancers are luminal B, which are also characterized as hormone positive but can be either HER2 positive or negative. These cancers have a high dividing rate as measured by Ki67. This distinguishes a variant of hormone positive breast cancers that though under the microscope can look similar to the luminal A variety, are more aggressive. The triple negative/basal-like variant occurs 15-20% of the time and is defined by being hormone negative and HER2 negative. These cancers are aggressive and more often seen in women who are younger, carry the BRCA 1 gene or found in African/American women. They do not respond to hormonal therapies nor to HER2 directed therapies. The fourth variant, the HER2 type, is HER2 positive which can also occur in the luminal B variant, but are hormone receptor negative.

Once these four variants of breast cancer were distinguished, further investigations have demonstrated that each category can be further subdivided. It is not clear at this point what the final number of subclasses will be, or whether further distinctions will have practical implications. I believe that the final product of this new classification, and others that will certainly follow it, are to point out the fact that biology is personal. We are now in an era where the concept of personalized medicine is the way we think. The expectation is that the personalized approach to diagnosis and treatment will have a better outcome for patients; so far, it appears that way.

WHAT'S NEW

PRESERVING OVARIAN FUNCTION DURING CHEMOTHERAPY (THE POEMS STUDY)

Many, but not all of the side effects caused by chemotherapy agents, can be anticipated by recognizing that chemotherapy works best against cells that are rapidly dividing. It is this differential that is exploited relative to chemotherapy's effect against cancer cells. However, many normal cells in the body are also rapidly dividing such as found in hair, bone marrow, ovaries and testicles. Consequently, these organs bear a disproportionate level of side effects.

The loss of ovarian function is a common side effect of chemotherapy. This may be of benefit in women with hormone receptor positive breast cancer, but in other patients it is viewed as an unwanted side effect. The probability of this occurring is

continued next page

WHAT'S NEW continued

influenced by the age of the patient, the choice of chemotherapy given and the length of chemotherapy treatment. In general, the older a premenopausal woman is when treated, the more likely it is that she will be made permanently postmenopausal. The drug most commonly associated with this side effect is Cytoxan which is frequently used in breast cancer. Three month adjuvant chemotherapy programs such as Adriamycin/Cytoxan or Taxotere/Cytoxan are less likely to cause this side effect than if therapy administration is longer. For some women, their menses stop, but if their hormonal levels are measured, they are not truly postmenopausal. For some, their induced postmenopausal state will only be temporary.

There are several consequences to early menopause. These include: menopausal symptoms (hot flashes, poor sleep, vaginal dryness, decreased libido, hair loss, moodiness, and weight gain), osteoporosis, and infertility.

For over 20 years we have sought ways to prevent or reduce the probability that young women would develop irreversible chemotherapy-induced ovarian failure. The question has been how to avoid it. From our colleagues in gynecology, we learned that ovarian function could be inactivated using a class of drugs called GnRH agonists. In brief, the idea was to purposely suppress ovarian function (put the ovaries to sleep) while giving chemotherapy, with the expectation that if the ovaries were in a sleep mode, they would experience less damage by chemotherapy. This solution was first suggested about 25 years ago, but it took many years before we were able to coordinate the proper resources to test this hypothesis. Part of the difficulty was the concern that the administration of GnRH agonists would by itself, reduce ovarian function. The other issue was related to the fact that it was not clear whether reducing ovarian function was perhaps the best thing to do for all women with a diagnosis of breast cancer. To a large degree, we were inspired to pursue this issue by the increasing number of young women with breast cancer who wanted to preserve their fertility and the ability to have children after breast cancer therapy. For some young women, this issue is so critical that they choose whether or not to have chemotherapy based on the probability of retaining fertility.

With considerable effort, we elected to design a study in premenopausal women with early, hormone receptor negative breast cancer, who planned to receive Cytoxan containing chemotherapy but not hormonal therapy. The study design was a randomization of premenopausal women ages 18-49 to either receive the GnRH agonist goserelin (starting just before chemotherapy and ending at about the same time as chemotherapy) or to not receive it. The original planned accrual was 416 women. However, the study was closed early because of loss of funding for distribution of the study drug. From 2004 to 2011, a total of 257 women were enrolled in the study in both the U.S. and Europe. The primary objective of the study was to determine how many women had lost ovarian function at the two year time point from chemotherapy treatment. Additionally, we wanted to measure how many women became pregnant and had children following therapy. We also planned to measure tumor recurrence and overall survival between the two treatment groups.

Of the 257 women enrolled, 24 were found to be ineligible and the data were not fully evaluable from another 15, leaving 218 women for the final analysis. The median age of the group was 38. The median time of follow-up was 4 years. Loss of ovarian function was defined as both not having menses during the preceding 6 months and having hormonal levels (FSH) in the postmenopausal range. Data on both these parameters at the 2 year time point were available from only 135 of the 218 evaluable participants. From most of the others, FSH measurement was lacking.

continued next page

WHAT'S NEW continued

In spite of the number of women who entered the study but were either not truly eligible or from whom part of the data were missing, several interesting conclusions were reached. Among the 135 women with two year data, ovarian failure was lower in those who received goserelin during their chemotherapy (8% versus 22%) versus those who did not. There were more pregnancies among the women given goserelin. These results suggest that this maneuver does provide some meaningful protection to the ovaries.

The most interesting results from this study, however, were the observations that the group given goserelin experienced less tumor recurrence and had a better overall survival. These findings were clearly surprising, as we had chosen to perform this study only in women who had hormone receptor negative breast cancer in whom one would not anticipate that altering their ovarian function should have any effect on their cancer. It is unclear what to make of these findings. Should they be ignored since they appear biologically illogical? Should these results prompt a larger study in similar hormone negative patients to see if we can confirm these findings? I personally do not believe that based on this modest sized trial we should change medical practice and give all premenopausal women with hormone negative breast cancer a course of GnRH agonists during their adjuvant chemotherapy.

Beyond the conclusions reached from this study, I believe that there is another critical point that this study illustrates; that is, many clinical trials that seek to explore basic principles of how we should treat patients are very difficult to conduct. The obstacles are many. Some obstacles are related to the type of patient that a protocol includes or excludes. Others are related to a natural resistance that both patients and doctors have to the concept of randomization. Many obstacles are related to the financing required to conduct a study. It is easier to find funding when a drug is new and its sponsoring pharmaceutical company is interested in gathering data to support FDA approval for their drug rather than when the study involves an older drug that already has approval for other uses. This study suffered from all of these issues, including the fact that for many of the patients there was a lot of missing data such as the performance of a blood test to measure FSH levels.

This important but difficult to conduct trial was under the leadership of Dr. Halle C.F. Moore from the Cleveland Clinic Foundation. Dr. Moore presented the data on behalf of participating colleagues (myself included) at the 2014 meeting of the American Society of Clinical Oncology (ASCO).

QUESTIONS & ANSWERS

(Q) Dr. Martino, I had breast cancer two years ago and chose to be treated with bilateral mastectomies. I did that because I did not want to ever have to deal with breast cancer again. I wanted to be done with it. We now have moved to a different state and I have a new oncologist. He has told me that even though I had bilateral mastectomies, I still have a risk of getting breast cancer again. How can this be since I don't have breasts anymore?

(A) Your question does not tell me whether you had invasive breast cancer or not. If you did, you have two basic risks; one is a recurrence from the original breast cancer, and the other is a risk that you will develop a brand new breast cancer. I suspect that your question is focused on the second risk. Your present oncologist is correct. In spite of having had bilateral mastectomies, you still retain some risk of developing a second breast cancer. The reason for this has to do with the fact that even with a mastectomy, there is still some breast tissue that remains behind and that in time can become cancerous. It is not possible to technically remove all breast tissue since it is intertwined with other structures in the body. The area where most tissue remains is in the axilla.

(Q) Dr. Martino, I am 48 years old and I was recently diagnosed with breast cancer. I have no friends or family members with a

continued next page

DISCLOSURE

QUESTIONS & ANSWERS continued

similar diagnosis, so I feel like I have no one to talk to who can really understand me. My doctor has given me the names of breast cancer groups that I can attend, but I really don't like talking to a group. I really would like an individual who I could talk to. I also don't have a lot of time since I have three small children. I also don't feel well enough to drive a long distance to meet with anybody. What can I do to find someone with an experience like mine?

(A) I believe that finding someone to talk to when you have a diagnosis of cancer can be very useful. For many people, a group setting is very satisfying, but I have learned from my own patients that there are men and women who do not favor a group environment and are more comfortable with a one-on-one situation. There are support groups that function based on this more personal model. If you have not already discussed your preference with your oncology team, I would advise you do so. They can probably guide you to a local program. You can also try the American Cancer Society in your local area, as they keep lists of support programs. I have found that many busy women only want someone that they can talk to via phone or email and don't necessarily want face-to-face contact. One such service that I am familiar with is BREASTMATES. They can be contacted at breastmates4u@gmail.com.

(Q) Dr. Martino, I had cancer of the colon a few years ago. I was treated with surgery and chemotherapy, and have done very well. Recently, I was diagnosed with breast cancer which I have been told is early and I am expected to make a full recovery. My question has to do with the fact that my doctor asked me to participate in a breast cancer study using a new treatment. I agreed to do it, but then I was told that I was not eligible because of my history of colon cancer. Why does that matter? My colon cancer was treated successfully and I have not had a recurrence.

(A) It is common for studies to exclude patients who have had more than one cancer. The reason for this is because even though you have done well relative to your first cancer (colon), there is still a possibility that you might recur in the future. The study that was offered to you is trying to determine whether the therapy that is being evaluated will prevent your breast cancer from recurring. Should you have a cancer recurrence in the future, it might be difficult to be certain whether the recurrence might be from the colon cancer or the breast cancer. This uncertainty would complicate the results of the present study and would render the data obtained from you less reliable.

DR. WATSON, I PRESUME?

I have generally been suspicious of "artificial intelligence." I first learned about it from the husband of one of my colleagues about 25 years ago. Her husband was a neurologist and somewhat of a geek. He was working on creating artificial intelligence as his research goal. He tried to explain it to me, but I did not find it attractive. I perceived it as a way to ultimately replace people with a machine. This might be acceptable by cultures where people do not like to physically touch each other but, for me as an Italian, a machine seemed clearly inferior.

I find the idea of artificial intelligence even less satisfying in the field of medicine where much of what is needed is the ability to comfort and console. How can one do that without using touch? How can you do a physical exam without touching the patient? This appeared to me to be even more inappropriate in my own chosen field of oncology.

I also observed another change taking place in medicine. It came to my attention while I was teaching internal medicine residents at Wayne State University in Detroit, Michigan. During "morning report," when the residents on-call the previous night described the patients who had been admitted during the night, I noticed that they would start their presentation with a brief description of

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

DR. WATSON continued

the patient's presenting symptoms and then quickly proceed to describe the results of the laboratory tests and scans that had been performed. Their diagnosis was based almost entirely on these tests. Their history and physical exam of each patient was minimal at best. My habit was to interrupt them in their rehearsed recital and force them to give me more details obtained directly from their interaction with the patient, and to force them to give me a probable diagnosis based on their assessment of the patient directly and, subsequently, provide information from X-ray and laboratory examinations. Though I persisted in this behavior, it became clear to me that medical schools were training the next generation of physicians in a new way; decisions were being increasingly based on information obtained from the machines of medicine. The introduction of the "no touch technique" of medicine had begun. Since then, better scans and more laboratory test have been developed that now provide much more detail about the human body and its physiology and pathology.

Another pivotal event occurred to me about eight years ago. I needed to know the dose of a drug. As I waked into a meeting, I asked the question of one of my senior colleagues. While he was trying to recall the answer to my question, a much younger colleague seated next to him pulled out her cell phone, pushed a few buttons and gave me the answer. From this scene, it became clear to me that the repository of our knowledge had changed. Older generations of doctors, myself included, had stored knowledge primarily as memory of facts, while the newer generation of physicians stored their knowledge in the internet. This is a big difference. I confess that I was forced to acknowledge that the internet based younger physician had given me the information sooner than the older, personal-memory based colleague. It forced me to reconsider my bias. Perhaps the internet is a better place to store data. Along with this event, I have also come to recognize that I no longer remember addresses, phone numbers, recipes and a lot of other things that I previously committed to memory. This wheel has been put in motion, and I do not believe that it can be retrieved.

Another event that has contributed to the storage of information in the "cloud" is the increasing use of medical guidelines. These are decision trees that suggest treatments. They serve several purposes: they standardize therapy, they tell you what to do, and they easily lend themselves to computerized decisions. Ahh, perhaps this is the whole point. I predict that in the not too distant future, medicine can be practiced by a computer.

Some of you may already be familiar with IBM's Watson computer. This artificial intelligence gained fame when it beat human champions of the TV show "Jeopardy." Watson is now being trained by various prestigious cancer centers such as MD Anderson in Houston and Memorial Sloan Kettering Cancer Center in New York to provide opinions on appropriate cancer care. You could say that Watson is going to medical school. Certainly its ability to speed read all available books and its ability to retain/retrieve information will be superior to human medical students. I think it will test well and pass with flying colors. Is there anything it won't be able to do? It is hard to know. Perhaps it won't be able to comfort in the same way as a human doctor, but I suspect that in time someone will figure out how to teach it skills that mimic empathy and perhaps even love.

It is not hard to imagine a near future where you and I will walk up to a terminal-it will take our blood, scan our body, ask us questions on how we feel, and in a few minutes make a diagnosis, prescribe therapy, fill prescriptions, refer us to another computer if a surgical procedure is indicated, bill our insurance, take our copay, answer our questions, provide instructions, and smile at us as we walk away. It may be less personal, but it may be more accurate. Perhaps, that's all that matters, anyway.