

Breast Cancer Advisor

BY DR. SILVANA MARTINO

June 2015



Dear Readers,

This and the next issue of the Breast Cancer Advisor will deviate from the usual format so that I can provide updates from the recent meeting of the American Society of Clinical Oncology (ASCO), which took place in Chicago from May 29 through June 2, 2015. As with other meetings, I will select data that I consider most relevant to patient care.

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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REPORT FROM THE ASCO 2015 MEETING

The American Society of Clinical Oncology is an international organization that meets in the U.S. on an annual basis. One third of ASCO members are now from countries other than the U.S. This year's conference was attended by nearly 30,000 participants.

This meeting is important not only because of its size, but because of its status as where most researchers from all around the world like to present their new data for maximum exposure. Multiple presentations are scheduled simultaneously, so no one can attend all presentations. We each choose what is most meaningful to us, knowing that other presentations will either need to be viewed on-line or read about in subsequent publications. The meeting can be an overwhelming experience, yet a most valuable one.

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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.

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There were four central themes to this year's meeting: (1) global oncology, (2) an emphasis on how to provide and determine "value" in medical care, (3) continuing developments in the field of immunology, and (4) restructuring how research trials are done in this era of "individualized medicine." These themes are not specific to breast cancer but span the entire field of oncology. I believe that each of these themes will have considerable influence and are worthy of some discussion. I will discuss the first two topics in this issue and the third and fourth in the next issue.

GLOBAL ONCOLOGY

It is becoming increasingly obvious that cancer is a major cause of morbidity and mortality worldwide. It is not a disease confined to developed nations. Approximately 70% of new cancer cases diagnosed each year occur in countries with limited resources. Their medical systems are poorly prepared to deal with this increasing burden. Survival rates are generally less than half that of more affluent countries. As an example, Africa has nine times the incidence of cervical cancer than does the U.S., and 24 times the mortality rate. What is lacking is not knowledge, it is the ability to implement what is already known about cancer prevention and treatment. ASCO has recognized and acknowledged the problem. Can it now involve itself in providing solutions?

A new initiative has been launched that will focus attention on this global issue. This will take many forms and the formation of many bridges with various other organizations. A first step will involve a relationship between ASCO and the College of American Pathologists to help underserved countries improve their diagnostic skills so that a correct diagnosis is made from biopsy material. Africa has been recognized as being at particular need and will be a major focus in this global reach.

Dr. David Kerr has been chosen as the founding editor-in-chief of the new ASCO publication, Journal of Global Oncology (JGO). This journal will be focused exclusively on cancer research, treatment, and care delivery in countries with low resources.

As with all new initiatives, they start with recognizing a problem and then trying to find reasonable solutions. The global cancer burden is without question, an important issue. We will have to see how much effort will be placed on this problem and what fruit it will bear.

VALUE-BASED HEALTH CARE

This is a deeply philosophical topic that is not easy to define, yet is at the heart of how care is provided. It deals with how to provide the best care, how to measure outcomes and how to pay for it. This topic was presented by Michael E. Porter, PhD, from the Harvard Business School. In 2006, he co-authored the book **Redefining Health Care: Creating Value-Based Competition on Results**, in which he concluded that health care, as delivered in the U.S., is not structured to deliver value for patients. He defined value as "the patient health outcomes achieved relative to the costs required."

Inherent in this definition is understanding that there are two parts to this equation; measuring outcomes and measuring cost. We commonly measure outcomes from the perspective of the process of medicine. For example, we might measure how long you waited in the office before you were seen by the doctor or whether the doctor followed current recommendations (guidelines) on how to treat your condition. We do not specifically measure how well a therapy worked in reducing certain symptoms that were most bothersome to an individual patient, or if the patient was cured, or whether good control of the disease was achieved with the chosen therapy. We do not judge whether the method of therapy used by one physician

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resulted in better disease control versus another. We do not measure whether the same degree of control could be achieved by a less costly therapy. Nor do we measure the total cost of treatment incurred by patients.

There is no question that the cost of medical care in our country has risen out of proportion to the cost of other goods and services. A large portion of this is due to the cost of new drugs. When the FDA approves a new drug, by law, it is not allowed to take the cost of the drug into consideration. As new drugs are developed in the U.S., drug companies are allowed to charge any price that they believe the market will tolerate. The result is that each new drug is more expensive than the last one. The concept of value-based health care suggests that drugs should be priced based on how well they treat a disease. If two therapies are equally as effective, they should be priced the same. If one therapy is not quite as effective as another, it should cost less.

Dr. Porter expressed optimism that within the next decade, the U.S. and other countries will move in the direction of a value-based health care model. I found his ideas to be insightful. They represent a way to measure what is truly valuable as a medical outcome, and base payment on the value provided to patients by a therapeutic option. They can provide both a way to improve outcomes and reduce cost.

ASCO BREAST CANCER NEWS**BREAST CANCER IN YOUNGER WOMEN**

Several speakers discussed issues that are specific to younger women. In general, younger women have breast cancer that is somewhat more aggressive. Features such as higher grade, hormonal negativity and BRCA positivity are more common in a younger population. Issues of fertility make their care more complex.

One topic considered was whether all premenopausal women with hormone positive breast cancer treated in the adjuvant setting should undergo ovarian suppression; and if so, should everyone also receive an aromatase inhibitor? Are we ready to stop using tamoxifen in the adjuvant setting? Dr. Hope Rugo from the University of California in San Francisco provided the following recommendations based on current data: The patients who benefit most by ovarian suppression and an aromatase inhibitor are women who are age 35 or younger and women of any age with nodal involvement who are at a higher risk of recurrence. For other premenopausal women with hormone positive disease though, this same approach is an option; tamoxifen alone may be just as reasonable.

Several speakers discussed the topic of ovarian function preservation in premenopausal women for the purpose of preserving fertility. The consensus was that this issue should be discussed with all breast cancer patients of child bearing age. Further, this discussion should take place early in the course of their diagnosis and treatment. It is a topic that surgeons should become comfortable discussing so that appropriate referrals to a fertility specialist can be made early rather than waiting until the patient is ready to start chemotherapy. Fertility specialists now have multiple techniques that have proven successful and allow patients the opportunity to have children following diagnosis and treatment for breast cancer.

A common side effect of chemotherapy is suppression of ovarian function. This leads to menopausal symptoms and to loss of fertility. The addition of GnRH agonist hormones during chemotherapy have been shown to help preserve ovarian function. This maneuver, however, is advised only for women with hormone negative breast cancer. For women with hormone positive breast cancer, reduction of ovarian function is part of their anticancer therapy and, therefore, the use of GnRH agonists for ovarian function preservation is counterproductive. A study is

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in progress where premenopausal women on hormonal therapy for their breast cancer are being treated for two to three years and then therapy is held to allow them a period when they can try to achieve a pregnancy. Thereafter, their hormonal therapy is resumed and completed. This is an observational study only without randomization, but it should provide some information on the safety and success of this strategy.

Dr. Barbara Smith, a surgeon from Massachusetts General Hospital, discussed the topic of local recurrence in premenopausal women. Both with DCIS and invasive disease, women ages 35 and younger experience more local recurrence. This is likely a result of the fact that younger women present with more nodal involvement, higher grade lesions and are more likely to be BRCA 1 or 2 positive. She raised the question of whether this should result in treatment with mastectomy in this younger population rather than lumpectomy and radiation. She summarized several studies conducted over the years that have demonstrated that a mastectomy results in the same recurrence rate as lumpectomy and radiation. The increased local recurrence rate seen in this younger population is seen with both treatments. Systemic therapy has been demonstrated to reduce local recurrence in all patients whether treated with mastectomy or lumpectomy and radiation. Women who are known to carry the BRCA 1 or 2 genes may favor a mastectomy since in this subgroup, prophylactic mastectomy of the other breast is often also performed.

Dr. Smith added that there is increasing data demonstrating that nipple sparing mastectomy appears safe. It is not clear whether this is equally as safe in women who are BRCA 1 or 2 positive.

TREATING BRAIN METASTASES

The brain is a frequent place of spread for several tumors including breast cancer. This pattern is more typical in triple negative and HER2 positive breast cancers. Surgical resection is no longer a common treatment approach. It has been replaced by whole brain

radiation and/or radiosurgery. Radiosurgery is a targeted radiation approach. To a great degree, whether whole brain radiation is necessary or not is determined by the number, location and size of the metastatic lesions. If they are numerous and in multiple locations, whole brain radiation is necessary. If they are few and relatively small, radiosurgery alone may be adequate. Often, both are done in combination for maximal effect.

Dr. Paul Brown from the MD Anderson Cancer Center in Houston, Texas, presented the results of a study in a group of 213 patients with 1-3 brain metastases, each less than 3 cm in size and from various tumor types. The patients were randomized to treatment with radiosurgery alone or the combination of radiosurgery plus whole brain radiation. The primary objective of the study was to evaluate cognitive function at three months, in addition to evaluating tumor control and overall survival.

Dr. Brown reported that their study found that the patients who were treated with both modalities experienced more decline in cognitive function; specifically, in immediate recall, memory and verbal fluency. Additionally, though there was better control of the brain lesions with the combined modality, overall survival was not improved by using both treatments. He concluded that when technically possible, especially with early brain metastases, radiosurgery alone is preferred, as it results in less deterioration of brain function.

Additional information specific to patients with brain metastases from HER2-positive breast cancer was presented by other researchers. The risk of brain metastases in this category of breast cancer is higher and may be up to 40%. However, these patients tend to do better than other breast cancer patients with brain involvement. In part, this may be because there are several effective anti-HER2 drugs, and some of these drugs are able to get into brain tissue and treat the brain metastases. In general, the brain has a functional barrier called the blood-brain barrier

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which most drugs are not able to cross and, therefore, most drugs are not able to treat brain metastases.

The following drugs and drug combinations have shown activity in brain metastases in patients with HER2-positive breast cancer: Avastin/Carboplatin with or without Herceptin, Lapatinib, Xeloda, Neratinib, TDM-1 and several new experimental agents. A study looking at Herceptin given intrathecally (directly into the cerebral spinal fluid) is also ongoing. Because of the increased frequency of brain metastases in both HER2-positive and triple negative breast cancer, often seen in patients whose disease is otherwise under control, finding the optimal and least toxic therapy to treat brain metastases is becoming increasingly important.

A NEW THERAPY FOR DCIS

Ductal carcinoma in situ (DCIS) is considered an early form of breast cancer. It is believed to be a precursor to more advanced invasive breast cancer. Therapy for DCIS includes surgery and radiation similar to the treatment of invasive disease. For women with hormone positive DCIS, the hormone tamoxifen has been shown to reduce the probability of recurrence of both the DCIS itself and the development of an invasive breast cancer. At the 2015 ASCO meeting, Dr. Richard Margolese from The Jewish General Hospital, McGill University in Montreal, Canada, presented the results of the first study comparing the efficacy and safety of tamoxifen versus Arimidex (the aromatase inhibitor-anastrozole).

The study was a multicenter, phase III trial conducted by the NRG Oncology group and the NSABP. They enrolled 3,104 postmenopausal women who had a diagnosis of hormone receptor positive DCIS, and had been treated with lumpectomy and radiation therapy. Participants were randomly assigned to take either tamoxifen (20 mg/day) and placebo, or Arimidex (1 mg/day) plus placebo, for five years. The primary objective of the study was to see which therapy resulted in less second breast cancer events—either DCIS, invasive

cancer or contralateral disease. The women were further divided into two groups; those age less than 60 and those age 60 and greater. The average follow-up as of this presentation was 8.6 years.

Dr. Margolese reported that among the 722 women less than 60 years of age who received tamoxifen, there were 58 breast cancer events versus 31 events among the 725 women assigned to Arimidex. Of the 816 women ages 60 and over treated with tamoxifen, 56 breast cancer events occurred versus 53 events among the 814 participants in the Arimidex treated group. He concluded that in the younger age category, the difference was “conspicuous.” But he added, that in the older age group, they did equally as well with either therapy.

The investigators also evaluated these women for side effects. No new or unexpected side effects were reported. As anticipated, there were more osteoporotic fractures with the Arimidex therapy (69 per 1000 women with Arimidex versus 50 with tamoxifen annually). More uterine cancers were seen with tamoxifen (annual rate of 17 per 1000 women with a uterus on tamoxifen versus 8 with Arimidex).

This study is important because it provides another option to the standard use of tamoxifen for women with hormone positive DCIS. These data apply only to women who are postmenopausal. Tamoxifen remains the drug of choice for premenopausal women with DCIS. It is not clear why the group that had the most advantage from Arimidex was the group younger than age 60. In older patients, the side effect profile of the two drugs can be used to assist in making a choice. Therapy was confined to five years, so whether longer therapy is better remains unknown.

PALBOCICLIB—A NEW DRUG

Dr. Nicholas Turner of the Institute of Cancer Research in London, presented the results of the PALOMA 3 trial which were also simultaneously published in the New England Journal of Medicine. This drug has engendered a lot of excitement

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because it is a new type of drug. Palbociclib is the first cyclin-dependent Kinase (CDK) 4/6 inhibitor. It targets two specific kinases, or enzymes, that help tumor cells to grow. In February 2015, it was given accelerated approval as therapy for hormone positive, HER2 negative breast cancer in combination with the aromatase inhibitor drug letrozole (Femara), in postmenopausal women with metastatic disease. The approval by the FDA was granted based on limited but promising data.

The PALOMA 3 trial was a phase III trial that included both pre- and postmenopausal women with hormone positive, HER2-negative, metastatic breast cancer that had progressed on prior hormonal therapy. The participants were randomly treated with either the hormonal drug fulvestrant (Faslodex) plus placebo or fulvestrant with Palbociclib. The primary end-point of the study was to assess the time to disease progression between the two groups. The results demonstrated that the combination of Palbociclib plus fulvestrant improved the time to disease progression by 5.4 months. This confirmed the efficacy of the new agent when added to a hormone, and also demonstrated that it is effective in both pre- and postmenopausal women. This suggests that it may be a way to further improve on the effectiveness of all hormonal drugs. At present, this specific combination is not approved for general use.

Hormone positive breast cancer is the most common subtype of breast cancer in both pre- and postmenopausal women. It appeared that we had reached a limit in developing new hormonal drugs, and no new hormonal therapies were anticipated. However, there are now agents which, though not hormones themselves, work in concert with hormonal therapy and are able to either extend the effectiveness of various hormones or are able to reverse resistance to hormonal therapy. The agent Palbociclib is a welcomed addition. It is obvious that as we further our understanding of biology, new pathways and new solutions are being found.

BISPHOSPHONATES IN EARLY BREAST CANCER

Metastases to bone are a particularly common event in all subtypes of breast cancer. It is also likely that bones, especially the bone marrow, represent a place where breast cancer cells can hide and rest for many years before other evidence of spread is noted. Therapies that reduce estrogen, such as many hormones and chemotherapy, generally also increase osteoporosis. This results in osteoporotic fractures and many also weaken the bone's ability to resist bone metastases from breast cancer.

Based on this understanding of bone biology, several studies have been done using bone sparing agents such as the bisphosphonates; both as a way to reduce osteoporotic fractures and also as a way to attempt to reduce tumor spread to bones.

Dr. Julie Gralow of the Seattle Cancer Care Alliance and the University of Washington School of Medicine presented the results of SWOG S030. This phase III trial in early breast cancer was started several years ago when it was anticipated that the use of a bisphosphonate would reduce breast cancer recurrence. Based on this supposition, this trial was designed as a comparison of three different bisphosphonates to determine if one was better. Patients with stages 1-3 early breast cancer were randomized to three years of either intravenous zoledronic acid (Zometa), oral clodronate (Bonfos), or oral ibandronate (Boniva). About 60% of the women were postmenopausal and 50% had node negative disease.

The results of this trial, which enrolled 6,097 women with early breast cancer demonstrated that, with a median follow-up of 5.4 years, the three drugs were equivalent. All three groups did well. Disease free survival was about 88% and overall survival was about 93%. Lacking an untreated control group, the true benefit of these agents cannot be evaluated.

Osteonecrosis of the jaw, an uncommon but serious side effect of this class of drugs was seen more often with zoledronic acid (incidence was less than 2%) than with the other two agents.

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