BreastCancerAdvisor

BY **DR. SILVANA MARTINO**

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Dear Readers,

The Angeles Clinic and Research Institute and the Angeles Clinic Foundation extend to each of you a Happy New Year! It is again time for each of us to renew our purpose and our spirit and to set new goals and expectations for the year ahead. Be bold; expect much; dare much.

Best regards,
Dr. Silvana Martino

BIOGRAPHY

Dr. Silvana Martino

Dr. Martino is board certified in internal medicine and medical oncology. She has specialized in the treatment and research of breast cancer for over three decades. Dr. Martino is a nationally recognized leader and educator 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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UPDATES FROM THE 2015 SAN ANTONIO BREAST CANCER SYMPOSIUM

From December 8th through December 12th, I attended the 38th San Antonio Breast Cancer Symposium. For those of you who are long term readers of this newsletter, you know that this is my favorite yearly educational event. Each day is long and intense, but very satisfying. I cannot say that there were any earthshattering revelations at this year's meeting, but clear progress was apparent along many fronts.

FIRST FDA APPROVED SYSTEM TO REDUCE HAIR LOSS FROM CHEMOTHERAPY

In December 2015, the U.S. Food and Drug Administration (FDA) cleared The DigniCap scalp cooling system that reduces hair loss caused by chemotherapy for women treated for breast

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The Angeles Clinic
AND RESEARCH INSTITUTE

A CEDARS-SINAI AFFILIATE

Santa Monica
2001 Santa Monica Blvd., Suite 560W
Santa Monica, CA 90404
(310) 582-7900

West Los Angeles
11818 Wilshire Blvd.
Los Angeles, CA 90025
(310) 231-2121

Cloverfield
2428 Santa Monica Blvd., Suite 103
Santa Monica, CA 90404
(310) 828-0061

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cancer. This is a major step forward as this system is easier to use that other systems, and FDA clearance should lead to insurance coverage for this procedure. The approval is not granted for all patients nor for all chemotherapy programs. It is presently restricted to those with a diagnosis of breast cancer. Proper positioning of the special cap does require some assistance. It has to be placed prior to chemotherapy administration and must remain in place for a period thereafter. Chemotherapy services will have to rent the cooling system. Each machine can service two patients at a time.

Since for most offices this will be a new system, some period of time will be required before most oncologists will have this available. Our own experience has been with a different system which is more cumbersome. None of the systems available provide complete protection of the hair; some degree of hair loss is seen in all patients. However, the majority of patients keep enough of their hair during treatment that they do not need to wear a wig. In the U.S. trial, patients were primarily treated with taxane drugs such as Taxol and Taxotere. Outside the U.S., there is considerable experience with anthracycline chemotherapy drugs such as Adriamycin and epirubicin.

You can find more information about using the DigniCap cooling system at **www.DigniCap.com**.

CIRCULATING TUMOR DNA MEASUREMENTS

The concept of measuring something in one's blood that would allow the diagnosis of cancer and allow monitoring of how cancer behaves is not a new concept. Many have sought such a test. It appears that we may be getting closer. This test may turn out to be the measurement of circulating tumor DNA.

It is believed that as a cell dies, its internal content is spilled into the circulation. The body mechanisms will in time clear this content but, at least for a period, various components will be measurable in variable quantities in blood. The material of particular interest is the cell's DNA content, which is its genetic material. Techniques now exist that allow the detection of this material, which is present in very small quantities in a sample of blood. Once it is identified and separated from free circulating DNA from normal cells, it can then be studied and analyzed.

In theory, there could be many applications for circulating DNA analysis. In patients with a known diagnosis of cancer, this procedure could serve as a "liquid tumor biopsy." At initial diagnosis, it could be used to determine whether the tumor has already spread when all scans are still negative. It could be used to judge if therapy has worked by demonstrating the clearance of circulating DNA in blood. It could be used to watch patients to see if the tumor is returning before scans and other exams become positive. It could be used to let us know how a tumor is changing from time to time so as to guide therapy more effectively. Ultimately, it could be used to tell us if a person has a cancer before any other signs developed. Improved technology now allows detection of minute quantities of circulating DNA and may soon prove useful.

A related technique which is already in use is the collection of blood in cancer patients for the purpose of testing for "circulating tumor cells". Here, the goal is to identify whole cells rather than their DNA content. The concept and potential applications are similar. A research group from Germany presented the results of a new study looking at circulating tumor cells in patients with newly diagnosed early breast cancer. In a group of 3,754 patients, they are performing serial collections of blood samples looking for circulating tumor cells. The initial sample is at the

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time of diagnosis prior to starting chemotherapy, then again once chemotherapy has ended, and finally at two years and five years after diagnosis. At least one cancer cell must be found for the test to be considered positive.

At this meeting they presented results from samples taken at two years in 1,087 patients that have been followed for about three years. The main objectives of the study are to compare the recurrence rate and survival of those with a positive test result versus those with a negative result. Thus far, they have found that the patients with a positive test at the two year point have a higher recurrence rate and a worse survival than those who have a negative test. Patients with a positive test both at the time of diagnosis and who remained positive at the two year time point have the worst outcome. Interestingly, this relationship was not observed in patients with HER2-positive breast cancer. It is not clear why this is so. Perhaps there are simply too few patients in their sample with HER2-positive breast cancer for sufficiently reliable observations to be made at the present time.

The question at present is what to do with this information. Should patients with a positive blood test after their initial chemotherapy be treated differently? Should they be treated more aggressively? Would this make a difference? At this point we do not know the answer. There are patients with positive tests who have not recurred, and patients with negative tests who have recurred. It is clear that cancer is a complex process and that this is not a perfect test.

OPTIONS FOR THE TREATMENT OF DCIS

There is perhaps no more controversial version of breast cancer than ductal carcinoma in situ (DCIS). Is it cancer or is it not? Many have argued that it is not cancer and this entity should be renamed. Many prefer to call it ductal intraepithelial neoplasia (DIN), removing the word carcinoma. For many, it is the most obvious example of over diagnosis, over screening and over treatment. DCIS is now 15% to 25% of all screen detected breast lesions. Is it an entity unto its own, or is it simply an extension of atypia that should be observed rather than treated? Controversy persists and much of it is justified.

One way to approach DCIS, is to ask, "What are we trying to prevent by treating DCIS?" Ultimately we are trying to prevent metastatic breast cancer, since this is what can cause death. Studies have suggested that from 15% to 50% of DCIS lesions will eventually lead to invasive disease. The problem is that presently, we do not know how to clearly identify which DCIS lesions or whose DCIS lesions will go on to transform into an invasive process leading to metastases. Consequently, we treat every lesion aggressively.

To some degree, we can anticipate who is more likely to develop invasion. A list of clues including Ki67 level, p16, younger age, cribriform or solid lesions, presenting as a palpable mass, and positive margins at resections may be useful. Others such as size, grade and subtype are inconsistent as clues. The Oncotype DX test can be helpful but not yet widely adopted for this purpose.

For hormone positive DCIS, the use of hormonal therapy with either tamoxifen or an aromatase inhibitor has become common systemic therapy. Both can be used in postmenopausal women, with tamoxifen being used in premenopausal women. Dr. Jack Cuzick updated the results of the IBIS II trial comparing five years of tamoxifen versus five years of Arimidex. This international trial of nearly 3,000 postmenopausal women was designed with a primary endpoint of measuring "any recurrence." At ten years, the rates of any recurrence are 6.6% in the Arimidex group and 7.4% with tamoxifen; a non-significant difference. There were less invasive recurrences observed in the Arimidex group, but

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the difference was insignificant. Overall survival is too early to assess. Only four deaths have occurred in the entire population; again, attesting to the overall good prognosis of DCIS.

Dr. Patty Ganz updated the results of study NSABP B-35, also in postmenopausal women with hormone positive DCIS, randomized to tamoxifen versus Arimidex for five years. This trial also had about 3,000 patients. The recurrence rate in the tamoxifen group was 6.5% versus 10.8% in the Arimidex group. Of particular importance was the observation that this difference became apparent at about year ten of follow-up and not before. This difference was statistically significant. This suggest, that DCIS studies with short observation times may be misleading. Upon further scrutiny, the difference in benefit only applied to women less than age 60. For those over 60, the use of tamoxifen or Arimidex were the same.

An important aspect of the results from trials that have used hormones as part of the therapy of DCIS, is that there is a reduction in cancers of the opposite breast. In some studies this is the dominant benefit, especially when the primary lesion has been treated with lumpectomy and radiation.

The side effect profiles for these drugs are well established, so patients can make their choice based on which side effects might be more tolerable for them.

A question from the audience was perhaps key, yet, went unanswered; "When will we stop treating most patients with DCIS?"

OPTIONS FOR HER2-POSITIVE BREAST CANCER

It is in the treatment of HER2-positive breast cancer where the most progress has been made in the past 15 years. Dr. Dennis Slamon from UCLA presented the updated results of the BCIRG-006 trial which compared Adriamycin and Cytoxan followed by Taxotere (AC—T) versus AC—T plus Herceptin (H) versus TCH (Carboplatin). This mature analysis provided both disease free survival and overall survival results. At ten years of follow-up, both Herceptin containing treatments remain superior to the non-Herceptin containing regimen. The difference between the two Herceptin therapies is insignificant.

Where the two Herceptin treatments differ is in the observed side effects. A total of nine patients have developed leukemia, eight in the AC treatment groups combined and only one in the TCH treated group. Cardiac events have also been more apparent in the AC treated groups, though no deaths from cardiac causes have been reported. These mature data establish TCH as the preferred treatment option.

The value of Herceptin in HER2-positive patients is unquestionable. The question now is whether other similar agents can augment its benefit, provide benefit to those whose disease does not respond to Herceptin, or prevent/reverse resistance to Herceptin.

The drug lapatinib (Tykerb), though demonstrating benefit in metastatic disease, proved disappointing in the treatment of early breast cancer when added to Herceptin. Pertuzumab (Perjeta) has been successful in both metastatic disease and the neoadjuvant setting. Results of trials using pertuzumab in combination in the adjuvant setting are eagerly awaited.

Dr. Arlene Chan presented an update of the EXTENET trial using Neratinib after Herceptin-based adjuvant therapy in early-stage HER2-positive breast cancer. Initial promising data were presented at the two year time point. The study has been extended so that five year data will be obtained. The small positive benefit seen initially has persisted beyond year three. The benefit is most apparent in HER2-positive/hormone-positive patients. It is unclear whether any benefit occurs in the HER2-positive/hormone-negative population. Diarrhea remains the dominant side effect to this agent.

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DISCLOSURE

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The drug TDM1 (Kadcyla), which combines both Herceptin and a chemotherapy agent (emtansine), continues to demonstrate a real advantage. The WSG-ADAPT trial reported by Dr. Harbeck treated 375 patients with HER2-positive/hormone-positive disease in the neoadjuvant setting with 12 weeks of either TDM1 alone, TDM1 combined with hormonal therapy or Herceptin plus hormonal therapy. The primary objective was pathologic complete response rate (pCR). The results demonstrated that Herceptin plus hormones yielded a pCR of only 15%, while both TDM1 treatments had a pCR of 41%. This improvement was seen in both pre- and postmenopausal patients. This suggests that single agent TDM1 alone results in a good response rate. It is a particularly appealing therapy in patients where the use of multiple agents or the use of additional chemotherapy is not favored. This study further demonstrated that a tumor biopsy done at three weeks to measure tumor cellularity and Ki67 was able to predict which tumors were more likely to have a favorable response.

IMMUNE THERAPY IN BREAST CANCER

Though the concept of harnessing the immune system to control or eradicate cancer is probably the single most exciting idea in the field of oncology, its use in the therapy of breast cancer is still in the early stages. Results from the JAVELIN trial were reported at this meeting.

This is a large study that involves the use of the drug Avelumab, an anti-PD-L1 antibody in the treatment of many solid tumors including breast cancer. Within this large trial of over 1,000 patients, 168 patients with advanced breast cancer were included. Their disease had progressed on other therapies, but they still had a good performance status. The mean age of the group was 55 years. Most had triple-negative disease.

The response rate was low at 4.8%. One patient had a complete tumor response and seven achieved a partial response. Interestingly, as has been seen in patients with melanoma when treated with these types of agents, those that achieve a response tend to stay in response for a long time. Also as seen in melanoma, some patients appear to get worse before their disease stabilizes.

The side effects noted with this drug are typical of this class and different from those seen with chemotherapy. Because one is increasing the activity of the body's immune system, certain autoimmune reactions are noted that involved the endocrine system and other organs. Clinicians require some experience in learning to manage these side effects.

This low response rate should not be viewed as totally discouraging. As with melanoma, it took time to learn how to maximize the effects and benefits of these agents. Yet, they do hold the promise of long term control not often seen with other agents such as chemotherapy, and appear to benefit the more aggressive cancers.

THE CONCEPT OF DE-ESCALATION

It is important to understand not only which patients should be treated, but also which patients should not be treated. When treatment is needed, is there a minimal amount of therapy that will achieve the necessary outcome? Who will not benefit from added therapy? These questions represent the concept of "treatment de-escalation." The issue is not how much therapy can be given, but how little is necessary since all therapies have side effects.

De-escalation as an approach is clearly evident in breast cancer surgery. Carefully conducted trials have demonstrated that the results from extended radical mastectomy could be maintained while successively reducing the extent of surgery to both the breast and lymph nodes. Similarly, modifications in radiation therapy have demonstrated that for most patients, radiation

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time can be decreased while maintaining equal benefit. For some patients, radiation can be completely avoided. This same philosophy is now being applied to drug therapy, especially in the adjuvant setting.

Identifying which tumors not to treat is based on an initial assessment of probability of disease recurrence and survival. If a tumor has qualities that suggest that the probability of recurrence and death are low (small size, well differentiated, hormone positive, HER2-negative), then therapy, especially chemotherapy, is unlikely to improve the odds to any meaningful degree. In this setting, even modest side effects are not warranted. Various tests such as the Oncotype DX test have improved our ability to identify patient groups for whom chemotherapy adds essentially nothing and should be avoided.

There are many patients with node negative disease where most oncologists now feel comfortable avoiding chemotherapy. Results from the TAILORx trial using Oncotype DX testing have confirmed that node negative patients in the very low risk category do well without chemotherapy. In the next few years, the TAILORx trial will report results from the modified intermediate risk category. From those results, we should know whether this group benefits from chemotherapy or not.

XELODA AS TREATMENT FOR RESIDUAL DISEASE

A question that plagues most clinicians is what to do in patients who demonstrate residual invasive disease after neoadjuvant therapy is completed. Should additional chemotherapy be given or should one simply proceed with only hormonal therapy or HER-2 directed therapy as indicated based on tumor subtyping? This question has become increasingly important since now many patients are treated with neoadjuvant therapy rather that adjuvant therapy, when all drugs are given after surgery.

An interesting study addressing this dilemma was presented by researchers from Japan. It involved a group of 900 patients who, following neoadjuvant chemotherapy, did not achieve a pathological complete response; but rather, had residual invasive disease. More than 80% had received prior treatment with anthracycline/taxane therapy. Both node negative and node positive patients were included. The group was composed of a young population of patients with a median age of 48 years.

Following surgery, the patients completed further standard therapy consisting of hormonal therapy if their disease was hormone positive and/or radiation. They were then randomized to either no further therapy or eight cycles of capecitabine (Xeloda) given at a dose of 2,500 mg/m2 on days 1-14 every three weeks for a total of eight cycles. Only 40% of study participants completed all eight cycles. Both disease free survival and overall survival were reported. At five years, both measurements demonstrated a statistically significant improvement for the group receiving Xeloda.

It is unclear at this time whether all subgroups of patients benefited from the addition of Xeloda to standard therapy. The dose used in this study, though often recommended in study populations, is actually difficult for many patients to tolerate, resulting in considerable dose reduction and discontinuation. We applaud these researchers for performing this trial, as it asks an important question in the management of many patients. The issue is whether this study alone should serve as the basis for a change in management. It does at least offer an option for patients and oncologists who are faced with the dilemma of residual invasive disease. It is also not clear from this study whether patients with hormone positive disease who are scheduled to receive hormonal therapy postoperatively should receive Xeloda simultaneous to hormonal therapy or whether hormonal therapy should be delayed. Would this help or harm them? I confess that I remain uncertain at this point.