Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

As with the June issue, this issue varies from the usual format so that I can continue to provide you with an update of selected presentations from the 2015 meeting of the American Society of Clinical Oncology. I hope that you find this information useful and that this newsletter continues to expand your understanding of the progress being made in the thinking and management of cancer.

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

In this issue, I will continue to discuss information presented at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO) held from May 29 through June 2nd in Chicago. There were four main themes to this year's meeting: (1) global oncology, (2) how to provide and measure "value" in medicine, (3) continuing developments in the field of immunology, and (4) how to conduct research trials in the era of "individualized medicine." The first two topics were discussed in the June issue. Topics three and four will be discussed in this issue.

DEVELOPMENTS IN IMMUNOLOGY

Multiple sessions at the 2015 ASCO meeting were dedicated to the expanding field of immunology in the treatment of cancer. Developments in the treatment of melanoma (an aggressive

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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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skin cancer), continue to lead the way. Much has been learned from observing how melanoma responds to immune therapies; initially as single agents and now in combination. We are now learning to apply these therapies to many other tumors such as lung cancer, kidney cancer, malignancies of the gastrointestinal system, and others. My expectation is that nearly all types of cancer will be studied.

In using immunological drugs, it has become apparent that the way we measure a "response" must be re-evaluated. With prior therapies such as hormones and chemotherapy, we have used a consistent way to measure tumor response. If the tumor became smaller, we concluded that the therapy was working. This principle was believed to be universal.

There was a rare exception to this rule, and that was the occasional observation of what was termed a "flare response." This uncommon phenomenon was originally noted in hormone positive breast cancer, where therapy with a hormonal drug would initially result in a worsening of disease. Tumors would actually get larger, pain would worsen and calcium levels would rise. If you could deal with these worsening symptoms and continue treatment with hormonal therapy, the patient would subsequently demonstrate tumor shrinkage and do well. Interestingly, similar observations were made while treating melanoma with immunotherapies. An increase in tumor size can precede a subsequent reduction in tumor size and volume. A few other similar patterns have also been noted between breast cancer and responses seen with immune therapies in patients with melanoma. At times, only a stable pattern is achieved without tumor size reduction; yet, patients can remain in this state for long periods of time and have an improved survival. Similarly, as noted when treating hormone positive breast cancer, at times many months must pass before any improvement is apparent. These patterns of tumor behavior have resulted in having to discard prior response criteria classically used to judge most other therapies and create new rules by which to judge and compare the effectiveness of immune therapies.

We are also having to learn to recognize and deal with new side effects as these agents have toxicities that are distinctively different from chemotherapy. These include toxicities of the skin such as rash and itchiness; the gastrointestinal tract such as colitis, diarrhea and occasional bowel perforations; the endocrine system such as inflammation of the thyroid or pituitary glands; hepatitis; irritation of the eyes; dysfunction of the kidney and/or pancreas; hematologic abnormalities and neurological symptoms. Most side effects are reversible but, at times, can be severe and even fatal.

As our understanding of the immune system expands further, new check and balance points will be identified and new drugs will be developed. These therapies are expected to have far reaching effects not only within the field of oncology, but within medicine in general.

DESIGNING RESEARCH TRIALS IN THE ERA OF PERSONALIZED MEDICINE

As discussed in several previous issues of this journal, the concept of personalized medicine is inherent in the development of many new therapies. In great part, this idea became possible based on results from the Human Genome Project which outlined details of the human genetic code or DNA. Techniques that were developed during this project have subsequently been applied to the understanding of the genetic material that is part of cancers. From this work, it has become increasingly

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apparent that as each human being is different, a high degree of diversity is also typical of cancer. It has also become clear that cancers, like human beings, react and change over time.

With this new understanding of biological diversity and specificity, the manner in which we have conducted clinical trials now seems inadequate and outdated. Our prior methods of grouping patients together based on simple gross classifications of their disease such as the organ of origin of their cancer may no longer suffice. New understanding of tumor biology suggests that we should treat tumors based on specific mutations found in the cells of each tumor. New concepts of trial design now suggests that we should group patients into trials based on the specific mutations of tumors irrespective of the organ of origin of a cancer. For example, tumors such as lung cancer, breast cancer and gastric cancer that are HER2-posistive should be grouped together when investigating new anti-HER2 therapies.

This new approach has advantages. It is likely that grouping such patients would demonstrate a higher response rate since each of their tumors harbor the specific target mutation. Fewer patients should be needed to demonstrate larger effects, saving time and money for the conduct of a trial. The effects of targeted therapies might be longer lasting.

Individualized medicine also presents certain complexities. Testing for mutations generally requires a fresh tumor biopsy. For both technical and biological reasons, older preserved tissue cannot always be substituted. However, fresh biopsies are not always feasible, based on a patient's tumor distribution. Biopsies have risks and added cost. Even when mutations are found, not all of them are important to how the tumor behaves. Even when a functional mutation is identified, there is not always a drug available to treat that mutation. Even then, the drug may not work or may work only briefly.

The drug approval process in the U.S. was not designed to accommodate personalized medicine. A drug approved by the FDA for use in lung cancer, may not be easily available for a patient with breast cancer. Its use in breast cancer will likely result in non-payment by a patient's insurance company.

Ultimately, the real issue is whether treating patients with therapies chosen based on specific tumor mutations results in a better outcome. Will it improve survival? Will it reduce toxicity? Will it avoid drugs that don't work? Logically, the answer to each of these questions would appear to be yes. However, logic and biology are not always the same. We must prove that this new approach is superior before we adopt it as the new standard.

ASCO BREAST CANCER NEWS

BIOLOGY OF EXERCISE

The benefits of exercise in the prevention and treatment of major chronic conditions such as cardiovascular disease and type II diabetes are well established and widely accepted by both medical professionals and the general population. Consequently, dietary modification, weight control, and exercise are part of what is prescribed for these conditions similar to recommendations for various therapeutic drugs. In contrast, the concept that diet and exercise may prevent certain forms of cancer and improve outcome in cancer management has not yet been widely accepted. Neither patients nor their doctors engage in serious conversations on these topics. Certainly, these ideas have not risen to the level of prescriptions.

There is considerable observational evidence that regular exercise is associated with a 30%-50% reduction in the incidence of breast and colon cancers; as well as a 10%-30% reduction in the risk of other common cancers, such as prostate and lung cancers. Similarly, in patients with early breast cancer, several

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observational studies suggest that regular exercise is associated with a 10%-50% reduction in the risk of recurrence and of cancer specific death, even after adjusting for other risk factors such as age, BMI and therapy. Similar observational data are now emerging for early colorectal, prostate and ovarian cancers.

These observational data have led to the development of randomized phase III trials directly testing the effects of exercise. One such trial is The Colon Health and Life-Long Exercise Change (CHALLENGE) trial investigating the effect of regular exercise in patterns of recurrence and death in patients with early colon cancer.

As summarized by Dr. Lee W. Jones from Memorial Sloan Kettering Cancer Center in New York, the prevailing understanding is that exercise may influence biological events basic to both tumor initiation and/or progression by altering circulating growth factors that are part of metabolism, sex-hormones, the immune system, inflammation and other pathways that collectively determine our internal biological state. Most of the research that has been done so far has concentrated on muscle tissue as a regulator of insulin-glucose metabolism. Elevated circulating levels of glucose, insulin and insulin-like growth factors are associated with a higher risk of certain forms of cancer, as well as a worse prognosis following a cancer diagnosis. Chronic exercise, especially endurance training, has been shown to favorably influence these biological parameters.

Recent evidence has demonstrated that in response to chronic exercise, muscle tissues secrete various factors both locally and into the general circulation which, in turn, affect distant organs including the brain, liver, bone marrow, pancreas and fat tissue.

Whether the effects of exercise are equal among all cancer types is not clear. Research in breast cancer has found that regular exercise of approximately 150 minutes of moderate intensity endurance exercise per week, was associated with a relative risk reduction of death of only 9% in women with estrogen receptor negative tumors versus a 50% reduction in women with estrogen receptor positive tumors.

There is increasing evidence that regular exercise is beneficial and probably critical to many aspects of human health. That these same effects can be seen in cancer should not be a surprise. We are now at a point where investigating these effects both in the laboratory and in randomized phase III trials in patients has become an active area of research. Physicians are now being educated about this topic and I believe will soon recognize that good care of their patients will need to include instructions and recommendations for exercise. ASCO has a website dedicated to providing patient information (cancer.net/physicalactivity) that provides patient friendly information on this and many other topics.

Reference: Jones L W, Exercise Alterations of the Host-Tumor Interaction, ASCO Daily News, May 31, 2015, pg. 20.

THE ExteNET TRIAL

The use of Herceptin as part of adjuvant therapy for HER2-positive breast cancer has had a major impact on the outcome of patients with this aggressive form of breast cancer. Even so, some patients still recur and will require therapy for metastatic disease. The question addressed by the ExteNET trial is whether the addition of the anti-HER2 targeted drug neratinib (a tyrosine kinase inhibitor or TKI) after one year of Herceptin will result in further improvement.

The results of this study were reported by Dr. Arlene Chan who is director of the Breast Cancer Clinical Trials Unit at Mount Hospital in Perth, Australia. The trial enrolled 2,840 stage II and stage III, HER2-positive breast cancer patients who had been treated with adjuvant therapy including one year of Herceptin, and who had not had a recurrence. They were then randomized to one year of

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placebo or one year of oral neratinib at a dose of 240 mg daily. Median age of those randomized was 52 years. Twenty-four percent of the participants had node negative disease. The primary endpoint was the number of patients who were free of invasive disease at two years of follow-up. Other endpoints including survival, will be presented when the data are more mature.

The present results demonstrate that 91.6% of patients given placebo were disease free at the two year time point versus 93.9% of those given neratinib. This difference of 2.3% is statistically significant. The difference was most apparent in those with estrogen receptor positive breast cancer where it was 4.2%. Diarrhea was a prominent side effect reported by 95.4% of those given neratinib. It was at least moderately severe in 39.9%.

At this point I find that these data are interesting, especially in those with hormone positive disease. However, I am not convinced that this should become a new standard. An overall difference of 2.3% at two years may be statistically significant but perhaps not clinically significant. The data may become more impressive as they mature. I do think that longer follow-up and survival results are needed before we incorporate this therapy as a routine. It is also likely that better agents will be available in this setting.

EXTENDED CHEMOTHERAPY FOR HORMONE NEGATIVE EARLY BREAST CANCER

For many years, we have actively studied the length of therapy administration necessary to achieve the maximum benefit. The specific goal has been to identify the minimum therapy necessary, since all therapies are accompanied by toxicity. For example, studies were done with each chemotherapy and Herceptin when given for two years versus incrementally shorter time periods. Even the degree of breast surgery necessary was studied resulting in changing from extended radical mastectomy to lumpectomy. Hormonal therapy in the form of tamoxifen was also subjected to studies comparing five versus ten years with a resulting decision that five years was optimal. However, there have always been clinicians who have continued to wonder whether more or longer therapy would not be better. This has led to newer trials the results of which have been instrumental in extending hormonal therapy to ten years, and to studies such as ExteNET described above evaluating extended anti-HER2 therapy. The question of extended chemotherapy has also been re-considered.

Dr. Marco A. Colleoni, who is Director of the IEO Division of Medical Senology and Scientific Committee Chair of the International Breast Cancer Study Group (IBCSG), presented trial 22-00 designed to look at continuing chemotherapy for an additional year in patients with hormone negative early breast cancer. This group was chosen since their prognosis is less favorable and also because these patients are not given hormonal therapy.

A group of 1,081 patients with hormone negative (HER2-positive or HER2-negative) early breast cancer, who had received standard chemotherapy with or without Herceptin were randomized to either observation alone or to receive 12 months of further chemotherapy consisting of Cytoxan 50 mg orally daily plus oral methotrexate at a dose of 2.5 mg twice per day on days one and two of each week. The median age of the group was 52 years. Seventy-five percent had triple-negative breast cancer, and 43% had node positive disease.

The doses chosen for these two chemotherapy drugs were quite low and should be relatively easily tolerated. The proposed biology was that at these low doses, these drugs should work as antiangiogenesis drugs or drugs that interfere with blood vessel formation by the tumor. In spite of the low doses used, 13% of those randomized to the chemotherapy did not receive

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it. Further, only 39% of those who did start the chemotherapy received at least 75% of the planned dose.

The primary endpoint of the study was the difference in tumor recurrence (disease free survival) at five years. The data were presented at a median follow-up of 82.6 months. The five year disease free survival was 78.1% for those randomized to chemotherapy and 74.7% for the group randomized to observation only. This difference was not statistically significant.

I consider this to be an interesting and important question. Unfortunately, this trial suffered from the inability to maintain many patients on the planned therapy even though the dose chosen for each drug was modest. Because of this, it is difficult to conclude whether this approach is valuable or not. When the authors limited their analysis to patients with triple negative disease or to those who did take at least 75% of the planned dose, the results were statistically significant and in favor of the treated group. As was learned years ago, keeping patients without obvious disease on chemotherapy for a protracted period of time is very difficult to do. I do applaud this group for trying to answer this question.

THE TITAN TRIAL

The use of the combination of Adriamycin and Cytoxan (AC) followed by a taxane such as Taxotere or Taxol for the adjuvant treatment of early breast cancer is standard throughout the world. Some tumors are resistant to the taxane drugs and alternatives are necessary. One such alternative is the drug Ixabepilone (an epothilone chemotherapy drug). Prior studies have suggested that this family of drugs may be particularly useful in the treatment of triple negative breast cancers.

Dr. Denise Yardley from the Sarah Cannon Research Institute, presented the preliminary results of the Titan study conducted in patients with triple negative disease. The median age of their population was 54 years. Thirty two percent had node positive disease. Most of the patients were postmenopausal. This phase III trial randomized patients to either four cycles of standard dose AC followed by Taxol at the standard dose of 80 mg/m2 given once per week for 12 doses or to Ixabepilone at 40 mg/m2 given every three weeks for a total of 4 doses. Due to poor accrual, the planned number of participants was reduced with a total of 614 being randomized. The primary endpoint of the study was disease free survival (the number who did not have disease recurrence).

At a median follow-up of about three years, the authors found no difference in disease free survival between the two groups. The disease free survival for the Ixabepilone group was 88% versus 89% for the group that received Taxol. More toxicity, particularly neuropathy, was reported by the group given Taxol; this resulted in more therapy discontinuation and dose reduction.

As can be appreciated, poor accrual greatly reduced the value of this important trial. It is impossible to know if a larger more adequately conducted study would have the same results. If there is a difference in benefit between these two drugs following the administration of Adriamycin and Cytoxan, it may not be a large one. Perhaps, based on the limited information provided by the Titan trial, for patients who cannot tolerate either Taxol or Taxotere therapy, Ixabepilone can be viewed as a reasonable substitute.

In many well planned trials, poor accrual, which occurs for a multitude of reasons, remains a major limiting feature. This is particularly a problem in adjuvant trials where thousands of patients are often needed to obtain statistically valid conclusions when comparing different therapies. It is in great part because of this issue that many studies are now being designed as neoadjuvant trials where drug therapy is given prior to definitive surgery, with response in the intact breast as the primary endpoint. It is not yet clear whether these two ways of comparing different treatments are equally as reliable.