Breast Cancer Advisor

BY DR. SILVANA MARTINO

Summer 2016

Dear Readers,

This issue of The Breast Cancer Advisor varies from the usual format. Its content will summarize selected key presentations from the annual American Society of Clinical Oncology meeting that I attended in Chicago, Illinois from June 3 through June 7, 2016. We will resume our usual format, including answers to your question in the Fall issue. Until then, if you have questions, I will respond to you directly via e-mail.

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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WHAT'S NEW

The American Society of Clinical Oncology (ASCO) meeting is a yearly international event. It is the most prestigious conference dedicated to the field of cancer, where scientists from the basic sciences, clinical sciences and social sciences aspire to present their new research data. Because of the wide scope of this meeting, many presentations are scheduled simultaneously. Consequently, one can only attend a small portion of the many excellent presentations. Since the meeting is primarily dedicated to the sharing of new data, much of what is presented is preliminary, and not always immediately clinically applicable. I have selected topics that I believe will have a more far reaching influence on the management of breast cancer.

THE MOONSHOT INITIATIVE

Perhaps the most prominent presenter at this year's meeting was Vice President Joe Biden who discussed the "NATIONAL

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CANCER MOONSHOT INITIATIVE" first presented by President Barack Obama in his State of the Union Address, January 12, 2016. The intent of this program is somewhat reminiscent of the "War on Cancer" launched by President Richard Nixon in 1971. The rhetoric from that program has dominated how both the public and scientists have thought about cancer since then; namely, an act of war.

Though much of the logistics of this new initiative are yet to be resolved and implemented, some degree of structure has already been planned. A Task Force led by the Vice President will be created. A panel of experts will provide the Task Force with scientific input. Additional funding of $680 million dollars will be provided to the National Cancer Institute's budget for 2017. Additional resources are pledged for the Food and Drug Administration.

The goal of this initiative is to accelerate cancer research. The primary areas to be addressed include (1) cancer vaccines, (2) early detection, (3) single-cell genomic analysis, (4) cancer immunotherapy, (5) pediatric cancers, (6) data sharing, (7) the pursuit of novel ideas, and (8) the breaking down of barriers so that more cooperative research efforts will result.

Do we need a new initiative? There are reasons to believe that a new energized effort may prove fruitful. Our understanding of both normal and abnormal cell biology has expanded. In part this has been the result of technologies developed from the Human Genome Project and new data derived from the Cancer Genome Atlas. Our understanding of the immune system is vastly different now. The pharmaceutical industry has grown to view cancer as a major focus, thus contributing to the development of many new drugs with different mechanisms of action.

Whether this effort will result in substantial progress cannot be predicted at this early stage. Though the money pledged sounds impressive, it is actually quite modest. Will a long term commitment follow or will this simply be a short term engagement? This is the final year in office for the present administration. Will the next administration choose to continue this effort or not? A commitment earlier in time might have been more successful. It may be too little, too late.

The cost of cancer drugs has reached a level that many patients simply cannot afford. Unless this issue is also addressed, more expensive therapy, even if better than our present drugs, may be of limited usefulness. Much could be done by a responsible initiative. Much remains to be seen. Yet, we are hopeful.

BIG DATA

The treatment of cancers is primarily based on knowledge derived from the conduct of clinical trials. Without clinical trials, we would not know which therapy is best, what dose to give, nor what side effects to anticipate. What is often not recognized, is that less than 5% of adults with cancer participate in research trials. Consequently, what we know about the benefits and risks from various therapies is based on observations made on a small minority of people with a particular disease. It is also not generally appreciated that patients who participate in research studies are usually healthier and younger than other patients. Therefore, research participants do not fully represent the general population, and the results seen in them are probably superior to those experienced when the same therapy is given to the general population of patients.

Aware of these limitations, The American Society of Clinical Oncology has launched a program called CancerLinQ. This program has been designed to create a large database that

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will encompass detailed clinical information provided by many oncology practices. Physicians will input information from all of their patients; those treated on clinical trials and also the large number not treated on clinical trials. There are now 600 oncologists participating in this project, and the system is adding new practices at the rate of one every two weeks.

Considerable technical issues have had to be worked out to organize the acquisition of so much data. The use of electronic medical record systems (EMR) has facilitated the process. Yet, EMR systems are varied and not designed to allow communication with other systems. Working out how to code medical information from various medical record systems is a challenging and limiting feature.

The initial uses of this system will be to allow participating oncologists to observe how others treat patients with similar conditions and compare their own approach and outcomes to that of others. It is also a good system to allow an understanding of patients with more unusual presentations where a physician may have limited experience. CancerLinQ will provide a more realistic assessment of benefits and side effects from various treatments. For example, benefits and toxicity experienced by elderly patients who are often excluded from research trials, can be ascertained. Over time, one can anticipate many other uses for such a large body of data. No doubt, there will be uses that at present we cannot imagine.

The greatest asset that I see to this system is that if a high level of accuracy is maintained, these data can provide real world experience, and not data solely from a highly selected group of patients entered on clinical trials. It will allow a more accurate assessment of benefit and risk that can be useful in guiding individual patients.

The accumulation of BIG DATA is now doable and intellectually appealing. Whether it will become a tool used by the government and insurance companies or whether the average physician will learn how to use it in a manner that is advantageous for patients is the real question.

EXTENDED USE OF AROMATASE INHIBITORS

Hormone positive breast cancer is generally considered to be less aggressive than other forms of breast cancer. Its recurrence rate during the first five years following diagnosis is lower than hormone negative breast cancer. However, it is also characterized by a persistent pattern of recurrence extending many years following diagnosis. Studies have shown that for up to 30 years after diagnosis, those with hormone positive breast cancer continue to have a higher death rate than the general population. It behaves more like a chronic disease. For these reasons, the question of whether five years of adjuvant hormonal therapy is adequate has remained an important question.

From the ATLAS and aTTom trials, we learned that ten years of tamoxifen are better than only five years. From the MA.17 trial, we know that five years of tamoxifen followed by five years of an aromatase inhibitor (AI) such as letrozole is superior to five years of tamoxifen alone. The remaining question which was addressed by the MA. 17R trial is whether ten years of an AI is superior to only five years of an AI.

The results from MA.17R were presented by Dr. Paul Goss from the Massachusetts General Hospital Cancer Center and Harvard Medical School. This study was an extension of the MA.17 trial (five years of tamoxifen with or without five years of letrozole). It included patients from MA.17 and others. About 80% of the patients had already received five years of tamoxifen plus five years of an AI, and the remaining 20% had only received five years of an AI. The study enrolled 1,918 patients who were randomized to receive either five additional

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years of letrozole or five years of a placebo.

The primary objective of the study was to demonstrate whether there was a difference in disease-free survival (no tumor recurrence or second breast cancer) between the two groups starting from the time of entry on MA.17R. The median age of the participants was 65 years. They were followed for a median of 6.3 years. The results of this study demonstrated that disease-free survival was statistically superior for those receiving letrozole versus placebo. This was particularly so for the patients who had node positive disease. Further, the results demonstrated that though there was a difference in distant and local recurrence rates between the two treatment groups, most of the difference was in a decreased incidence of a new breast cancer in the other breast. The letrozole treated group also had a better survival rate than the placebo group, but the difference was small and not statistically significant.

The side effects noted during this extended period of letrozole use were those anticipated: more osteoporosis, bone pain and fractures with letrozole.

What are we to make of these results? Should all post-menopausal patients with early breast cancer now receive ten years of an AI therapy? The study did meet its primary endpoint of demonstrating a significant decrease in overall breast cancer events with the use of an additional five years of letrozole. For some physicians and patients this may be enough. Others I suspect will not adopt this therapy based only on this study and may prefer to use this extended therapy only in patients that are judged to be at a higher risk of recurrence such as those with node positive disease, larger tumors or high grade tumors. Since the dominant benefit was in reducing second breast cancers, this therapy may not be of sufficient value if a patient has had bilateral mastectomies.

As with all studies, the patients in this trial were highly selected. Most were postmenopausal women who had received ten years of prior hormonal therapy before entering this trial. They had not recurred during this period, nor had they had enough side effects to not want to continue with another five years of therapy. Nevertheless, I think we have now moved to a point where patients with hormone positive early breast cancer will be advised to have at least 10 years of hormonal therapy.

THE MINDACT STUDY

Does everyone diagnosed with early breast cancer need to be treated with chemotherapy? Data continue to demonstrate that the answer is NO! Not everyone benefits from chemotherapy. For several decades, this decision was based on clinical features such as tumor size, lymph node involvement, tumor grade, hormone receptor status, HER2 status, and the patient's age and overall health status. A computerized system called Adjuvant! Online, which mathematically integrated these clinical features to allow prediction of recurrence risk as well as reduction of risk following treatment with various therapies was later incorporated into clinical practice. More recently, genomic tests that measure certain genes in the tumor have been added to the decision process. The genomic tool most commonly used in the U.S. is the Oncotype DX test. The use of this test has resulted in a reduction in the number of patients receiving adjuvant chemotherapy.

A similar tool known as the 70-gene MammaPrint test was developed and used in Europe. This tool was chosen in developing the MINDACT study presented recently at the American Association for Cancer Research (AACR) annual meeting and discussed at ASCO. A total of 6,693 patients with early breast cancer (up to three positive nodes) from 112 centers in nine European countries participated. All patients were classified using both the Adjuvant! Online tool and the MammaPrint test to calculate their risk of recurrence. Those who were judged to be at high risk by both measurements were treated with chemotherapy. Those judged

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DISCLOSURE

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to be at low risk by both systems were not given chemotherapy. Those where the two tools gave discordant results, were then randomized to either receive chemotherapy or not. It is this group which is of particular importance since contradictory results leave both the doctor and the patient wondering which result they should trust in choosing chemotherapy or not.

In this large group of patients, 41% were found to be at low risk by both assays, 27% were found to be at high risk by both assays, and 32% were found to have discordant results. Of this last category, most (72%) were judged high risk by the Adjuvant! Online clinical tool and low by MammaPrint genomic testing. The remaining 28% were found to be low by Adjuvant! Online and high by MammaPrint testing. Both of the discordant groups were randomized to chemotherapy or not.

As expected, high risk patients had larger tumors, were node-positive, or had triple-negative disease. Low risk patients had tumors that were smaller, hormone positive, and node negative. Five-year, distant metastasis-free survival (DMFS) was 97.6% for the group at low risk by both tests not treated with chemotherapy, and 90.6% for those that were high risk by both methods and received chemotherapy. The discordant group had results that were between these two groups; 94.8% for the clinically low risk/genomically high risk and 95.1% for the clinically high risk/genomically low risk group. The study was not designed with sufficient power to demonstrate a statistical significant difference between those randomized to chemotherapy or not, but the observed difference was reported to be very small. Specifically, the DMFS in those with clinically high/genome low group was 95.9% for those who received chemotherapy versus 94.4% for those who did not. In the clinically low/genomically high group, the DMFS rates were 95.8% with chemotherapy and 95.0% for those without.

The primary conclusion drawn from this study, is that the MammaPrint test can be successfully used to predict who is at high risk of recurrence and who is not. Similar to the Oncotype DX test, it is most useful for patients with hormone positive disease, including those with up to three involved nodes and large tumors.

This large study does not answer all questions on this issue. It does demonstrate that those with discordant results have a risk of recurrence that is between those at high risk and those at low risk. It suggests that whether this group is given chemotherapy or not, their results appear similar. It does not prove that this is true. It also does not tell us how the MammaPrint test compares to the Oncotype DX test. Is one more accurate or are they the same? Like the Oncotype DX test, it does confirm that genomic testing can be used to separate most of those at high versus low risk of recurrence. It also confirms that clinical criteria remain valuable for most patients. As with the Oncotype DX test, there is a group of patients of intermediate risk for whom we are not completely sure that chemotherapy is of value. Other ongoing studies will have to answer this final question.

CDK4/6 INHIBITORS

Hormone receptor positive breast cancer is the most common type of breast cancer. It dominates in postmenopausal women and is also commonly seen in premenopausal women and in men. For these tumors, hormonal therapy remains the most effective form of therapy in both the adjuvant and metastatic setting. The various hormonal therapies in use are all fairly old, and many of us wondered if anything new could be identified that would add further benefit against these tumors.

New advances in our understanding of the biology of the hormone receptor system in cells has demonstrated that the estrogen receptor does not function in isolation. In fact, it is connected to and influenced by many other pathways in the cell. Exploring these other pathways has resulted in novel ways

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to influence hormone receptor positive cells.

The drug everolimus (an mTOR inhibitor) was the first such drug to be approved by the FDA. Though everolimus (Afinitor) is not a hormone, when combined with certain hormones, it enhances their activity. More recently, data has been presented exploiting a second mechanism; inhibition of the CDK4/6 cellular pathway.

Dr. Maura N. Dickler from the Memorial Sloan Kettering Cancer Center in New York presented the results of the MONARCH 1 trial. This study administered the drug abemaciclib as a single agent to 132 patients with hormone positive/HER2-negative breast cancer who had been previously treated with both hormones and chemotherapy and had progressive disease. Most patients had extensive disease with involvement of several organs including lung and liver. The main objective of the study was to measure tumor response rate. They observed a response rate of 19.7% and stable disease in an additional 22.7% of patients. Median duration of response was at least six months in 70.4% of patients and 12 months in 28.2%. Abemaciclib was well tolerated, with only 7.6% of patients discontinuing therapy due to side effects. Based on these results, two new studies will follow, each combining this agent with hormonal therapy.

Results from the drug palbociclib (Ibrance), another CDK4/6 inhibitor, were presented by Dr. Dennis J. Slamon from UCLA. In an earlier study, the PALOMA-1 trial, the addition of palbociclib to letrozole (Femara) versus letrozole alone in hormone positive/HER2-negative patients as first line therapy for metastatic breast cancer, had demonstrated an improved progression-free survival of ten months with the combination therapy. Based on these results, the FDA granted accelerated approval for this combination. A confirmatory trial was required for full approval. This led to the PALOMA-2 trial, the results of which were presented at the ASCO meeting.

The PALOMA-2 trial was a double-blind, placebo-controlled study that randomized 666 patients with advanced hormone positive breast cancer in a 2:1 ratio to palbociclib plus the hormone letrozole or to letrozole plus a placebo.

As in the PALOMA-1 study, the patients were enrolled in this trial at the time of their first treatment for metastatic disease. Slightly more than one-half of the patients had received prior neoadjuvant and/or adjuvant hormonal therapy. The median age of the group was around 61 years. All had good functional status. The primary endpoint for the trial was assessment of progression-free survival (PFS) as judged by the treating physician.

With a median follow-up time of 22 months, the results of this trial demonstrated a PFS of 24.8 months for the group receiving palbociclib plus letrozole versus 14.5 months for the group receiving letrozole with placebo. This difference was statistically significant and clinically meaningful. A second analysis was performed by an independent review group who reported a PFS of 30.5 versus 19.3 months, confirming the benefit of palbociclib.

More toxicities were apparent in the palbociclib plus letrozole group versus the letrozole with placebo group. These included lowered blood counts, fatigue, nausea, joint pain, hair loss, diarrhea, cough, back pain, headache and hot flashes. Serious side effects occurred in 19.6% of those treated with palbociclib versus 12.6% of those in the letrozole with placebo group. Permanent discontinuation due to toxicity was 9.7% in the palbociclib treated group versus 5.9% among those receiving letrozole plus placebo. Overall survival data is still premature and will be presented at a later date.

Though much attention is given to triple-negative and to HER2-positive breast cancer because of their more aggressive nature, we must be mindful of the fact that most patients are diagnosed with hormone positive disease. Progress made in the treatment of this version of breast cancer remains critically important as well.