Dear Readers,

Thank you for all of your comments and critiques on the last issue. I particularly want to thank the doctors and nurses who also reviewed the newsletter. They provided some of the most detailed advice and insight. A few readers offered to provide artwork for subsequent issues. I know that some of my own patients are accomplished artists and photographers. I rather like the idea. If any of you wish to contribute artwork for consideration, please exclude personal family photos.

In this issue, I want to introduce a new feature titled GUEST WRITER. There are topics about which I feel someone else is more of an expert than I am. I will ask other medical practitioners to contribute material that I feel will assist you.

Again, your comments, questions and critiques are welcomed and appreciated.

Wishing each of you the very best,
Dr. Silvana Martino

Breast Cancer Advisor

BY DR. SILVANA MARTINO • SEPTEMBER 2011

BIOLOGY BASICS

The topic that I will review in this issue is what is known as the STAGE of a cancer. This concept is not specific to breast cancer, but is applied to cancers in general. STAGE is a way of summarizing the extent of a cancer. It takes into account whether the disease is invasive or not, the size of the primary tumor, if lymph nodes are involved, and whether the disease is apparent in other organs of the body. The STAGE of a cancer informs you about prognosis, and assists in deciding what treatments are needed. The TNM classification is most commonly used for this purpose, where T is the tumor size, N is a description of lymph node involvement, and M refers to involvement of other organs by the cancer. The stage of a cancer can be based on physical exam, biopsy, and imaging tests (called the clinical stage) or all of these plus the results of surgery (called the pathologic stage). The pathologic stage is preferred as it contains more detailed information about a tumor. The pathologist's report about the breast and the lymph nodes is more accurate than information gathered by a physical exam and various films.

The TNM staging system is not static; it is periodically refined and updated as new information about the biology of cancer is discovered.

The stages of breast cancer can be summarized in this way:

- Stage 0: This stage is usually ductal carcinoma in situ (DCIS). Lobular carcinoma in situ (LCIS) is also classified here, but most oncologists do not consider it

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cancer at all. Paget's disease of the nipple without an underlying invasive cancer or a non invasive process such as DCIS or LCIS is also included.

- Stages IA, IB, IIA, IIB, IIIA, IIIB, and IIIC: In these stages the tumor is increasingly larger in size; it may have grown into the skin or chest wall, or may have an inflammatory appearance. An increasing number of lymph nodes are involved. There is no obvious spread to distant organs.
- Stage IV: This cancer can be of any size, and may or may not have spread to lymph nodes surrounding the breast. It has spread to distant organs or to lymph nodes far from the breast.

Stages 0 through IIIC represent cancer which is potentially curable. Stage IV is most often not curable with present therapies. Even in this stage, many patients can do well for a long time. Much of the research that is done in the field of breast cancer is dedicated to Stage IV patients.

There are important features about a tumor that are not yet incorporated into the staging system such as hormonal receptor status, HER2/neu status, and rate of growth. These features about a tumor are very important in prognosis and choice of therapy. At some future date they are likely to be incorporated and will add further to the value of the staging system.

In the next issue we will discuss patterns of recurrence and the spread of breast cancer.

Reference: AJCC Cancer Staging Manual, seventh edition, published by Springer-Verlag, New York, NY.

WHAT'S NEW

1. Can we protect ovarian function while a premenopausal woman is receiving chemotherapy?

It is commonly held that many but not all side effects of chemotherapy result because chemotherapy is most effective in damaging a cell that is in the process of dividing. Cell division is necessary for growth of both cancers and normal tissues. Cells in some organs of the body divide more often than others. Hair, nails, bone marrow, the lining of the intestinal system, and the ovaries are examples. There is interest in preventing and preserving all of these structures from the damaging effects of chemotherapy. Preserving ovarian function is particularly important in women who are premenopausal and especially if they plan to have future pregnancies.

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Over the past several decades, physicians have been considering how to achieve this goal. The prevailing idea is that perhaps if one could first put the ovaries to sleep and then give chemotherapy, the ovaries would be damaged less than if they were fully functional at the time chemotherapy is given. To date, several studies have been done using this concept. First, one gives certain hormones called LHRH agonists (Luteinizing Hormone –Releasing Hormone Agonist) to put the ovaries to sleep, and then one gives the planned chemotherapy. The hormones are continued until the chemo is completed. Once the chemotherapy is finished, you stop the LHRH agonist and wait to see if menstrual cycles return.

A study using this strategy was recently reported by a German breast

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cancer research group. Sixty premenopausal women ages 18 to 45 were selected. They were receiving chemotherapy with Adriamycin, Cytoxan and a taxane for 4 to 6 cycles given every three to four weeks. Half of them also received therapy with an LHRH agonist hormone started two weeks prior to chemo. Importantly, they specifically chose women whose tumors were estrogen and progesterone receptor negative, so that no other hormonal therapy would be used as part of their cancer treatment. The need for other hormonal therapy such as tamoxifen or aromatase inhibitors always confuses this picture. The researchers made the following observations. Menstrual periods stopped temporarily in 93% of women given LHRH agonists versus 83% in those only given chemo. At six months after chemo, 70% with and 57% without LHRH agonist hormones had resumed their periods. Though this may seem like an improvement with the use of the protecting drug, it is a very small difference. By about 2 years, almost everyone had resumed their periods.

In summary, they found that there was minimal protection of the ovaries with this therapy and this standard chemotherapy. They also confirmed what has been known for a long time; specifically, that what matters most in how the ovaries tolerate chemotherapy is the age of the person. The younger a woman is, the more capable the ovaries are in preserving their function. It does matter what chemo you receive and for how long, but age is most important. There is another issue to keep in mind, however. Regaining one's periods after chemotherapy may not be the same as being able to conceive.

Another important point that needs to be kept in mind is that in tumors that are estrogen or progesterone receptor positive, reducing estrogen production is actually part of the goal of therapy. So preserving ovarian function in such women may be counterproductive.

Reference: Gerber B, von Minckwitz G, Stehle H, et al, Effect of Luteinizing Hormone-Releasing Hormone Agonist on Ovarian Function After Modern Adjuvant Breast Cancer Chemotherapy: The GBG 37 ZORO Study, Journal of Clinical Oncology, Vol 29, No 17, June 10, 2001, pg 2334-2341.

2. Breast Cancer, Obesity And Inflammation

It has long been recognized that postmenopausal women who are overweight have a higher risk of developing breast cancer. The mechanism by which this occurs is not entirely clear, but it is presumed to involve an increase in estrogen production by body fat. Over the past decade, scientists have demonstrated that being overweight triggers a chronic inflammatory process in fat throughout the body. Breast tissue is largely composed of fat, especially in postmenopausal women. The question is whether this process can affect the milk producing system of the breast (the ducts), which is where cancers begin. To investigate this idea, Dr. Andrew Dannenberg from the Weill Cornell Cancer Center compared breast tissue from obese mice that had been fed a high fat diet with breast tissue from lean mice fed a low fat diet. What his group observed, is that both fat from breast tissue and fat from other parts of the body contained the presence of "crown-like structures" that were not observed in fat from lean mice. These crown-like structures contained fat cells surrounded by cells from the immune system. Additionally, aromatase activity which suggests increased estrogen production was increased in obese mice. Similar results were observed in different mice that are genetically obese rather than obese based on a high fat diet.

The question of course, is whether this occurs in humans. To find out, Dr. Dannenberg looked at breast tissue from 30 women who had breast surgery at Memorial Sloan-Kettering Cancer Center in New York. They found that these crown-like structures were apparent in breast tissue of most obese and overweight women but in very few lean women. Well, where does all of this leave us? It adds another reason to control weight. It also may explain observations that have been made suggesting that drugs such as aspirin and ibuprophen which have an anti-inflammatory quality may reduce the incidence of breast cancer. The process of chronic inflammation may be at the root of the cancer process.

Reference: Andrew Dannenberg, presented during Joint AACR/ASCO Presidential Forum at the American Association for Cancer Research annual meeting.

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"They found that these crown-like structures were apparent in breast tissue of most obese and overweight women but in very few lean women."

3. The PARP inhibitor INIPARIB in triple-negative metastatic breast cancer

It is becoming increasingly clear that breast cancer is not a single disease, but rather it is a disease with many variations. It is for this reason that the outcome and response to therapies varies so much from patient to patient. As new scientific tools become available, we are able to biologically subdivide cancers more and more. One of the first distinctions that was recognized many years ago was that some breast cancers did well when treated with hormonal therapies and others did not. This clinical observation ultimately led to the discovery of the estrogen and progesterone receptors in many breast cancers. More recently, the identification of the HER2/neu receptor protein found in about 25% of breast cancers has provided another important distinction. These distinctions tell us about a tumor's probable behavior, but more importantly allow us to develop therapies that are targeted for certain features of a tumor. Targeted therapies are generally more effective and, therefore, preferred.

A version of breast cancer that has recently received considerable attention is the triple-negative variety. This is not a new type of breast cancer, but simply a cancer that lacks the estrogen receptor, the progesterone receptor and the HER2/neu receptor. The lack of each of these three receptors is the source of its name. Because it lacks the three well recognized receptors, it does not respond and is not treated with either hormonal therapies or HER2/neu directed therapies. This limits the available treatment options to primarily chemotherapy.

Because of these limited options for its treatment, there is considerable effort in finding new types of drugs that might be more effective against triple negative disease. One such therapy is the class of drugs collectively called PARP inhibitors. The details of how these drugs work will be discussed at another time. For now, let me summarize by saying that PARP inhibitors interfere with a method of repair that a cell uses when it is damaged by chemotherapy. If a cell cannot properly repair itself, it is more likely to die.

The data on iniparib was presented by Dr. Joyce O'Shaughnessy at the June 2011 American Society of Oncology meeting. 519 patients with metastatic breast cancer were divided randomly into two groups. One group received chemo alone (gemcitabine/carboplatin), and the other received the same chemotherapy plus iniparib. What they found was that the two groups did the same. The addition of iniparib did not cause more tumor shrinkage, nor did it keep the tumor from growing for a longer time, nor did it improve survival.

Clearly these data are disappointing. Especially since the same researcher had previously published that this drug with the same chemotherapy had shown great results in a smaller group of similar patients. Why do the results appear to be different? This is an important question and a frequent event in research. When a drug is new and we are all excited about it, we generally treat a small group of selected patients with it. If the results look promising, we get even more excited. But we know that the real test is to compare the effect of a standard therapy versus the same therapy but with the new drug added to it. This is a much more accurate and fair test of the new drug's real added benefit. It is when this type of comparison was done, that it became apparent that the results obtained in the first small study were actually the effect of chemotherapy and not a result of adding the new agent.

Proper drug testing is very critical, even if not always positive in its results. Without this type of testing, we fool ourselves by thinking that simply because a therapy sounds as if it should work; in fact, it really adds nothing but side effects and a higher price tag.

That this study demonstrated that this PARP inhibitor did not add benefit to this chemotherapy does not mean that this entire line of research is likely to fail. Other PARP inhibitors are being investigated and those results may be very different. Even this drug may be more effective in some other type of cancer. Even triple-negative breast cancers are not all the same. So, it may be that we need to figure out which patients and which tumors are best, even for this agent. Each of these questions is important.

Reference: O'Shaughnessy J, et al. A randomized phase III study of iniparib in combination with gemcitabine/carboplatin in metastatic triple-negative breast cancer. J Clinical Oncology. 2011; 29(suppl; abstr1007).

GUEST WRITER

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All About Lymph Nodes

Nestled in little clusters throughout your body are hundreds of pea-sized structures called lymph nodes, quietly working to clear your system of toxins, infections and other foreign particles. These products arrive to lymph nodes within a milky fluid called lymph. Lymph nodes occasionally become large enough to feel, such as when they become the swollen lumps in your neck that herald the onset of a cough and runny nose. Most of the time, these little organs go through life unnoticed.

In your axilla (arm pit) are dozens of lymph nodes. These nodes drain and filter the lymph fluid from your chest wall, which includes the breast tissue. An infection of the skin overlying the breast will send bacterial products through the axillary lymph nodes. In a similar fashion, cancer cells which have acquired the ability to spread (metastasize) into the lymph system will predictably flow to lymph nodes. When breast cancer cells have invaded the lymph system, they will typically flow to the axilla first, where they encounter a bed of lymph nodes.

Doctors have long observed the tendency for breast cancer to spread to axillary lymph nodes. Removing the axillary lymph nodes at the time of breast surgery allows the pathologist to count the number of lymph nodes involved by tumor. Patients may have from one to several lymph nodes containing cancer; however, most patients have all benign lymph nodes.

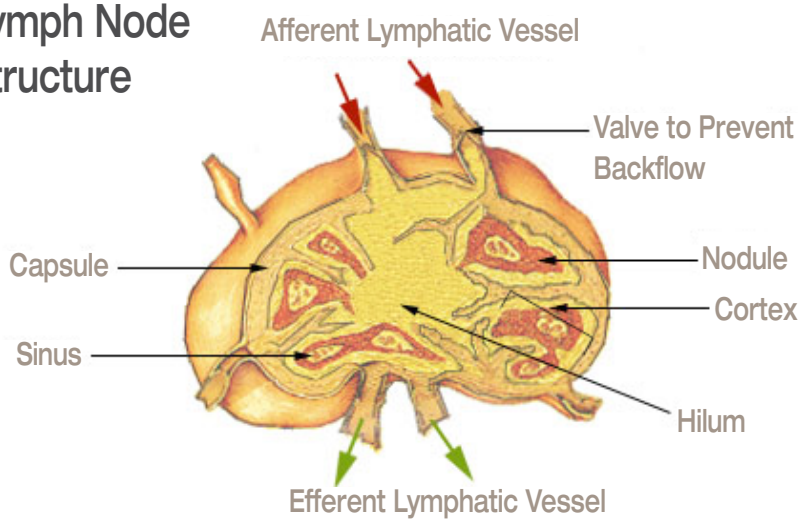
Doctors believed that many patients could be spared extensive lymph node removal and its undesirable side effects, but they needed a way to determine who those patients were.

Lymph nodes work in teams, but they are arranged in a chain-like hierarchy. Once cancer cells reach a set of lymph nodes, they filter through one or two lymph nodes first. The first lymph node(s) encountered is called the "sentinel node" and it can be identified by a surgeon with the assistance of a blue or weakly radioactive dye. If the sentinel node does not contain cancer, one can confidently predict that other lymph nodes are similarly uninvolved. Only patients with cancer in their sentinel lymph node are considered for more extensive surgery to remove other lymph nodes.

Because such important clinical decisions are based on the pathologist's examination of the sentinel node, this node is given very special treatment. After the surgeon removes the sentinel lymph node, it is put through an overnight process whereby it emerges forever preserved in a block of paraffin wax. Laboratory specialists cut thin slices of this paraffin-embedded lymph node and lay them on a slide for the pathologist to examine.

At this point, sentinel and regular ("non-sentinel") lymph nodes are handled very differently. A regular lymph node will be sliced one time and stained with a routine tissue stain (called H&E). A sentinel node is cut at two separate levels within the paraffin block, creating at least 4 slices of the node. Two of the slices are stained with the H&E stain, and two of the slices are stained with a special formula, called cytokeratin immunohistochemistry stain, which highlights any migrated breast cells. As a result of this diligent examination, a pathologist gains much more information about the sentinel lymph node. When doctors can say with confidence that a sentinel lymph node contains tumor or is benign, patients receive superior, personalized treatment for their breast cancer.

Lymph Node Structure



QUESTIONS & ANSWERS

(Q) Dr. Martino, I am 47 years old. I was diagnosed with node negative, hormone positive breast cancer 4 years ago. After surgery and radiation, I received chemo for three months and now I am on tamoxifen. I generally feel well, but from time to time, I get back pain. This has been going on for about two years. It is mild and after a while each time it goes away, but then comes back. My doctor thinks it's nothing. It's bothering me now and I am getting scared. What should I do?

(A) The first thing to keep in mind is that even though you have had breast cancer, it does not mean that you won't get your share of other medical issues. Not everything that bothers you is going to be related to the prior diagnosis of breast cancer. A general rule that is simple yet I have found very useful is the following: discomforts that come and go most often are not caused by cancer. On the other hand, discomforts that don't want to go away may still have another cause, but these should be investigated. Given the fact that your back pain has been with you on and off for two years, it most likely is benign. However, if it has not been investigated before, and something about it is now causing you to be fearful, I would favor that your doctor look into it.

E-mail your questions to:

smartino@theangelesclinicfoundation.org

Disclosure: The information contained in this newsletter is for educational purposes only. It is not designed to diagnose or provide treatment recommendations. Please consult your own physicians for all decisions about your care.

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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Upcoming Foundation Events

For more information, please call us at (310) 582-7909

Breast Cancer Education Seminar
October 24, 2011 • 7:30 PM
Temple Beth Am
Los Angeles, CA

The Wellness Community Breast Cancer Awareness Seminar
October 24, 2011 • 6:00 PM
Westlake Village, CA

Breast Cancer Education Seminar
November 16, 2011 • 11:30 AM
Temple Adat Ari El
Valley Village, CA