Dear Readers,

The Breast Cancer Advisor is now in its second year of publication. Writing is something I have always enjoyed, but in the past my audience has been my medical colleagues. Writing for breast cancer patients and the general public has been a new experience for me. I have found this style of writing very enjoyable. Communicating with you is very meaningful to me. I look forward to doing it. I like answering your questions and I hope that this newsletter makes it easier for you to understand information about breast cancer. As we go forward, please continue to send me your suggestions for ways to improve the Breast Cancer Advisor. I personally read and respond to all of your emails.

My gratitude and best wishes to each of you.

Sincerely,
Dr. Silvana Martino

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BIOLOGY BASICS

In this issue, I will continue to discuss the management of metastatic breast cancer. As a brief review of the preceding article, there are three important questions that must be addressed when recurrence or a metastatic process is suspected. These are: (1) is it truly a recurrence of the original cancer and are the estrogen, progesterone, and HER 2 receptors the same, (2) what organs are involved, and (3) are there symptoms of the disease which require immediate care? Once the preceding information is available, then one can proceed to finalize the treatment decisions. As I stated in the previous entry, the primary form of therapy that is used is drug therapy. Surgery and radiation have a limited role at this point since they are local therapies and the nature of the metastatic process is systemic. Therefore, what is used is therapy that can treat the body as a whole. Be aware that the brain and its surrounding structures are not adequately treated with drugs alone and require more specific therapy. This topic I will discuss at another time.

There are several types of drugs that one must consider. They are: (1) hormones and the drug everolimus (Afinitor) which helps extend the period of control...
from some hormonal therapies, (2) HER 2 directed therapies, (3) chemotherapy, and (4) experimental therapies that are still in the research phase of their development.

In choosing which drugs to use, several details about the tumor and the patient are considered. If the tumor is hormone receptor positive, hormonal therapy is preferred. If it is not, then hormonal therapy is unlikely to work and is not considered. In a similar manner, if the tumor is HER 2 positive, then HER 2 directed therapies are of value. Chemotherapy however, can be used in any set of circumstances. Hormones and HER 2 therapies are “targeted” therapies. Chemotherapy is more general in its effects.

The general principle is that one prefers to use targeted therapies if at all possible. They are more effective and generally result in fewer side effects. Chemotherapy drugs are reserved for tumors that are unlikely to respond to targeted therapies, but are also favored when the tumor appears to have a rapidly progressive course. Choosing among these therapies requires knowledge and clinical judgment. There is often a tendency to assume that more aggressive and intensive therapy must always be best. This is not correct.

The goals of treatment of metastatic disease are to reduce symptoms from the disease and to preserve a person’s functional capacity. This is achieved by trying to reduce the amount of tumor in the body and by this process allow the body to heal and function better. All therapies are used with these goals in mind.

Once a therapy is started, one must wait at least 6 to 8 weeks to allow the therapy to work before deciding if it is beneficial or not. Hormonal therapy may require even longer to be certain. The decision that a therapy is working or not is based on how the patient is doing and on measurements that reflect the size and quantity of disease such as X-rays, scans, tumor marker levels and level of circulating tumor cells. These measurements are compared to those taken when a therapy is started. At minimum, the disease should remain stable for a conclusion that it is probably working and should be continued. Tumor growth or new sites of disease imply that the therapy chosen is not sufficiently effective to continue it and an alternative therapy should be chosen.

We will continue discussion of this topic in the next issue.
Are there ways to help overcome the process of hormonal resistance? One way is with the use of the drug everolimus (Afinitor) which inhibits the mTOR resistance pathway within a cell. I have discussed this process in a previous issue in reference to treatment with the hormone exemestane. A small study has recently been published that suggests that this agent may also be able to reverse resistance to the hormone tamoxifen. A total of 111 postmenopausal women with metastatic breast cancer whose tumor was hormone positive and HER 2 negative and who had been previously treated with an aromatase inhibitor hormone and whose disease had progressed were randomized (like the flip of a coin) to either taking tamoxifen or tamoxifen plus Afinitor. The main measurement of effectiveness was the number of participants with either a decrease in tumor volume or at least disease that was stable. In addition, the side effect profile of the two treatments was evaluated. The group has been followed for about 2 years.

The results of this small study demonstrate that by the 6 month period, 61% of those treated with the combination of tamoxifen and Afinitor had at least stable disease versus 42% for those taking tamoxifen only. Time to disease progression was 4.5 months for those treated with tamoxifen alone and 8.6 months for women given both drugs. Survival also appears to be somewhat better with the combination. The main toxicities associated with the combination were fatigue, mouth sores, rash, loss of appetite and diarrhea. In 20% of participants the side effects were severe enough to require a dose reduction of the Afinitor.

This is a small study and alone cannot be used as clear proof that Afinitor adds to the benefit of tamoxifen. Nor does this study tell us that we should consider adding Afinitor to tamoxifen in patients who have not been previously treated with an aromatase inhibitor hormone. It does not tell us that this drug should be added in those without metastatic disease. It does add to our knowledge that we may be able to manipulate hormone resistant tumors. The larger study comparing the hormone exemestane to exemestane with Afinitor in a similar population was sufficiently positive to result in the approval of Afinitor in that combination. It is likely that this may be a more general biology and that Afinitor will to some degree reverse resistance to other hormones as well. Additional studies are underway.

2. Chemotherapy Dosing

In the August 10th issue of the Journal of Clinical Oncology, Dr. John Marshall and Dr. Otto Ruech from Georgetown University in Washington, DC, raised the question of how we choose the approved and recommended dose for each chemotherapy drug as well as some of the newer non-chemotherapy drugs. I have no doubt many of you have wondered about this issue. The question is not how we calculate a starting dose for each patient. That is relatively easy. For each drug there is a recommended dose which is generally multiplied by an individual’s meter-squared number. A person’s meter-square (m²) number is a mathematical relationship of their height and weight. For example, in the AC regimen (Adriamycin and Cytoxan), the dose of Adriamycin is 60 mg per m². Therefore, if you are 1.5 m², one multiplies 60 times 1.5 to calculate a total dose of 90 mg for that individual. The question discussed in this article is how we arrive at the first number, the Adriamycin number.

That number, which is different for every drug, is arrived at experimentally. When a drug is first studied in people, one begins at a low dose calculated from studies done in animals. As several individuals are treated at the low dose, one observes and records side effects. If there are no intolerable side effects, the dose is increased and a new group of people are treated with the higher dose. Again, if no intolerable side effects are noted, the dose is further increased for administration to another group. This process continues with increasing doses being used until a dose is reached where the toxicity is considered too high. The dose just below this toxic level is then chosen as the maximum tolerated dose and recommended for use. This schema which has been used for many years is based on the concept that more is better and if we could only manage to give a higher dose, we would be more effective against a tumor. What may appear to be a logical conclusion may not actually be a correct biological conclusion. It is not clear that anything in nature really works this way. As a simple example, if you give a plant too little water, it will not do well. Likewise, if you give it too much water it will also not do well. There is a level in the middle of the two extremes that works best. It is likely, that drug dosing also works in the same manner.

The authors of this article question the method by which we have chosen drug dosing in the past, and suggest that other ways should be considered. Ideally, there should be some aspect of how a drug interacts with its target in a cell that should guide us as to what dose achieves the desired effect in a cell. Though presently this is difficult to do with most drugs, it must be our goal. The concept of using toxicity to guide dose calculations cannot be the best solution.


What’s New continued

QUESTIONS & ANSWERS

(Q) Dr. Martino, I was told that as part of my breast cancer surgery, I had an axillary dissection that removed my lymph nodes. Does this mean that all of my lymph nodes were removed and now I don’t have any left in my arm pit?

(A) No, it does not mean that all of the lymph nodes in your axilla (arm pit area) were removed. There are not an exact number of lymph nodes in the axilla. The number varies from person to person. When an axillary dissection is done, the surgeon removes the tissue located in certain sections of the axilla and gives it to a pathologist. The pathologist then has the task of looking through the tissue and identifying and counting the lymph nodes. It is not the intent of your surgeon to remove all the lymph nodes. The goal is to remove a portion of them to see if they contain tumor. A study was done many years ago to try and figure out how many lymph nodes were left behind when an axillary dissection had been done. Patients were taken back to surgery and a further resection was performed. Additional nodes were found. When the number of nodes removed by both surgeries was added, some patients were found to have over 50 nodes total.

E-mail your questions to: smartino@theangelesclinicfoundation.org
Breast Density and Risk of Breast Cancer

Breast density describes the composition of a woman’s breast tissue. Breasts are composed of variable amounts of glandular tissue, connective tissue and fat. On a mammogram, areas of glandular and connective tissue show up as white and areas of fat appear black. Therefore, a higher breast density means that there is a greater amount of glandular and connective tissue compared to fat. There is no uniformly agreed method to measure breast density. Most often it is estimated by the radiologist reading the mammogram. There are software programs available to estimate breast density but none of these have been proven particularly useful at this time.

A woman’s breast density is usually inherited, although diet and exercise play a minor role. Approximately 40% of all women have breast tissue that is categorized as dense (over 75% glandular tissue). Younger women often have relatively higher breast density which becomes more fatty replaced with age. The process of fatty replacement is called involution and involves atrophy of the ducts and connective tissue. Older women who take hormone replacement therapy tend to have more dense breast tissue.

There has been ongoing controversy as to the role of breast density as a risk factor for breast cancer. In 1976, JN Wolfe developed a classification system to categorize breast tissue density. He suggested an association between higher tissue density and increased risk of breast cancer. Most experts are now coming to some agreement that this is true. Most now believe that women with dense tissue (75% or more of the breast) have a risk of breast cancer four to six times as great as the risk among women with little or no dense tissue.

Annual screening mammography remains the most important method to detect early forms of breast cancer. Although mammography remains the best detection method, it still misses 10-15% of all breast cancers. Many of these cancers are missed because they are hidden in the dense breast tissue. Standard Mammography (also known as Film-Screen) is performed on film. A newer imaging method called Digital mammography takes mammographic images digitally. This does offer some benefits for women with dense breasts including increased detection because the computerized images can be manipulated to magnify or sharpen them to allow detection of cancers which may be hidden behind dense tissue.

Thus, women with dense breast tissue face two significant challenges. They are not only at a higher risk for developing breast cancer but they also face limitations in detecting early forms of the disease.
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Breast Density continued

breast cancer, but mammography is more limited for these women. The state of California is making the unusual move of considering legislation to address this medical issue. The bill, SB 791 has been vetoed once by the governor but is expected to be reintroduced. This bill requires radiologists to inform women of their breast density as part of their mammography results. This legislation is opposed by many medical organizations who feel that the bill was “too vague and may lead to unnecessary tests.”

Women who have dense breasts may be offered an additional screening test. The following tests are under consideration.

Breast Ultrasound: Ultrasound uses sound waves rather than radiation to penetrate the breast tissue and create images. It is currently used as an effective tool in addition to mammography; however, it is not considered as a good screening method because it finds too many non-cancerous nodules that lead to unnecessary biopsies. More research needs to be done to determine if it may be effective in women with dense breasts who are a higher risk.

Breast MRI: Magnetic Resonance Imaging (MRI) forms images of the breasts using magnetic fields. MRI is very sensitive to cancer but it also finds many benign nodules that require biopsy unnecessarily. It is a very expensive test and requires contrast injection. MRI is currently indicated for breast cancer staging and screening of certain groups of high risk women. The approved groups of high risk women for MRI screening include those with gene mutations which predispose to breast cancer. Other groups of high risk women including those with dense breasts are being studied.

There are additional screening methods including Breast Tomosynthesis and Nuclear Medicine Breast Imaging which are currently being evaluated but not widely used. Breast Thermography has been determined not to be useful for detecting breast cancer.

Breast tissue density plays an important role in both breast cancer risk and detection. Screening mammography remains the most important method for detection of breast cancer for all women. Digital mammography offers benefit especially for women with dense breast tissue. Additional screening methods including Breast Ultrasound and MRI are available at this time, while others are under evaluation.

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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