Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

To those of you who live in cold climates and are enduring the hardship of winter, remember that spring is just around the corner. In a few more weeks, nature will change again and will bring forth sunshine, flowers, birds, new plants and hopefully a feeling of new beginnings to each of you. It will be the perfect time to resume exercising outdoors.

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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BIOLOGY BASICS

In this issue, we will continue to discuss the topic of lymphedema. Last month, we covered the causes of lymphedema. This month, the emphasis will be on what to do to reduce the probability that you will develop lymphedema following breast cancer therapy and how it can be treated should it occur.

Over time, the amount of surgery done to treat breast cancer and, more specifically, the number of lymph nodes removed has decreased. As this has occurred, the probability of developing lymphedema and the severity of lymphedema has also decreased. However, the precautions and instructions that are given to patients remain essentially the same. Specifically, blood pressure measurements, drawing blood and placement of IV lines should be avoided on the side of surgery. These restrictions are lifelong and are not limited to the first few years. Please note that in a medical emergency, the arm may need to

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BIOLOGY BASICS continued

be used to provide life sustaining measures. In such an event, it is reasonable to do so.

The skin serves many functions; chief among them is that it is a barrier to infections. Therefore, anything that may injure or break the skin should be avoided. For example, it is common for minor burns to occur while cooking or baking. Using kitchen gloves and other protective items should be done during these activities. Likewise, gardening is an activity where scratches can often occur. Again, wearing protective gloves and clothing is advised. When a manicure is performed, aggressive trimming of cuticles should be avoided. Keep in mind that even minor injury to the skin can serve as a way for infection to occur. Sunburn should be avoided in general, but especially on the side of surgery. Heavy purses, computer bags or other heavy objects should not be carried on the side of surgery. Some advise the use of a compression sleeve during airplane flights. Research has shown that the use of saunas should also be avoided. Being overweight also has been found to increase the chances of developing lymphedema. Weight control is important in many ways, including its relationship to this problem.

Please note that none of these are complex ideas. Further, you may do everything possible and still develop lymphedema. Nevertheless, these simple measures have been found to be useful in reducing the likelihood that lymphedema will develop.

To some degree, the rigor with which the arm on the treated side needs to be protected has decreased as less surgery has become the standard approach. Radical mastectomy procedures have been replaced with lumpectomy. Lymph node dissection has been replaced with the sentinel node technique. These advances have reduced the probability and severity of lymphedema. Even so, the treated arm and hand still need to be guarded.

There has been a change in how we think about exercise and lymphedema. For many years it was believed that the treated arm should be allowed minimal exercise as exercise was thought to cause or increase lymphedema. More current research has suggested that gradual and moderate exercise, including the use of weights and resistance training are to be encouraged as they can reduce the probability of developing lymphedema and can improve the condition even when it has already occurred.

The goals of treating lymphedema are to reduce swelling, reduce pain, preserve mobility and avoid infection. Several modalities are available to treat lymphedema. Some are simple and can be done by the patient. Others are more complex and require guidance and management by a lymphedema specialist.

The simplest thing that can be done by the patient is elevation of the arm. Remember that lymphedema is primarily a liquid and is made up mostly of water. Gravity will pull the fluid downward. Consequently, it is the fingers, the hand and the lower part of the arm that will be most swollen. Elevating the arm will reverse that downward movement and decrease the swelling. The arm can also be gently massaged. The idea is to encourage the fluid to move from the fingers, up the arm and back into the body so that it can be eliminated as part of urine production. Therefore, the direction of the massage is up towards the shoulder and back into the body. All of the joints need to be kept mobile, so all the joints of the fingers, wrist, elbow and shoulder need gentle range of motion exercises. Water pills (diuretics) are not effective for lymphedema and are not recommended. Weight loss can be helpful long term.

When lymphedema develops, it is best to consult a lymphedema

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BIOLOGY BASICS continued

specialist to guide the proper management of the affected area. The specialist can treat both the condition as well as educate the patient and their family on acute and long term care. In my own practice, I have always preferred the involvement of such a specialist early rather than when the degree of lymphedema is more advanced. A physical therapist is not necessarily a lymphedema specialist, so it is important to identify a specialist who is particularly trained in treating lymphedema.

Several techniques are available to a lymphedema specialist including wrapping of the extremity, the use of special compression garments, special machines that provide compression and special massage techniques. Complex decongestive therapy (CDT) combining all of these modalities is considered optimal. It will take a series of visits to reduce the amount of swelling and improve function. Often patients are trained on how to apply some of these techniques at home. The care of an arm with lymphedema is generally a long term process but, with proper care, almost all patients are helped.

More recently, surgical techniques have been developed which can improve the flow of fluid and improve the degree of lymphedema. I have asked Dr. Jay W. Granzow from UCLA to provide an update on some of these surgical procedures. He is the GUEST WRITER for this issue.

WHAT'S NEW

CAN SIDE EFFECTS PREDICT BENEFIT FROM THERAPY?

The idea that the amount of side effects or toxicity induced by a therapy is predictive of the amount of anticancer effect is an old notion. Both patients and physicians tend to share this notion. It suggests that to achieve the greatest benefit, you must use the most "aggressive" therapy available. This is not necessarily correct. Examples of this fallacy are easily available in the field of breast cancer: (1) extended radical mastectomies to treat breast cancer were not found to be better than less surgery to the breast area, (2) for most patients, axillary lymph node dissection has not been found to be better than the sentinel node procedure, and (3) higher doses of chemotherapy as in the era of bone marrow transplant therapy did not give better results when compared to standard dose chemotherapy. Nevertheless, there still remains a mindset that more aggressive therapy must be better.

A similar bias has existed within the field of hormonal therapy for adjuvant breast cancer. Early observations with the use of tamoxifen suggested that women who experienced more vasomotor side effects such as hot flashes were less likely to have a recurrence of breast cancer. The introduction of the aromatase inhibitors such as Arimidex, Femara and Aromasin extended these observations to not only vasomotor (hot flashes, poor sleep patterns, vaginal dryness) symptoms, but also to musculoskeletal side effects which are the hallmarks of these drugs. The presumed underlying biology is that these side effects are the result of reduced estrogen levels which is the goal of breast cancer hormonal therapy.

The optimal length of time to administer hormonal therapy for the treatment of early breast cancer is increasing. The standard of five years of tamoxifen has now been expanded to ten years. The aromatase inhibitors are at present prescribed for five years. Studies looking at ten years of aromatase inhibitors versus five years are ongoing. For many patients, these long periods of treatment mean long periods of side effects. Many patients respond to these side effects by either reducing the amount of drug they are taking or discontinuing therapy altogether.

As with tamoxifen, several studies using aromatase inhibitors

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WHAT'S NEW continued

have demonstrated that the more side effects a patient experiences the better the outcome relative to their cancer. These results have been welcomed by both patients and doctors, with the belief that the side effects are a sign that the drug is working well. When viewed in this manner, patients can be encouraged to tolerate their discomforts. At times, this belief has led to a change in therapy with the purpose of finding the drug that caused more side effects and discarding a drug that appeared less toxic to an individual. The question of whether side effects accurately predict disease outcome remains unsettled, as existing studies have not resolved the question to everyone's satisfaction.

A new study looking at this issue was recently published by Dr. Vered Stearns on behalf of a large group of international collaborators in the Journal of Clinical Oncology. NCIC CTG MA.27, was a randomized, phase III, multinational trial that included 7,576 postmenopausal patients with hormone positive, early breast cancer. They were randomized to receive five years of one of two aromatase inhibitors, Arimidex or Aromasin. The primary goal of the study was to compare recurrence rates and survival. In this respect, both groups did very well and they found no difference between the two drugs. As part of this study, the researchers also wanted to investigate whether participants who developed more of the usual side effects typical of these drugs (vasomotor and musculoskeletal problems) did better than those who did not.

Patients were given a questionnaire to evaluate side effects at the start of the study, and then at six and 12 months. They could also see their physicians at times other that these visits if they experienced problems. At the time of enrollment, 34% of the participants already experienced some degree of vasomotor or musculoskeletal discomfort, while the others did not. Of the 66% without symptoms at baseline, 25% had new symptoms by six months and 53% had symptoms by 12 months.

After four years of observing the participants, the researchers found that the development of new or worsening side effects did not correlate with disease outcome. They did observe that women age 55 or younger were more likely to develop symptoms compared to older women. About 30% of patients in this study stopped their hormonal therapy prior to completing the planned five year schedule. Though there was a variety of reasons for discontinuation, the most common reason was joint pain.

To summarize, the recent results from NCIC CTG MA.27 are different from other trials (the ATAC and TEAM trials) that have suggested a positive relationship between the degree of side effects and disease recurrence and survival. It is not clear why these results differ. It may be a function of the fact that both the Arimidex and Aromasin groups had a disease free survival at four years of over 90%. This excellent level of outcome for both groups, makes it mathematically very difficult to demonstrate a relationship between side effects and tumor recurrence even if one existed. There may be other characteristics that distinguish these patients from those of other studies that resulted in a different outcome.

So, what can we reasonably conclude on this issue at this time? Several points are valid: (1) not all patients will develop side effects from hormonal therapy, (2) whether side effects are a way to predict outcome is not yet certain, (3) other factors such as age, other medical conditions, use of prior hormonal replacement therapy, pain medications, and anti-inflammatory agents will influence vasomotor and joint symptoms and their severity, (4) changing hormonal therapy to find one that does cause symptoms as a way to insure effectiveness is not advised, (5) patients should be encouraged to complete the entire planned time of therapy. To achieve this, their symptoms must be well managed to prevent dose reduction or discontinuation of therapy due to side effects, and (6) the final chapter on this issue remains to be written.

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DISCLOSURE

GUEST WRITER

SURGICAL OPTIONS FOR LYMPHEDEMA

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Lymphedema is a disease involving the swelling of a body part, typically an arm or leg, due to the accumulation of lymphatic fluid. Lymphatic fluid is part of the body's natural drainage system and helps clear toxins and other foreign debris and cells from the body. While little attention often is given to the lymphatic system, our knowledge of the lymphedema disease process has advanced tremendously in recent years. Where previously little more than conservative therapy was recommended, safe surgical alternatives now exist which can provide tremendous, long-term improvements.

Blockages in the natural lymphatic circulation can occur as part of the necessary treatment for cancer with surgery and/or radiation. For example, in patients with breast cancer, treatment with axillary lymph node dissection surgery and/or radiation therapy for cancer that has spread to the lymph nodes in the armpit can carry a significant risk of lymphedema in the arm. Fortunately, the introduction of sentinel lymph node biopsy has decreased the need for lymph node dissection in many breast cancer patients.

At first, lymphedema swelling is composed mostly of lymphatic fluid. In this early stage, the swelling still may be amenable to conservative treatment. Patients have also responded well to lymphedema surgery to reverse or greatly decrease the swelling. Over time, the lymphatic fluid can bring about permanent deposits of solids in the tissues which are much more difficult to treat. Lymphedema swelling also greatly increases the risk of dangerous infections, called cellulitis, which usually are much more severe in patients with lymphedema. Arm swelling can progress to such an extent that functional impairment may occur and interfere with work and activities of daily living.

Traditional lymphedema therapy has consisted of a regimen that may include manual lymphatic drainage/massage, use of compression garments, specialized skin care and exercises and even use of specialized compression pumps. It is important that therapy is administered by an experienced lymphedema specialized therapist to ensure proper management and treatment of lymphedema. Lymphedema therapy generally is most effective early in the disease process, when the swelling is still mostly due to fluid accumulation.

Effective lymphedema surgeries have existed for many years and continue to be refined and improved. We have found that best results are achieved when surgery is performed as part of a comprehensive system of treatment involving specialized lymphedema therapy and surgery. Proper patient selection for the appropriate surgery is critical. The success of lymphedema surgeries also depend on the training and relevant expertise of the surgeon and their knowledge of the disease.

Lymphedema surgeries have been shown to produce significant and lasting reductions in the size of the affected arm (or leg) and the amount of therapy and compression garments required for treatment.[1,2] Individualized lymphedema therapy integrated into the treatment plan before and after surgery is essential in achieving excellent results.

The fluid predominant portion of lymphedema may be treated effectively with surgeries that use either direct connections from the lymphatic system to the veins, called lymphaticovenous anastomoses (LVA), or vascularized lymph node transfer (VLNT). VLNT surgeries involve the microsurgical transfer of a small number of lymph nodes from another part of the body to the area affected by lymphedema. LVA and VLNT are microsurgical surgeries that can improve the patient's own physiologic drainage

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GUEST WRITER continued

of the lymphatic fluid, and we have seen the complete elimination for the need of compression garments in some of our patients. Safety and surgical expertise are critical, as rare reports exist of lymphedema occurring at the donor site. The use of reverse lymphatic mapping (an x-ray technique to visualize parts of lymph nodes and lymphatic drainage) also can minimize this risk.

The stiff, solid-predominant swelling often found in later stages of lymphedema might be treated effectively with a surgery called suction-assisted protein lipectomy (SAPL). SAPL surgeries allow removal of lymphatic solids and fatty deposits that are otherwise poorly treated by conservative lymphedema therapy, LVA, or VLNT surgeries. We have reported average volume reductions of 111% in arms and 86% in legs with the SAPL surgery. This surgery appears also to improve the lymphatic drainage in the arm or leg after healing has occurred, and reduces the risk of dangerous infections by about 80%. The safety of SAPL surgery has been studied and as published in the medical literature, it has been found that the function of the lymphatics were unaffected by the surgery.[3] Continuous compression garment use following the surgery is essential to prevent the reaccumulation of the pathologic lymphedema solids and fat.

New ways of effectively treating lymphedema now include using multiple surgeries with proper therapy. For instance, the possibility now exists for a VLNT surgery to be performed once healing after the SAPL surgery is complete to help address the persistent accumulation of lymphatic fluid. We have documented significant reductions in the requirement for postoperative garment use in medical literature and this combination of surgeries represents the next step in the treatment of lymphedema.[4]

Overall, multiple effective surgical options for lymphedema exist. When performed by an experienced lymphedema surgeon as part of an integrated system with expert lymphedema therapy, safe, consistent and long-term improvements can be achieved.

[1] Granzow JW, Soderberg JM, Kaji AH, Dauphine C. An Effective System of Surgical Treatment of Lymphedema. Ann Surg Oncol. 2014 Apr; 21(4):1189-94.

[2] Granzow JW, Soderberg JM, Kaji AH, Dauphine C. Review of Current Surgical Treatments for Lymphedema. Ann Surg Oncol. Ann Surg Oncol. 2014 Apr; 21(4):1195-1201.

[3] Brorson H, Svensson H, Norrgren K, Thorsson O. Liposuction reduces arm lymphedema without significantly altering the already impaired lymph transport. Lymphology 1998; 31:156-172.

[4] Granzow JW, Soderberg JM, Dauphine C. A Novel Two-Stage Surgical Approach to Treat Chronic Lymphedema. Breast J. 2014 Jun 19.

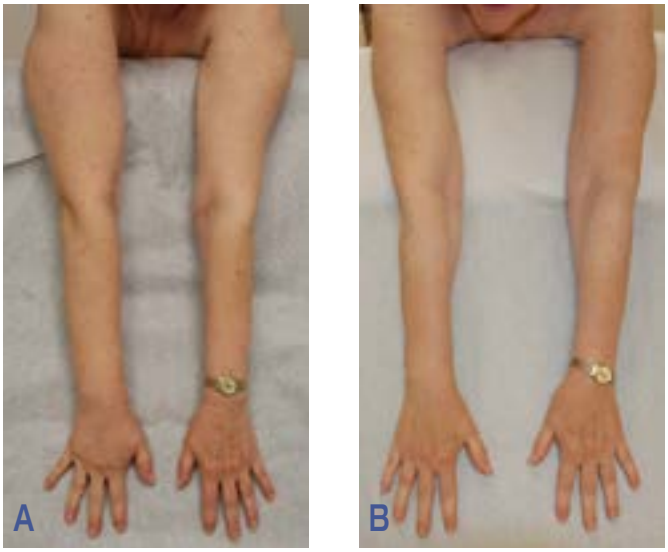

Figure 1: Patient with right arm lymphedema following treatment for breast cancer with bilateral mastectomy, right lymph node dissection and radiation therapy. A) Prior to surgery. B) 3-year stable result following VLNT performed together with a DIEP flap for breast reconstruction. She requires no daily garment or therapy.

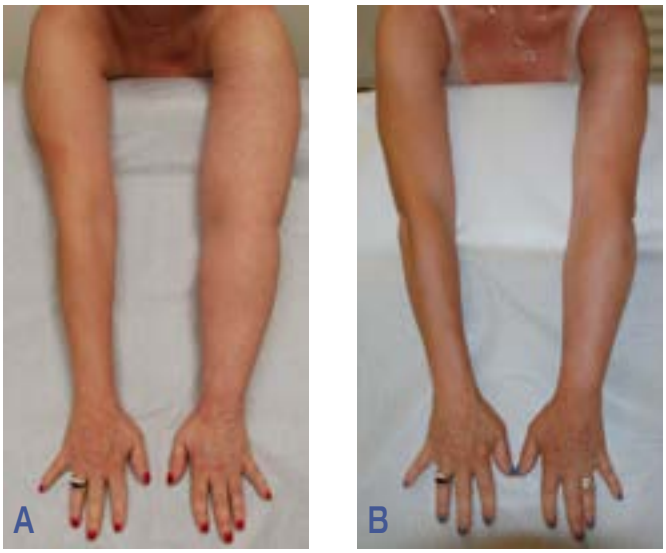

Figure 2: Patient with a history of left breast cancer treated with left lumpectomy, lymph node dissection and radiation therapy. A) Prior to surgery. B) 22 months following combination of SAPL followed later by left VLNT. She achieved both a 75% reduction in volume and significant reduction in compression garment use.