

*A SPECIAL RESEARCH REPORT OF THE NEW JERSEY COMMISSION ON CANCER RESEARCH*

## **INFLAMMATORY BREAST CANCER: AN UPDATE FOR PRIMARY CARE PHYSICIANS** *Spring 2008*

### **Epidemiology and Etiology:**

Inflammatory Breast Cancer (IBC) is an aggressive carcinoma that accounts for about 1-6% of all breast cancer cases (2). In fact, the rapid progression of disease symptoms from first sign to diagnosis can be less than or up to three months (5). It is usually prevalent in younger women who are pre-menopausal and approximately 20% of patients with IBC have gross distant metastases at the time of diagnosis (3, 4, 5). The disease itself is considered rare; the incidence of women diagnosed with IBC is approximately 1.0 per 100,000 cases (ACS Facts & Figures 2007-2008). Approximately 50 women are diagnosed each year in New Jersey with IBC (NJ SEER REGISTRY 2000-2004).

In the past, a lack of awareness of the disease led to mis- or late diagnosis, resulting in under-treatment with surgery alone. Unfortunately the survivability based on localized treatment alone only ranged from approximately 12-36 months (5). With a growing awareness of the aggressive nature of IBC, however, current treatment has taken a more systemic approach, and as a result, survivability has improved considerably (3, 5). The current approach uses multimodality therapy including chemotherapy, surgery and radiation. The five-year survival rate for inflammatory breast cancer is 36% nationally, and New Jersey rates for five-year survivability appear similar (7).

### **Warning Signs and Symptoms:**

There are many warning signs and symptoms of inflammatory breast cancer, making diagnosis difficult. All symptoms are not always present at time of diagnosis and the severity can vary from patient to patient. Cases have often been confused for benign conditions unrelated to cancer such as cellulitis (4). The radiologic findings on mammography and MRI can vary from diffuse skin thickening (edema) to a direct mass to diffuse breast involvement with tumor.

However, display of any of the following symptoms should be aggressively investigated as potential IBC and treated immediately (1-5).

- Breast warmth or hotness
- Redness
- Skin texture similar to that of an orange peel (peau d'orange)
- Retraction of nipple
- Rapid breast swelling (two to three times its normal size)
- Nipple discharge
- No detectable tumor mass or a very ill defined one because the disease is diffused

### **Clinical Course of the Disease:**

The progression of IBC occurs very rapidly (5). The reason for such aggressiveness is the diffuse nature of the tumor making it prone rapid spread to the axillary lymph nodes and other parts of the body (3). The diagnosis of IBC can be made by combining the clinical signs previously described without pathologic diagnosis of invasive ductal carcinoma. Pathologically, a diagnosis of IBC may be made in the absence of clinical findings by demonstrating dermal lymphatic involvement of tumor.

The tumor formation in IBC has been described as different from other breast cancer tumors in that the tumor cells have a high S-phase fraction, lack hormone receptor expression (of both estrogen and progesterone), and are aneuploid (2, 3). IBC cells have also been shown to have a higher expression of epidermal growth factor (EGF), of vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF), which may explain why IBC presents greater angiogenic and vascular characteristics (2, 3). They also express higher levels of E-cadherin, a transmembrane glycoprotein involved in cell-to-cell adhesion, which is believed to contribute to the invasion of IBC into the lymph nodes (2, 3). Identification of several genes and high mutation rates and activity levels are also being used as indicators of IBC. These genes include p53, pS2, RhoC, and HER-2 (5). Researchers believe that the molecular profiling of IBC will yield more information into the nature and treatment of the disease.

### **Treatment:**

Current treatment of IBC relies on a team of specialists including pathologists, surgeons, radiotherapists, diagnostic imagers, and medical oncologists (2). Initially, IBC is tackled via neo-adjuvant therapy (2). The primary objective is to reduce the size of the tumor to make surgical solutions viable. If chemotherapy yields success and a response is generated in the patient, the next step involves either surgery (usually a mastectomy) and radiotherapy (3). Post-surgery involves additional chemotherapy and then radiotherapy (3). While radiation typically follows surgery, the reverse can also occur. The critical dynamic is that both are included in the treatment plan. If the patient does not respond to initial chemotherapy, radiotherapy is used instead in hopes that the chemical treatment will eventually reduce the amount of cancer cells to either an operable level or completely diminish the cancer. Systemic treatment involving neoadjuvant therapy, surgery, and radiotherapy has yielded a higher survivability in patients than localized treatment alone (5). Investigations of genes involved in IBC formation are also holding future promise for understanding the nature of this aggressive disease and possibly new methods of therapy (5).

### **Research Updates:**

Clinical cancer trials continue to investigate various options to treat this disease. In addition to looking at differing scheduling and doses of known agents, attention is being focused on novel biologic agents such as trastuzumab, targeting the her2neu pathway or bevacizumab, targeting the vegf pathway. The goal in this approach is to maximize patient survivability (6).

Other research studies are focused on newer approaches to therapies. Analysis of gene expression of IBC has revealed distinguishing characteristics that separate it from other forms of breast cancer. Core biopsies of tumor tissue/cells allowed RNA, DNA, and protein examination of IBC through the construction of cDNA and use of microarrays (5). Results indicated that IBC has higher expression of genes related to increased metabolic rate, lipid signaling, and cell turnover with respect to non-IBC tumors (5). IBC was shown to have statistically higher levels of the following genes: Ki-67, a gene involved in cell proliferation and BAX, a gene involved in cell apoptosis and turnover (5). E-cadherin and p53 were also found at high levels as well as Bcl2, another gene involved with apoptosis (5). It was also observed that the tumor cells were negative for steroid hormone receptors - estrogen and progesterone (5). Further analysis revealed that the apoptotic nature of BAX can be neutralized when it binds to Bcl2 or members of the Bcl2 family (5). Reducing or negating the apoptotic effects of this gene may be the next potential target for introducing gene therapies (5).

Current studies in New Jersey for IBC can be found at [www.njctc.org](http://www.njctc.org) or [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Innovative studies include novel chemotherapeutic agents in new combinations and high dose chemotherapy with stem cell transplant.

#### **IMPLICATIONS FOR PRIMARY CARE PHYSICIANS**

- *It is imperative that the signs and symptoms of IBC are aggressively investigated. The sooner it is diagnosed, the better chance of patient survival.*
- *IBC is a fast growing cancer more prevalent in pre-menopausal women. All three modalities, surgery, radiation and chemotherapy, are vital to the treatment of IBC.*
- *Current treatment is yielding better survival time in patients, and current research is focusing on more effective treatment, with particular investigation into gene and molecular targeting.*

#### **Guest Editors:**

**Generosa Grana, MD, Director, Cooper Cancer Institute, Camden, New Jersey**

**Kenneth Adler, MD, Medical Oncologist, Atlantic Health System, Morristown, NJ**

**Science Writer: Jennifer Smith**

#### **Resources:**

- 1) Ardavanis A., Scorilas A., Tryfonopoulos D., Orphanos G., Missitzis I., Karamouzis M., et al. (2006). Multidisciplinary therapy of locally far-advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin, vinorelbine, and fluorouracil chemotherapy, surgery, and radiotherapy: long term results. *The Oncologist* Vol.11, No.6: 563-573. Retrieved 25, October 2007 from: <http://theoncologist.alphamedpress.org/cgi/content/full/11/6/563>.
- 2) Cristofanilli M., Buzdar A.U., & Hortobagyi G.N. (2003). Update on the management of inflammatory breast cancer. *The Oncologist*, Vol.8, No.2: 141-148. Retrieved 25, October 2007 from: <http://theoncologist.alphamedpress.org/cgi/content/full/8/2/141>
- 3) Giordano S.H. & Hortobagyi G.N. (2003). Review, inflammatory breast cancer, clinical progress and the main problems that must be addressed. *Breast Cancer Research* Vol. 5, No. 6: 284-288. Retrieved 25, October 2007 from: <http://breast-cancer-research.com/content/5/6/284>.
- 4) Hance K.W., Anderson W.F., Devesa S.S., Young H.A., & Levine P.H. (2005). Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the national cancer institute. *Journal of the National Cancer Institute* Vol. 27 No.13: 966-975. Retrieved 25, October 2007 from: <http://jnci.oxfordjournals.org/cgi/content/full/97/13/966?ijkey=6fc34d37c3027af9ff96829a4570028ff08b78fe>
- 5) Nguyen D.M., Sam K., Tsimelzon A., Li X., Wong H., Syed M., et al. (2006). Molecular heterogeneity of inflammatory breast cancer: a hyperproliferative phenotype. *Clinical Cancer Research*, Vol.12: 5047-5054. Retrieved 25, October 2007 from: <http://clincancerres.aacrjournals.org/cgi/content/full/12/17/5047>
- 6) National Cancer Institute: Clinical Trials. Retrieved 30 November 2007 from: <http://www.cancer.gov/search/ResultsClinicalTrialsAdvanced.aspx?protocolsearchid=3883492>
- 7) Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Incidence - SEER 17 Regs Limited-Use, Nov 2006 Sub (1973-2004 varying) - Linked To County Attributes - Total U.S., 1969-2004 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.