



Review Article

Inflammatory Breast Cancer: Mini Review

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ABSTRACT

Inflammatory breast cancer is aggressive type of breast cancer characterized by rapidly enlarge tender, firm, erythematous breast, often without distinct palpable mass. The changes that appears on the skin are resembles to inflammation and it differs from other forms of breast cancer regarding its symptoms, prognosis, and treatment. It account for approximately 2–5% of rest of the breast cancers. It has hazardous course with a low 5-years survival rate. Management includes psychosocial support, the preoperative chemotherapy, radiation therapy and mastectomy. In the present review the epidemiology, clinical presentation and the management options of inflammatory breast cancer are summarized.

Introduction

The Inflammatory breast cancer (IBC) is aggressive type of breast cancer characterized by rapidly growing, tender, firm, enlarged breast. This happens due to the invasion of cancer cells in skin dermal lymphatics of breast. The blocked lymphatics produce characteristic changes in skin like erythema, warmth, edema that resembles inflammation¹.

Inflammatory breast cancer is rare form of breast cancer, accounting for approximately 2–5% of among all breast

cancers². It has highly harmful course with a low 5-year survival rate³. Its treatment includes preoperative chemotherapy, mastectomy, and radiation therapy that has been shown to improve prognosis⁴.

Inflammatory breast cancer is rare, representing from 1 to 6% of breast cancer diagnoses. A current study data suggested that incidence of IBC could be rising; 2% from 1988 to 1990 and 2.5% from 1997 to 1999². Inflammatory breast cancer is much



more common in black women with mean age 50 to 58 years.

Studies that were conducted in North Africa, showed that 50% inflammatory breast cancer cases were present having obesity and younger age giving first birth⁵. It can occur among all adult age groups. Most of patients are diagnosed among 40 and 59 years old, age fondness is less pronounced than in non-inflammatory breast cancer.

The overall rate is 1.3 cases per 100000, black women (1.6) have the highest rate, Asian and Pacific Islander women have the lowest (0.7) rates⁵. In inflammatory breast cancer, breast often looks swollen and red, or inflamed. Obstruction of the local lymphatic ducts impairs drainage and causes edematous swelling of breast. As skin of breast is bind by suspensory ligaments, the fluid accumulation may cause the skin of breast to assume a dimpled appearance similar to an orange peel (peau d'orange). Sometimes, it is misdiagnosed with insect bite or breast infection. IBC, generally not present lump or tumor as in other types of breast cancer.

Symptoms include:

- Swelling of breast
- Skin changes
- Pain in breast
- breast itching
- Reddened area with surface resembling the peel of an orange (peau d'orange)
- Nipple retraction or discharge
- Swelling of lymph nodes under arm or in the neck
- Unusual warmth of affected breast
- Breast is harder or firmer

Other symptoms may rarely include:

- Swelling of the arm
- Breast decreases instead of increasing
- Although a dominant mass is present in many cases, most inflammatory cancers

present as diffuse infiltration of the breast without a well-defined tumor.

- A lump may become present and grow rapidly

Most patients do not experience all the symptoms of inflammatory breast cancer⁵.

Physical Examination

In most of the patients with IBC, no distinct mass is palpable on clinical examination. Breast enlargement than usual and changes in the skin overlying the breast are generally the first presentation of the disease that brings patients towards the physician. Because IBC is rare, most physicians might understand the lack of a palpable tumor as excluding a diagnosis of the breast cancer. Early erythematous discoloration of skin can further progress to intense red or purple color involving entire breast. Most common clinical sign on skin is the peau's orange/ orange peel appearance which shows presence of underlying skin edema⁴.

Screening and Diagnosis

The first investigation for inflammatory breast cancer is generally a mammogram. The classic changes that can be seen on a mammogram are thickening of skin, trabecular and stromal thickening, and increased breast density⁷. Inflammatory breast usually do not associated with breast mass or tumor, therefore, absence of mistrustful masses on mammogram is not helpful in ruling out IBC⁵ Ultrasound of the breast and axillary lymph nodes can be useful in ruling out IBC. Ultrasound might detect masses that are not noticeable on palpation or mammography⁶. Magnetic resonance imaging (MRI) can detect breast tissue abnormalities and can be used to guide a biopsy of those abnormal areas. MRI is newly advance imaging technique having

high sensitivity in detection of breast parenchymal lesions and skin abnormalities.

Magnetic resonance imaging (MRI) can detect breast tissue abnormalities and can be used to guide a biopsy of those abnormal areas. MRI is a newly advance imaging technique that has high sensitivity in the detection of breast parenchymal lesions and skin abnormalities. Findings on MRI may help guide skin punch biopsies. On MRI, skin thickening and abnormalities are seen in 90-100% of patients with IBC. MRI may be useful tool for differentiating of patients with IBC from patients with locally advanced non-IBC. In the study at MD Anderson Cancer Center of patients with IBC, breast MRI detect all breast parenchymal lesions, mammography identified 80%, and ultrasonography identified 95% of breast parenchymal lesions⁷. When mammography and ultrasonography shows no breast parenchymal lesion, MRI then advised in patients with suspected IBC. Diffusion-weighted MRI is useful technique for IBC patient. Diffusion weighted MRI is in vivo imaging technique which may raise the diagnosis of breast cancers without the need for the administration of contrast material through use of the micro structural properties of tissues related to water diffusion.

Diffusion has been usually shown to decrease in malignant tumors and is quantified by the apparent diffusion coefficient. Breast cancers generally show low diffusion coefficient values as compared to normal breast tissue, although there is some overlap between benign and malignant lesions^{8,9}. CT (computed tomography) of the different areas of the body is sometimes done to look for extent of cancer^{8,9}.

CT (computed tomography) of the different areas of the body is sometimes done to look for the extent of cancer. A PET (positron emission tomography) also useful

in finding areas of cancer metastasis to lymph nodes and distant sites¹⁰.

Management of Inflammatory Breast Cancer

Patients with IBC need to be treated in a multidisciplinary breast oncology clinic that specializes in the treatment of IBC. The patient suffering from IBC requires management of medical, surgical, and radiation oncology as well as nursing and other supportive disciplines.

Chemotherapy

Management of IBC can done by combined-modality therapy¹¹. A study was conducted to review at combined-modality approach against inflammatory breast carcinoma at M. D. Anderson Cancer Center. In the past 20, years a total of 178 patients with inflammatory breast cancer were treated by a combined-modality approach under four different protocols. Each protocol consists induction chemotherapy, then local therapy (radiotherapy or mastectomy), and, if mastectomy was performed, adjuvant radiotherapy. The follow-up data show that with a combined-modality approach significant number of patients (28%) remained free of disease beyond 15 years compare to single-modality treatments¹². Owing to the skin involvement of IBC, the risk of loco-regional and distant recurrence is too high to justify instant mastectomy. Preoperative chemotherapy is hence standard care¹¹. Before giving chemotherapy, a core biopsy is done to confirm the diagnosis and evaluate the hormone-receptor and HER-2/*neu* (human epidermal growth factor receptor 2) status of the tumor. A metastatic response of the disease excluded through bone scans, chest x-ray scans, and abdominal ultrasound scans. The purpose of chemotherapy is to eradicate micrometastatic disease and reduce

inflammation in the breast, making tumors acquiescent to surgery and radiation.

Targeted therapy

Several molecules for targeted therapy for IBC have been investigated. These therapies exhibit clinically beneficial effects on HER-2 and epidermal growth factor receptors. HER-2 over expression in 36-60% of IBC cases. Several clinical trials suggested that combinations of trastuzumab and systemic chemotherapy have role in IBC treatment¹³, Lapatinib is dual tyrosine kinase inhibitor of epidermal growth factor receptor and HER-2. Clinical trials show that Lapatinib exhibits similar efficacy as that of trastuzumab in patients with HER-2 breast cancer.

Lapatinib is given for treatment of IBC, which has over expression of HER-2 positivity. Phase II clinical trial concluded that Lapatinib in combination with paclitaxel as neoadjuvant therapy exhibits better clinical response in 95% of HER-2 positive patient. Molecular targets for angiogenesis, lymphangiogenesis, and vasculogenesis have shown greater potential for IBC than for non-IBC¹⁴. Over expression of angiogenic factors has been seen in IBC, and antiangiogenesis therapies (bevacizumab and semaxanib) have shown some clinical effect in clinical trials¹⁵. E-cadherin over expression seen in IBC. In general, E-cadherin expression decreases when cancer progresses and loss of E-cadherin expression is related to epithelial-mesenchymal transition¹⁶. This distinctive pattern of E-cadherin expression in IBC could make E-cadherin a target for treatment of IBC, and this plan has been investigated in IBC xenografts¹⁷. EIF4G1, recently discovered to be the target gene of eukaryotic translation initiation factor 4 γ , may be related to the role of E-cadherin in IBC¹⁸. In IBC Over expression of this gene

was observed more frequently (80%) than in normal cells and non-IBC cells¹⁴.

Surgery

Surgery plays an important role in the management of IBC. Historically, mastectomy was the only treatment of IBC. However, it failed to create any survival advantage in patients with IBC. 5-year survival rates after surgery alone were 0%–10%¹⁹. The most complementary surgical procedure for patients who respond to neoadjuvant chemotherapy is mastectomy with axillary lymph node dissection. The objective of surgery should be complete removal of remaining disease with negative surgical margins. The most appropriate patients for surgery are those whose negative margins are expected. At the time of presentation involvement of axillary lymph node is 55%–85% in patients with IBC²⁰. Axillary lymph node condition indicating survival upshot; therefore, complete axillary lymph node dissection is standard of concern for IBC patients¹⁴.

Radiation therapy

When mastectomy is practicable after neoadjuvant chemotherapy, the next approach for patient with IBC is to deliver postmastectomy radiation therapy. At present, accelerated hyperfractionated radiation therapy delivered to patients with significant residual disease after chemotherapy, patients with positive surgical margins and patients aged less than 45 years²¹ Trials from preoperative radiation therapy showed that complication rates are comparatively higher in patients who receive preoperative radiation therapy than in those with no preoperative radiation therapy, and the risk for operative complications is dose dependent¹⁴.

The IBC treatment takes about 1 year. Patients are advised to visit the nearest emergency department if they experience

any adverse effects. Patients taking taxane chemotherapy feel bony pain or myalgias. This pain may relieve with acetaminophen, but can be severe enough to require opioid treatment as well²².

Survival rate of IBC

Women with IBC have worse prognoses, when compared with other breast cancer patients presenting at the same stage. In addition, up to 25% of women present with metastatic, incurable stage of disease²³. Overall survival for IBC patients is 2.9 to 4.2 years²⁴. Lower survival rate is seen among black women and those with estrogen receptor–negative tumors². Over the past 30 years this survival rates have not changed, emphasizing the aggressive nature of the disease²⁴. Newer anticancer compounds such as trastuzumab and lapatinib might improve outcomes for patients with IBC¹¹.

According to statistics from NCI's Surveillance, Epidemiology, and End Results (SEER) program, the 5-year survival for women diagnosed with inflammatory breast cancer during the period from 1988 through 2001 was 34 percent, compared with a 5-year relative survival of up to 87 percent among women diagnosed with other stages of invasive breast cancers.

Advances in inflammatory breast cancer research

As the inflammatory breast cancer is uncommon, it is difficult for researchers to search women to study and learn the best treatments options. But recent advances have made in understanding and treating IBC. Over the past couple of decades, IBC has become more common, then other forms of breast cancers. Researchers are still not rule out the exact etiology of inflammatory breast cancer.

From the recent studies this is come to know that DNA and other molecules from

IBC have some important differences than other usual types of breast cancer. Researchers believe that these differences account for the distinctive and aggressive way that IBC spreads and grows. They are optimistic that understanding these differences will go in front to help in finding out more effective target molecules specific to IBC. Clinical studies have shown doctors how to amend the usual breast cancer treatments (chemotherapy, radiation, hormonal therapy, and surgery) so that they are best suited for women with IBC. For example, studies have shown the value of inducing chemotherapy as the first treatment, before surgery or radiation.

Chemotherapy

Studies are looking at different chemotherapy combinations to treat inflammatory breast cancer, such as epirubicin (Ellence®), albumin-bound paclitaxel (Abraxane®), and gemcitabine (Gemzar®).

Targeted therapy

Targeted therapy is a newly introduced cancer treatment that uses drugs to identify and attack cancer cells and produce little damage to normal cells. Each type of targeted therapy works differently, but all alter the way a cancer cell grows, divides, repairs itself, or interacts with other cells. They work differently from other standard chemo drugs and often have less side effects.

Drugs for HER2-positive cancer

In women whose disease has stopped responding to regular chemo plus trastuzumab, the targeted drug lapatinib (Tykerb) can be a useful treatment. This is proved by several studies. The lapatinib was given alone, without other chemo drugs. It produces its effects by shrinking the tumor size. Afatinib is another drug that target

HER2. This drug also being studied for IBS¹⁰.

Other targeted drugs

Clinical trials are also looking at other targeted therapy drugs besides those targeting HER2 for the treatment of inflammatory breast cancer. Some of the drugs being tested include dovitinib and pazopanib¹⁰.

Future Prospects and Conclusion

IBC is uncommon disease and because of its rarity, it is important for institutions to collaborate by establishing a cancer registry for collecting data and tissue from patients with IBC worldwide and by sharing resources to deal with this deadly disease. Current research, particularly at molecular level, will raise our perceptiveness about the pathogenesis of inflammatory breast cancer. This knowledge should make possible the development of latest treatments options and more precise prognoses for women diagnosed with this disease. It is essential, therefore, that women who are diagnosed with inflammatory breast cancer converse with their doctor about the opportunity of participating in a clinical trial.

Conflict of Interest

The authors have no conflict of interest.

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