RESEARCH ARTICLE

Inflammatory Breast Cancer: a Single Centre Analysis

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Abstract

Background: Inflammatory breast cancer (IBC) is an aggressive form of locally advanced breast cancer characterized by rapidly progressive breast erythema, pain and tenderness, oedema and paeu d'orange appearance. It accounts for 1-3% of all newly diagnosed cases of breast cancer in the west. Data on IBC from India are lacking. The aim of our study was to assess the clinical-pathological parameters and outcome of IBC at, All India Institute of Medical Sciences, a large tertiary care centre. Materials and Methods: We screened 3,650 breast cancer cases registered from January 2004 to December 2012 and found 41 cases of IBC. Data included demographics as well as clinical, radiological and histopathological characteristics, and were collected from clinical case records using the International Classification of Diseases code (C-50). Patients who presented with IBC as a recurrence, or who had a neglected and advanced breast cancer that simulated an IBC were excluded from this study. Results: The median age was 45 years (range 23-66). The median duration of symptoms was 5 months. The American Joint Committee on Cancer stage (AJCC) distribution was Stage III - 26 and IV - 15 patients. Estrogen receptor (ER), progesterone receptor (PR) positivity and human epidermal growth factor receptor 2 (HER2/neu) positivity were 50%, 46% and 60%, respectively. Triple negativity was found in 15% of the cases. All the non metastatic IBC patients received anthracycline and/ or taxane based chemotherapy followed by modified radical mastectomy , radiotherapy and hormonal therapy as indicated. Pathological complete remission rate was 15%. At a median follow-up of 30 months, the 3 year relapse free survival and overall survival were 30% and 40% respectively. Conclusion: IBC constituted 1.1% of all breast cancer patients at our centre. One third of these had metastatic disease at presentation. Hormone positivity and Her2 neu positivity were found in 50% and 60% of the cases, respectively.

Keywords: Inflammatory breast cancer - treatment - outcome - hormone charateristics - India

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Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer, characterized by the rapid appearance of erythema, edema, and peaud' orange of breast as a result of occlusion of breast dermal lymphatics by tumor emboli (Kim et al., 2006). It accounts for 1% to 3% of all breast cancer cases in the west (Low et al., 2004). It is suggested, that along with a tissue diagnosis, peau d'orange should be involving one third or more of the breast for a diagnosis of IBC to be made (Chevallier B.,et al). Patients with IBC tend to progress rapidly and have a poor overall outcome (Harris et al., 2003). Multimodality therapy is now widely accepted as the standard of care for this disease with the reported 5-year overall survival (OS) rates ranging from 46% to 61% (Dawood et al., 2011).

To date, there has been no published study from India on IBC. The aim of this study was to analyze the clinicopathologic characteristics and outcome of IBC in our patients.

Materials and Methods

We screened 3650 cases registered from January 2004 to December 2012 and found 41 cases of IBC with all base line parameters including hormonal profile. Patient's records were obtained from the computer database using International Classification of Diseases code (C-50).The diagnosis of IBC was made clinically by a multidisciplinary team consisting of an onco- surgeon, a medical oncologist, and a radiation oncologist. Patients who had presented with IBC as a recurrence, or who had a neglected and advanced breast cancer that simulated an IBC were excluded from this study. All the patients were included in this study, who at least received two modality of treatment at our hospital. All the non metastatic IBC patients received neo adjuvant chemotherapy (NACT)

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followed by modified radical mastectomy (MRM) , radiotherapy and hormonal therapy when indicated. Patients were considered to have a clinical complete response to neoadjuvant chemotherapy if they had no evidence of skin changes or a palpable mass on physical examination, and had no evidence of disease on imaging. Patients were considered to have a pathologic complete response to neoadjuvant chemotherapy if there was no residual invasive cancer in the resected breast or lymph node specimens on histologic examination. Locoregional recurrence was defined as recurrence of disease in the ipsilateral chest wall, skin, muscle, or in the ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. All other recurrences were classified as distant metastases, including spread of the disease to the contralateral breast.

Statistical analysis

Relapse free survival (RFS) (non-metastatic patients) was defined as the time period from diagnosis to the occurrence of relapse (loco-regional/systemic) or a metachronous breast cancer. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Baseline categorical variables were analyzed using Chi-square test or Fisher's exact test. Non-categorical variables were analyzed using t-test or Mann-Whitney test. RFS, PFS and OS were determined by Kaplan Meier analysis. Results were considered statistically significant for values of $p<0.05$. Statistical Package for the Social Sciences (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL) version 10 software was used for analysis.

Results

A total of 41 patients were included in this study and as per the American Joint Committee on Cancer (AJCC) staging system, distribution was, Stage III-26 (63%) and IV-15 (37%) patients. The median age was 45 years (range 23-66) and the median duration of symptoms was 5 months. Estrogen receptor (ER), progesterone receptor (PR) positivity and human epidermal growth factor receptor 2 (HER2/neu) positivity was 50%, 46% and 60%, respectively, while triple negativity was found in 15% of the cases. Table 1 outlines the baseline features of the patients. The median follow-up time was 30 months. The most common chemotherapy regimen used (for non metastatic IBC) was six cycles of DEC(Docetaxel 75 mg/m^2, Epirubicin 75 mg/m^2, Cyclophosphamide 500 mg/m^2 on Day1 , 3 weekly with growth factor support . Nine patients received six cycle of FEC, 5-Fluorouracil 600 mg/m^2, Epirubicin 75 mg/m^2 Cyclophosphamide 600 mg/m^2 and 3 patients received single agent Docetaxel 85 mg/m2. For metastatic disease, ten patients received four cycles of FEC, 5-flurouracil 600 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 600 mg/m^2 followed by 4 cycle of docetaxel, 85 mg/m^2 and in two patient we used the CMF regimen- Cyclophosphamide, Methotrexate and 5Flurouracil in standard doses and rest were received 6 cycles of FEC regimen. Modified radical mastectomy was done in 29 patients (three in metastatic disease). Based on hormone positivity, twenty one patients received hormonal treatment in adjuvant or palliative setting. Median progression free period was 15 months. There were 20 deaths during the study period. For all patients, estimated survival at 3 years was 40%. None of the patients received trastuzumab. Among the patients who received preoperative chemotherapy , 4 patients (15%) had a pathologic complete response. At last follow-up, 14 patients had relapsed, of which three patients had a loco regional and eleven patients had a systemic relapse (lung,liver, brain followed by bone). The median time to relapse was 24 months and 3 year RFS was 30%. Fifteen patients presented with metastatic disease at baseline, the most common site of metastasis being lung, followed by bone and brain.

Table 1. Patients and Disease Characteristics

Tumor characteristics'(n=41)	No. of patients
Median age in years (range)	45 (23-66)
Laterality	
Right	20
Left	21
Menopausal status	
Premenopausal	26
Postmenopausal	15
Clinical stage	
III	26
1V	15
Grade (n=19)	
intermediate grade	9
High grade	10
Hormone profile (available)	
ER-positive (n= 36)	18
PR-positive (n=36)	16
HER2/neu IHC +++ (n=30)	18
TNBC	5
Pathological complete remission	4

*ER=Estrogen; PR=Progesterone receptor; IHC=Immunohistochemistry; TNBC=Triple negative breast cancers; HER2=Human epidermal growth factor receptor

Discussion

The diagnosis of IBC relies on a pathological confirmation of invasive carcinoma, and a set of clinical criteria,which include, diffuse erythema, edema involving more than two-thirds of the breast, warmth, tenderness, and rapid enlargement of the breast (Baldini et al., 2004). The non specificity of the clinical criteria has been a source of variability in the diagnosis and a limiting factor in comparing results of various studies that have examined the prognostic relevance of IBC (Perez et al., 2011; Mamounas et al., 2012). Most of the studies have documented a higher frequency of ER/PR negativity and a higher incidence of HER2 overexpression (Bear et al., 2012; Cristofanili et al., 2007; Class et al., 2009). Lack of expression of hormone receptors has been shown to be associated with a more aggressive clinical course and is associated with a decreased overall and breast cancer-specific survival among women with IBC (Baldini et al., 2004). HER2 overexpression is typically associated with a poor outcome in non- IBC patients, however, the

prognostic significance of HER2 overexpression among women with IBC is unknown (Harris et al., 2003; Turpin et al., 2002; Baselga et al., 2012). In our analysis the Estrogen receptor (ER), progesterone receptor (PR) positivity and human epidermal growth factor receptor 2 (HER2/neu) positivity was 50%, 46% and 60%, respectively, which is similar to the reported studies. Triple negativity was found in 15% of the cases. Most women with IBC have locoregional disease at presentation and in the presence of extensive skin involvement, upfront surgery is not the desired primary mode of treatment, therefore, an International panel of experts on IBC recommends, that all women with IBC be offered primary systemic chemotherapy as the first line of treatment with the goal of down staging the tumor, to allow for definitive surgery. A one third of our patients presented with metastatic disease at baseline, which is more than the published literature and indicates towards an aggressive disease biology (Ellis et al., 2011). Over all IBC is an aggressive form of LABC and required multimodality therapy, with neoadjuvant chemotherapy followed by locoregional therapy. Anthracycline and taxane containing regimens are most commonly recommended , however the optimal chemotherapy regimen and sequencing of agents have yet to be defined. All the available guidelines are based primarily on retrospective studies, small prospective studies, and extrapolation of data available from prospective trials evaluating women with non-IBC tumors (Baldini et al., 2004; Cristofanilli et al., 2007; Gianni et al., 2012). One of the largest study on IBC showed that an anthracycline-based regimen followed by local therapy resulted in a 5- year survival rate of 40% (Baldini et al., 2004). The incorporation of taxanes has also been shown to be associated with higher pCR rates and better survival outcomes (Low et al., 2004; Kaufmann et al., 2010; Slamon et al., 2011) A recent prospective study that randomized women with locally advanced breast cancers, including those with IBC, to anthracycline based chemotherapy with or without 1 year of trastuzumab (preoperative followed by adjuvant) demonstrated that the addition of trastuzumab significantly improved the pCR rates (38% *vs* 19%, p=0.001) and event free survival (3-year event-free survival 71% *vs* 56%, HR 0.59, p=0.013) (Gianni et al., 2010) In our cohort, the 3 year RFS was 30% and the pathological CR rate was 20% with an antracyline and taxane based regimen and none of them received trastuzumab. IBC patients treated with NACT followed by surgery and RT have reported five year DFS rates of 20 -45% and OS rate of 30 to 70%. Patients who achive complete pathologic response (cPR) from chemotherapy have a significantly higher disease-free survival and overall survival. High dose chemotherapy followed by autologous stem cell transplantation has been investigated in patients with IBC but it is associated with markedly increased toxicity and worse quality of life compared with standard dose chemotherapy, hence it is not recommended. Following NACT, standard locoregional treatment includes mastectomy and radiation therapy. Patients who do not achieve optimal tumor debulking or who remain inoperable should receive radiation therapy with subsequent surgery. MRM is generally considered as standard practice, but some studies pointed out, whether MRM can be replaced with BCS or RT alone, especially for patients who achieve a complete clinical response to neoadjuvant chemotherapy (Kaufmann et al., 2010). In contrast others have shown in case series that MRM improves local control, DFS, and cancer-specific survival (Harris et al., 2003). IBC is associated with a particularly poor prognosis and high risk of early recurrence. Data from the United States Surveillance, Epidemiology and End Results (SEER) database had suggested an improvement in 20-year cancer specific survival for patients with IBC who were treated in 1995 compared to 1975 (20% *vs* 9%) (Kuerer et al., 1999). These improvements were attributed to advances in multidisciplinary treatment. However, in a subsequent report from the SEER database, for breast cancer cases diagnosed between 2004 and 2007, the two-year breast cancer-specific survival rate of patients with IBC remained significantly worse than for women with noninflammatory LABC (84% *vs* 91%), despite improvements in treatment (Dawood et al., 2011) Limitations of this study are, its retrospective design and a small sample size because of the relative rarity of this disease, precluding further analyses for prognostic factors. Although it is first study from India, depicting its incidence, hormonal profile and outcome.

In conclusion, inflammatry breast cancer constituted 1.1% of all breast cancer patients at our hospital .One third of these presented with metastatic disease at baseline. Hormone positivity and Her2 neu positivity was found in 50% and 60% of the cases respectively. IBC remains a therapeutic challenge despite advances in systemic therapy. Further, prospective studies are required to optimize treatment guidelines and identify more active biologic agents for this aggressive disease

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