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INFLAMMATORY BREAST CANCER IN A TUNISIAN UNIVERSITY HOSPITAL FROM 2007 TO 2012 : HOW TO MANAGE INFLAMMATORY BREAST CANCER WITH LIMITED RESSOURCES

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ABSTRACT

IBC is the most aggressive and deadly form of breast cancer and is frequently misdiagnosed and therefore considered as a rare entity. The typical clinical presentation of a quickly developing locally advanced disease shows the obvious limitations to the early diagnosis of the disease with radiological screening approaches. Management involves coordination of multidisciplinarymanagement. This multimodal therapeutic approach has significantly improved patient survival. **Objectives:** assess the clinical-pathological parameters and outcome of IBC at the center of Tunisia. **Materials and Methods:** We screened 1260 breast cancer cases registered from January 2007 to December 2012 and found100 cases of IBC. 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 51 years (range 29-85). The median duration of symptoms was 4 months. The American Joint Committee on Cancer stage (AJCC) distribution was Stage III- 57 and IV- 43 patients. Estrogen receptor (ER), progesterone receptor (PR) positivity and human epidermal growth factor receptor2 (HER2/neu) positivity were 57%, 46% and 36 %, respectively. Triple negativity was found in 35% 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. The pathological complete remission rate was 21 %. At a median follow-up of 149 months, the 3 year relapse free survival and overall survival were 15% and 28 % respectively. Median overall survival was 18 months, and its influencing factors according to our results were: estrogen receptor positivity, presence of extracapsular extension and M tumor stages, lymphovascular space invasion and adjuvant chemotherapy. **Conclusion:** IBC is an aggressive subtype of locally advanced breast cancer; it is heterogeneous with various factors influencing survival.

KEYWORDS: Inflammatory breast cancer – Epidemiology- treatment - outcome –prognostic factors- Tunisia.

INTRODUCTION

Inflammatory breast cancer (IBC) is the most aggressive and deadly form of breast cancer and is frequently misdiagnosed and therefore considered a rare entity.[1] Its accounts for 5-7% of all breast malignancies in Tunisia.[2-3] The disease begins in the breast duct tissue and spreading quickly to the lymphatic vessels in the skin and surrounding tissue. IBC is called "inflammatory" because the breast often looks swollen and red or inflamed. The diagnosis of IBC is primarily clinical; however, a tissue diagnosis is still necessary to establish invasive breast cancer. The extent and duration of clinical signs required for IBC has not been well standardized;[4] the sixth edition of the American Joint Committee on Cancer (AJCC) suggests that diffuse erythema and edema (peau d'orange) should involve a third or more of the breast.[5] Neglected locally advanced breast cancers presenting late in the course of the disease are not to be considered IBC.[5] While the incidence of IBC in western countries is very low (1- 2% of all breast cancers) and the average age of onset of the disease is ~ 55 years,[6] in other parts of the world, such as North Africa, the picture is much worse. Indeed, 10% of all breast cancer cases are inflammatory and patients are diagnosed at young age (<45)[7-8] causing a serious public health problem.

Recent studies conducted by Schairer and colleagues compared percentage diagnosis of IBC at the National Cancer Institute, Egypt, and Institute Salah Azaiz (**ISA**),

Tunisia, and they suggested that the increase in IBC cases in North Africa may be due to misdiagnosis of IBC with other types of locally advanced breast cancer.[9] In addition, the lack of breast cancer national registry programs in developing countries should also be taken into consideration.

The aim of our study was to evaluate the clinical-pathological parameters and outcome of IBC in our patients and to analyze factors impacting overall survival.

MATERIALS AND METHODS

The medical records of 100 patients with IBC treated at University Hospital Farhat Hached (UHFH) in central Tunisia from 2007 to 2012 were reviewed. The diagnosis of IBC was made clinically by a multidisciplinary team consisting of an cancer 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. Patients were classified according to the sixth edition of the UICC guidelines.[10,11] 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 for histologic examination.

Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up.

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. Differences between groups were analyzed the chi-square test for categorical variables and Student's t test for continuous variables. The median follow-up was 149 months which was sufficiently long to allow relevant survival analysis.

Survival and interval rates were calculated by the Kaplan–Meier method, and groups were compared using a log-rank test. Multivariate analysis was carried out to assess the relative influence of prognostic factors using the Cox stepwise procedure.[12] Results were considered statistically significant for values of $p<0.05$. Statistical Package for the Social Sciences (SPSS) version 20 software was used for analysis.

RESULTS

1) Patient and tumor characteristics

During 5 years from January 2007, 1260 patients were treated in the Oncology department at University Hospital Farhat Hached of Susa (Tunisia) for breast cancer, among them 100 cases (8 %) had inflammatory forms.

Patient and tumor characteristics **(Table1**) were as follows: median age at diagnosis was 51 with an age range of 29 -85 years with 30 % younger than 45 years. There were 99 females and 1male (f: m = 99:1). IBC occurred during pregnancy in 4% of cases. Obesity defined by BMI ≥ 30 was seen in 42% of cases. Fourty patients had premenopausal status (41 %).

76 % patients had an aspect of orange peel "Peau d'orange". 77 % had a tumor mass. Mean clinical tumor size was 7.9 cm (range0-24).

The mean duration of disease prior to presentation at a health centre was 32 weeks. The histopathologic types of the breast cancers were Invasive ductal carcinoma 85 (85 %), while 5 (5%) were Infiltrating lobular carcinoma. Tumor emboli was observed in 22 %. Tumor grade was II-III in 88 % of cases, HR was negative in 35 %, HER2 was over expressed in 36,3 % while triple negativity was found in 33 % of the cases.

Lymph node involvement was observed in over 42 % of the IBC tumors. Most patients (25%) had more than 3 invaded axillary lymph nodes. Forty three of 100 patients with inflammatory breast cancer (43%) had metastases at the time of presentation. Fifteen patients had more than one site of metastatic disease. The most common site of metastasis being bone (74 %), followed by lung and liver.

Table 1: Patient and tumor characteristics (n=100).

Tumor characteristics'(n=100)	No. of patients
Age in years	
Median (range)	(28-89)
≤ 50	46
> 50	54
Menopausal status	
At diagnosis	
Premenopausal	41
Postmenopausal	59
Clinical tumor size (mm)	
Median (range) 79 (0 -240)	
≤ 70	47
> 70	47
Clinical nodal stage	
NO	26
N1	30
N2	35
N3	9
Hormone receptors	
ER positive (n= 91)	52
PR positive (n= 92)	43
Her2/neu IHC+++ (n= 66)	24
TNBC	34
Histologic grade	
Intermediate grade	44
High grade	44

*ER=Estrogen; PR=Progesterone receptor; IHC=Immunohistochemistry; TNBC=Triple negative

breast cancers; HER2=Human epidermal growth factor receptor

2) Response to treatment and outcome

71,7 % of the non metastatic IBC patients received anthracycline and/ or taxane based chemotherapy followed by modified radical mastectomy, radiotherapy and hormonal therapy as indicated. The most common chemotherapy regimen used (for non metastatic IBC) was cycles of FEC (Epirubicin 100 mg/m2, Cyclophosphamide 500 mg/m2, 5FU 500 mg/m2) and Docetaxel 100 mg/m 2. 14 patients received only FEC 100. Among the patients who received preoperative chemotherapy, 8 patients (21%) had a pathologic complete response. After neo-adjuvant chemotherapy, pathologic tumor size was known in all of the cases. Median tumor size was 3.0 cm (range 0–9 cm). Patients were more likely to have positive axillary lymph nodes (42 %). The median number of nodes removed was 3 (range 0–25). According to Sataloff's classification, the complete pathological response rate in breast (TA) and nodes (NA) was18 % and11 % respectively. 57,5 % patients with HR-positive tumors received endocrine therapy consisting of tamoxifen alone (28,5%); aromatase inhibitors (18%); sequential association (11%). Among the 24 patients with over expressed Her-2 tumors, 5 (20 %) received trastuzumab for a year. Adjuvant RT was administered to 32 patients.

For metastatic disease, sixteen patients received four cycles of FEC, 5-flurouracil 500 mg/m², Epirubicin 60 mg/m², Cyclophosphamide 500 mg/m² and in eleven patients we used the FEC 75. Modified radical mastectomy was done in 40 patients (two in metastatic disease). Twenty one patients received hormonal treatment in palliative setting. Only one patient received Trastuzumab in metastatic disease.

3) Follow up

At the last follow-up, 28 patients had relapsed, of which eight patients had a loco regional and twenty patients had a systemic relapse. The most frequent site of first recurrence was lung (61, 5%). The median time to relapse was 12 months and 3 year recurrence-free survival was 15 %.

Overall survival at 5 years was 28 % (**figure 1**). Median survival was 40 months for stage III and 13months for stage IV. Of 72 deaths, 70 were certified as due to breast cancer, 2 as not due to breast cancer.

Overall survival influencing factors were were estrogen receptor positivity (**P = 0.05**), presence of extracapsular extension (**P = 0.001**) ,lymphovascular space invasion (**P = 0.001**) and M tumor stages (**P=0.001**). (**Table 2 and Figures 1-4**).

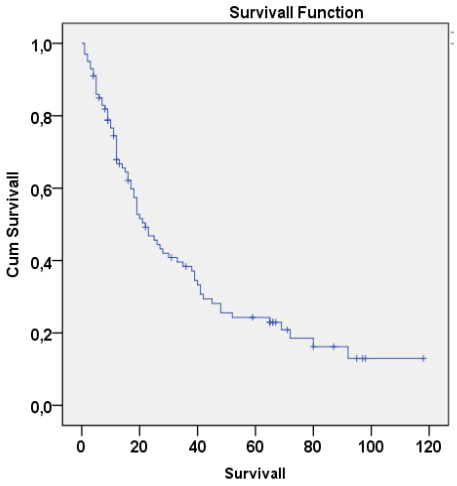

Figure 1: Overall survival curve (months).

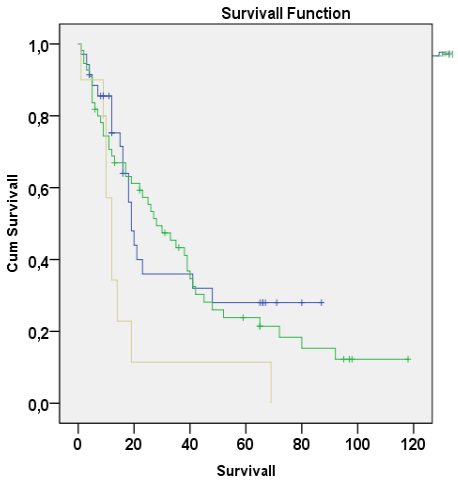

Figure 2: Estrogen receptor positivity impact on overall survival.

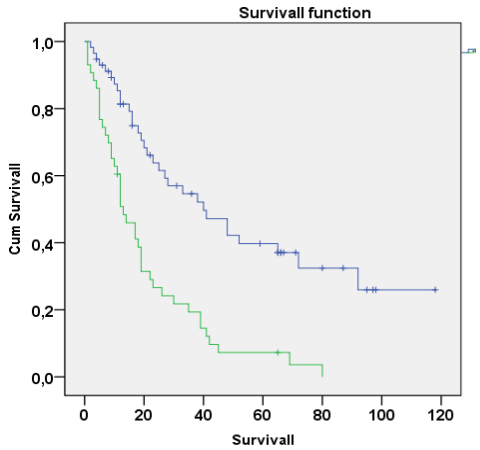

Figure 3: M tumors stage impact on overall survival.

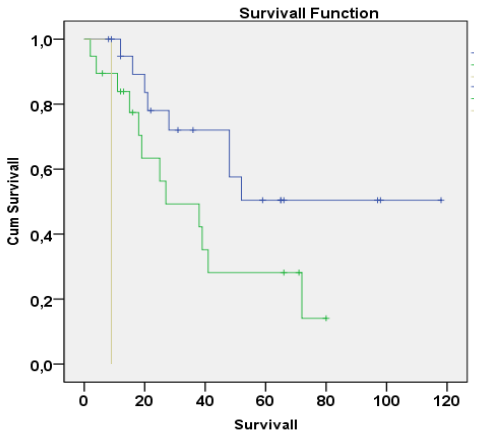

Figure 4: Presence of extracapsular extension impact on overall survival.

Table 2: Prognostics factors of overall survival.

Characteristics	Number	Mean overall Survival (Months)	Confidence interval 95%	*p* value
RH positive	55	39.94 ± 5.26	29.63 - 50.62	0.05
RH negative	35	37.01 ± 6.28	24.68 - 49.33	
M0	57	55.55 ± 6.65	42.52 – 68.59	0.001
M1	43	20.26 ± 3.04	14.3 – 26.23	
EC Extension +	19	37.86 ± 6.71	24.69 – 51.03	0.001
EC Extension -	21	75.63 ± 10.96	54.13 – 97.12	
LVSI +	6	61.85 ± 8.48	45.21 – 78.48	0.001
LVSI -	36	34 ± 11.42	11.61 – 56 .38	

DISCUSSION

Inflammatory breast cancer is a clinicopathological entity characterised by diffuse erythema and oedema of the breast, often without an underlying mass. The inflammatory nature of the tumour could be due to its angioinvasive and angiogenic properties, with many tumor emboli filling the dermal lymphatic system.[13] 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.[14-15]

IBC is the most lethal form of the disease and constitutes 1–2% of all breast tumors in the USA.[16] However, a high proportion of cases is reported in Arab populations-eg, in Tunisia 7–10% of all breast cancer are inflammatory.[17] Findings of an epidemiological analysis of all new cases of breast cancer diagnosed in our country showed that inflammatory breast cancer accounts for 6% of all cases.[18-22]

Our retrospective analysis suggests also that the percentage of reported IBC cases in central Tunisia has been steadily declining. In our analysis, IBC constituted 8 % of all breast cancer patients. However, from 1990 to 1996, Ben Ahmed et al. reported 729 breast cancer cases in central Tunisia, 14% having T4d.[23] This gradually decreasing rate of IBC in our institute suggests a significant improvement of socioeconomic conditions and an increase stringency of criteria for early diagnosis. The median duration of signs before a medical consultation among confirmed IBC cases in our study (4 months) was considerably lower than the mean delay of 11.6 months reported among 160 patients with breast cancer showing local or T4 disease in central Tunisia.[24]

Women with IBC typically presentat a younger age than NIBC.[25] Four large population-based studies have reported a higher incidence in young African-American women. The cause of racial disparities has not yet been elucidated.[16-17] It has been noted that Hispanic women had the youngest mean age of onset (50.5 years) compared with 55.2 years for African-American women and 58.1 years for Caucasian women.[6] This very young mean age at initial diagnosis of IBC is confirmed by Tunisian retrospective series,[19-26-27] it was 43 years according to the Boussen series[19] and 44 years in the series of labidi.[26] however the mean age at IBC diagnosis has been estimated at 53 years in ours serie; this rate is comparable to Moroccan series. Similar median age was reported by Soliman. AS et al., with 112 patients diagnosed by AJCC standards as IBC at Ibn Rochd Oncology Center in Casablanca, Morocco between 2005–2007.[28]

Most of the studies have documented a higher frequency of ER/PR negativity and a higher incidence of HER2 over expression.[29-30] Up to 83% of IBC tumors lack the estrogen receptor (ER) expression compared with other forms of locally advanced breast cancers which are mostly ER positive.[31] Generally, the absence of oestrogen receptors and progesterone receptors has been correlated with a shorter overall survival and poor clinical outcome.[32] Our study showed a significant

positive impact of estrogen receptor positivity on survival in IBC patients.

HER2 over expression is also more likely in inflammatory breast cancers, with around 40% of cases being HER2-positive, compared with a rate of half that for non-inflammatory disease.[33] In our analysis the Estrogen receptor (ER), progesterone receptor (PR) positivity and human epidermal growth factor receptor2 (HER2/neu) positivity were 57 %, 46, 7 % and 36, 3 %, respectively, which is similar to the reported studies. Triple negativity was found in 33% of the cases in our study. No difference in OS was seen between the HER-2 positive and HER-2 negative IBC. Although little can be drawn from this observation in this small series, our findings are nevertheless similar to those of Prost et al.[34] They found 36 % of IBC were HER-2 positive .In multivariate analysis negative hormone -receptor status and extension of disease were the only factors associated with a worse outcome.

Approximately, 20–30 % of patients with IBC present with distant metastasis at diagnosis (classified as stage IV disease).[6–35] The incidence of metastatic disease in our series was considerably higher, with over a half of cases (43%) having metastatic disease at presentation which is more than the published literature and indicates towards an aggressive disease biology.[6-36] Identifying metastatic disease at presentation affects treatment choices and also provides important prognostic information. Our findings show that patients with stage IV inflammatory breast cancer at diagnosis have worse survival outcomes than those patients with stage III inflammatory breast cancer , these results are similar to those of Daoud et al.

They showed using data from the Surveillance, Epidemiology and End Results database that among patients with IBC, women with metastatic disease at diagnosis had significantly lower 2-year IBC-specific survival and OS rates than women with stage IIIB or IIIC disease.[37]

Although IBC is the most lethal form of breast cancer affecting young women, there is insufficient evidence from prospective randomized clinical trials for an optimal management for those patients. However, over the past 2 decades, different studies led to the accord that all those patients with primary IBC should receive systemic chemotherapy followed by breast cancer surgery and radiation therapy. IBC treatment strategies showed that a combination of a taxane and anthracycline increase the response rate to primary systemic chemotherapy, and improves prognosis and efficacy in the neoadjuvant treatment of IBC. It has been indicated that taxanes may improve outcome in IBC patients treated with anthracycline-based regimens.[38] Most of the studies, however, have included a limited number of patients and no randomized clinical trial has confirmed these results. in our series, fourteen patients received taxanes as adjuvant chemotherapy and we find an impact of this chemotherapy on survival.

As regards targeted therapy, the rate of pathological complete response (pCR) after primary anthracycline-taxane - based chemotherapy (CT) ranges from 15 to 30% only (63% for HER-2 IBC) when trastuzumab is added,[39] and the 5-year survival remains around 40% despite a multimodality treatment. In our study, only 32 % of HER2 over expressing patients received Trastuzumab.

A multidisciplinary approach is crucial for the management of IBC. Even so, the survival rates for women with IBC are still poor, ranging from 35%-40%, significantly lower than those for other breast cancers.[40]

In our cohort, The survival of Tunisian patients is poorer than that in American and European series due to many factors including more aggressive disease, socioeconomic conditions with limited access to new drugs like trastuzumab and lack of supportive care services.

This study is subject to the limitations of all retrospective analyses and a small sample size because of the relative rarity of this disease, precluding further analyses for prognostic factors.

CONCLUSION

In summary, the results from this preliminary analysis support the benefit of early initiation of aggressive treatment and neoadjuvant targeted therapy for IBC. Timely diagnosis and treatment, increased awareness of the disease, close follow-up, and aggressive salvage therapy, all of which are more easily achieved in a specialized multidisciplinary IBC clinic, could also contribute to the observed improvement in survival outcome.

Conflict of interest

The authors declare no competing interests.

Funding source

The authors declare that there isn't a study sponsor.

Authors'contributions

All the authors have managed the patients and contributed to the writing of the manuscript in ways that conform to ICMJE authorship criteria. All the authors have read and approved the final version of the manuscript.

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