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ORIGINAL ARTICLE

Molecular subtypes in patients with inflammatory breast cancer; A single center experience

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Summary

Purpose: *The purpose of this study was to investigate the frequency and prognosis of inflammatory breast cancer (IBC) according to molecular subtypes.*

Methods: *Demographic data were examined for 78 patients diagnosed with IBC among breast cancer patients monitored in our clinic. Patients were staged according to the 2010 AJCC guidelines. Physical examination and radiographic findings classified on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were employed in the evaluation of clinical response to systemic therapy. Subtype analysis was performed in patients with IBC and subtypes were compared. Patients were divided on the basis of metastatic or non metastatic status and survival analysis was performed on the basis of molecular subtypes.*

Results: *Distribution analysis of molecular subtypes revealed a lower incidence of luminal A and a higher incidence of both HER 2 (+) and triple negative breast cancer in IBC. Molecular subtypes had no effect on survival in the non metastatic (p=0.61) and metastatic patient group (p=0.08).*

Conclusion: *This study showed that IBC frequency is higher in HER2 overexpressing and triple negative subtypes. No survival differences were noticed in relation to molecular subtypes in IBC patients.*

Key words: *breast cancer, inflammatory, prognosis, survival, treatment*

Introduction

IBC proliferates rapidly and is the most aggressive form of breast cancer [1]. IBC possesses a unique series of diagnostic criteria. The American Joint Committee on Cancer (AJCC) specifically classifies IBC as T4d, defining it as "a clinicopathologic entity characterized by diffuse erythema and edema of the breast, often without an underlying palpable mass" [2].

In addition to being the most significant prognostic factors for breast cancer, hormonal receptors/HRs (estrogen (ER) and progesterone (PR) receptors) and HER2 status are also the strongest predictors of response to treatment. These predict tumor behavior and permit breast cancer to be classified into molecular subtypes. HER2 is the best established target in breast cancer. Therapies targeting this marker have proved indispensable for breast cancer treatment and achieving better clinical outcomes. However, these markers (ER, PR and HER2) have only been studied in small populations of IBC patients.

The purpose of this study was to assess the demographic data for patients under monitoring for IBC in our center and to determine the prevalence of its molecular subtypes. A further aim was to investigate whether or not molecular subtypes affect survival in metastatic and non metastatic groups.

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Methods

Patients

We reviewed the records of all patients treated for IBC at our institution from June 1998 through December 2014. A clinical diagnosis of IBC required the presence of diffuse erythema, heat ridging, or peau d'orange (corresponding to T4d stage in the AJCC system). All cases were assessed at the time of diagnosis and confirmed as IBC by a multidisciplinary team. Patients with secondary skin changes from locally advanced disease were not included. The initial staging protocol involved bilateral mammography and ultrasound of the breasts and lymph nodes, bone scans and thoracic and abdominal CT.

Patients were staged according to the 2010 AJCC guidelines. Physical examination and radiographic findings classified on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were employed in the evaluation of clinical response to systemic therapy [3].

Medical records were employed to extract patient characteristics such as age, menopausal status, body mass index (BMI), clinical stage, nuclear grade, and ER and PR status. ER and PR status had previously been determined using immunohistochemistry. During this analysis, a cutoff of 10% of cells staining positively was considered a positive result. HRs status was determined as positive (HR+) if ER, PR or both ER and PR were positive, and as negative (HRs–) if both ER and PR were negative. HER2 status was considered negative (HER2–) if (i) IHC results were 0 to +1 or (ii) IHC results were +2 and FISH results were negative. HER2 status was considered positive (HER2+) if (i) IHC results were +3 and FISH results were not available, or (ii) if the FISH result was positive (amplification ratio ≥2.0) regardless of the IHC result. Subtype analysis was performed in patients with IBC, and subtypes were compared.

Some patients in our study group were operated after neoadjuvant therapy, while others received adjuvant therapy after surgery. The metastatic patient group received medical treatment. Pathological response levels were assessed in the neoadjuvant therapy group.Pathological complete response (pCR) was defined as absence of any evidence of invasive carcinoma in the breast or the axillary lymph nodes at the time of operation [4].

Pathologies were reassessed postoperatively. Lymphatic invasion and vascular invasion were determined to be present if mentioned in the postsurgical pathology report. Patients were divided on the basis of metastatic or non metastatic status, and survival analysis was performed on the basis of molecular subtypes.

Statistics

Endpoints were death at the time of last follow-up.

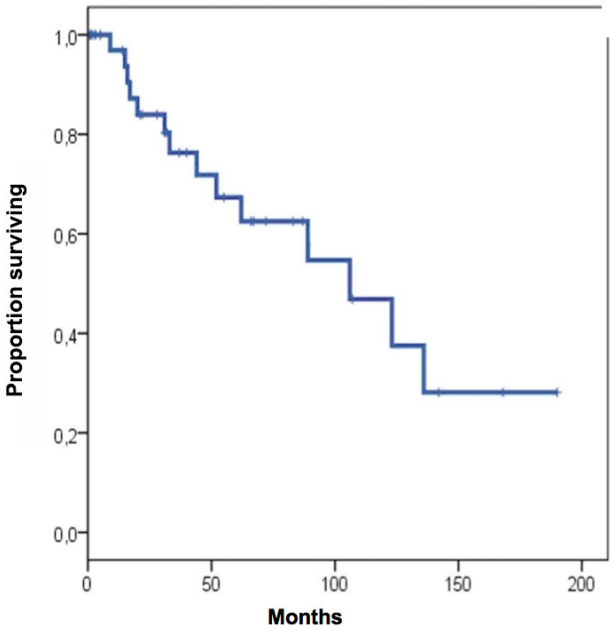

Figure 1. Overall survival rate, all IBC patients included.

Overall survival (OS) was calculated from date of diagnosis to the date of death using Kaplan-Meier analysis. The log rank test was used to compare intragroup survival differences. Subgroups were compared using the chi-square test and the Wilcoxon rank sum test when appropriate. All p values were 2-sided, and a p value< 0.05 was considered to be statistically significant.

Results

Demographic data

The incidence of IBC in our series of 3500 breast cancer patients was 2.2%. The study involved 78 IBC patients under monitoring and a follow-up duration of 22 months (range 3-190). Patient characteristics are shown in Table 1.

Invasive ductal carcinoma was observed in 66 (84.9%) patients. ER, PR and HER2 statuses were evaluated and molecular subtypes were determined: 34.6% (N=27) were luminal A, 17.9% (N=14) luminal B, 20.5% (N=16) triple negative and 24.4% (N=19) HER 2 (+). Luminal A breast cancer was determined in 66.3% of the patients under observation for breast cancer in our clinic, luminal B in 12.4%, HER2 (+) in 9.0% and triple negative breast cancer in 12.3%. While the incidence of luminal A was decreased in the IBC patients, an increase was observed in the incidence of both HER 2 (+) and triple negative breast cancer.

Twenty-eight (35.9%) patients diagnosed

Table 1. Demographic characteristics of patients with inflammatory breast cancer

Characteristics	*N*	*%*
Age, years, median (range)	49 (27-87)	
Body mass index, median (range)	27.8 (18.8-41)	
Menopausal status		
Perimenopausal	6	7.7
Premenopausal	36	46.2
Postmenopausal	32	41
Oral contraceptive use		
Yes	7	9
No	65	83.3
Hormone replacement therapy		
Yes	9	11.5
No	63	80.8
Comorbidity		
Diabetes mellitus	7	9.1
Hypertension	12	16.8
Dyslipidemia	2	2.6
Coronary artery disease	7	9.1
Operation type		
Simple mastectomy	1	1.3
Modified radical mastectomy	48	61.6
Radical mastectomy	2	2.6
Histology		
Invasive ductal carcinoma	66	84.9
Others (invasive lobular, metaplastic, mixed, mucinous, signet ring cell)	9	11.9
Grade		
I	2	2.6
II	21	26.9
III	42	53.8
Molecular subtype		
Luminal A	27	34.6
Luminal B	14	17.9
Triple negative	16	20.5
HER2(+)	19	24.4
Type of therapy		
Adjuvant	17	21.8
Neoadjuvant	30	38.5
Metastatic	28	35.9
Chemo/hormono/Mab therapy		
AC+ paclitaxel	32	41.6
CAF	9	11.7
CEF	3	3.9
TAC	6	7.8
Herceptin	26	33.8
Tamoxifen	21	26.9
Aromatase inhibitor	18	23.1
Radiotherapy		
Received	56	71.8
Not received		21.8
Neoadjuvant therapy response		
Complete	3	0.1
Partial	16	53
Stable	1	0.33
Progressive	1	0.33
Site of metastasis		
Brain	4	5.2
Bone	27	35.1
Visceral	33	42.9
Skin	5.2	5.2

with metastatic disease received treatment at the time of diagnosis. Of the remainder of the group (stages III B and III C), 36% (N=17) received adjuvant therapy and 63% (N=30) neoadjuvant therapy. Modified radical mastectomy (MRM) was performed on 61.6% (N=48) of the patients undergoing surgery, and radical mastectomy (RM) on 2.6% (N=2).

In terms of medical treatment, 41.6% (N=32) of the patients received AC+taxane (cyclophosphamide 600 mg/m^2+adriamycin 60 mg/m^2 for 4 cycles, every 21 days and weekly paclitaxel 80 mg/m^2 x12 weeks), 11.7% (N=9) received CAF (cyclophosphamide 500 mg/m^2+adriamycin 50 mg/m^2 + fluorouracil 500 mg/m^2, every 21 days for 6 cycles), 3.9% (N=3) received CEF (cyclophosphamide 500 mg/m^2+epirubicin 75 mg/m^2 and fluorouracil 500 mg/m^2, every 21 days for 6 cycles) and 7.8% (N=6) TAC (taxane 75 mg/m^2+adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, every 21 days for 6 cycles).

Fifty-three percent (N=21) of the HR positive patients (N=39) received tamoxifen and 46% (N=18) received aromatase inhibitor therapy. Additionally, 33.8% (N=26) of the patients received trastuzumab therapy.

Analysis of response of patients receiving neoadjuvant therapy revealed complete response in 0.1% (N=3) patients, partial response in 53% (N=16), stable disease in 0.33% (N=1) and progressive disease in 0.33% (N=1).

Metastatic locations were identified in the brain, bone, viscera and skin. Brain metastasis was determined in 5.2% (N=4) of the patients, bone in 35.1% (N=27), visceral in 42.9% (N=33) and skin metastasis in 5.2% (N=4) of the patients.

Median overall survival was 52 months (Figure 1). Effects of molecular subtypes based on whether patients were metastatic or not on survival were investigated.

Survival analysis in the non metastatic group

Survival analysis on the basis of molecular subtypes was performed in the non metastatic patient group. Median OS was 123 months in the luminal A type, 52 months in luminal B, 16 months in triple negative and 106 months in the HER2 (+) group. No statistically significant difference was determined (p=0.611), possibly due to the small number of patients (Figure 2).

Survival analysis in the metastatic group

Survival analysis by molecular subtypes was

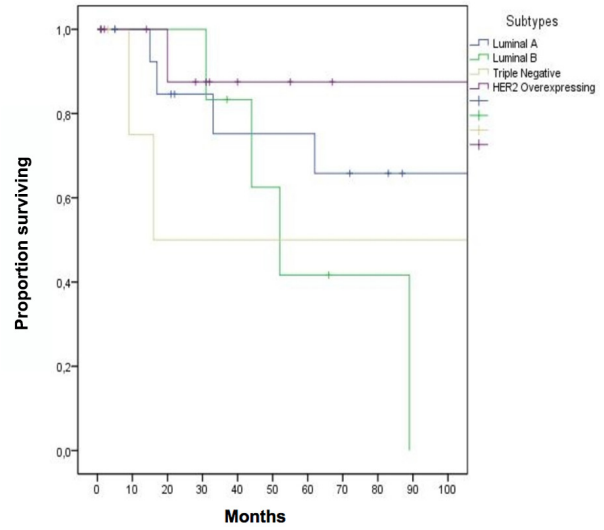

Figure 2. Overall survival rates according to subgroups in non-metastatic IBC patients (p=0.611).

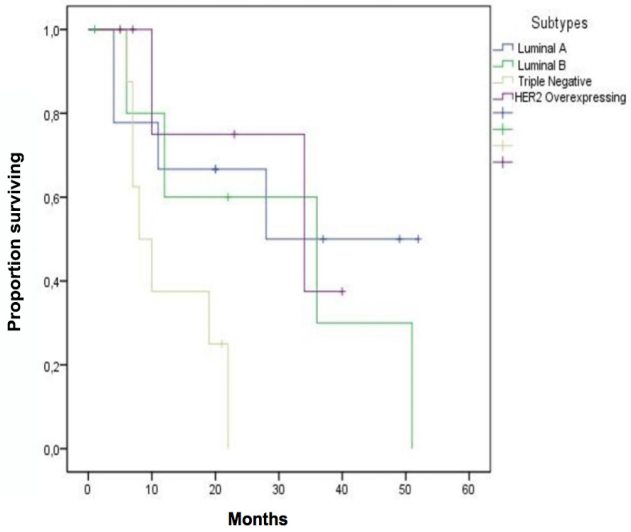

Figure 3. Overall survival rates according to subgroups in metastatic IBC patients (p=0.082).

also performed in the metastatic patient group. Median OS was 28 months in the luminal A type, 36 months in luminal B, 8 months in triple negative and 34 months in the HER2 (+) group. No significant differences were determined among the subtypes (p=0.082; Figure 3).

Discussion

The incidence of IBC in our 4500-patient breast cancer series was 2.2%. Median age at the time of diagnosis was 46 years, while a mean age of 56 years was determined on the basis of SEER data [5]. The incidence of IBC in the USA is reported at 1-5% of breast cancer cases [6]. However, the recurrence and mortality rates for IBC are quite high compared with those of non-inflammatory locally advanced breast cancer; IBC is responsible for 8–10% of all breast cancer-related deaths [6].

Panades et al. [7] and Gonzalez-Angulo et al. [8] investigated the outcome of IBC management over a period of 40 years and determined no significant progress in its treatment. According to the latest SEER analysis, however (survival analysis was performed for 7679 IBC patients treated between 1990 and 2010), considerable progress has been made in the management of IBC [5]. Before 1974 IBC was considered to be a uniformly fatal condition with a 5-year actuarial OS rate of < 5% and a median survival rate of 15 months [9]. A multidisciplinary management approach was subsequently adopted. This included an anthracycline-based chemotherapy regimen and radiation therapy, and the 15-year survival rate was increased up to 20-30% [10,11]. Median OS in our study group was 52 months.

The luminal A subtype is less common in IBC. However, it also exhibits a higher frequency of HER2-enriched subtype compared to non-IBC breast tumors [8,12]. In our group the figures were 34.6% (N=27) luminal A , 17.9% (N=14) luminal B, 20.5% (N=16) triple negative and 24.4% (N=19) HER 2 (+). Compared with breast cancer patients being monitored in our clinic, a decrease in the incidence of the luminal A type was observed in IBC patients, and a significant increase in the incidence of HER2(+) and triple negative breast cancer. These findings were compatible with the revelant literature.

At the time of diagnosis, 21.8% (N=17) of the patients received adjuvant therapy, 38.5% (N=30) neoadjuvant therapy and 35.9% (N=28) were treated for metastatic disease. The most frequent metastatic areas were the bone and visceral organs (lung, pleura and liver).

The median follow up period was 22 months (range 3-190) and median OS 52 months. The poorest OS rates in the literature are observed in triple negative IBC patients. The group with the lowest survival between the metastatic and non metastatic groups in our study was the triple negative breast cancer. Patients were divided on the basis of metastatic status and survival analysis was then performed according to molecular sub-

types. OS values in the non metastatic group were 123 months in the luminal A type, 106 months in the HER2 (+) group, 52 months in the luminal B and 16 months in the triple negative type. No statistically significant difference was determined (p=0.611). Interestingly, however, survival in luminal B type was poorer compared to HER2 (+) breast cancer. Masuda et al. [13] determined no significant difference in OS and disease-free survival (DFS) between the HR (+) group and the HER2 (+) and HR (-) groups.

General survival in the metastatic patient group was 28 months in the luminal A type, 36 months in luminal B, 8 months in triple negative, and 34 months in the HER2 (+) group. Interestingly, survival in the HER2 (+) group was better than that in the luminal A group, although the difference was not statistically significant (p=0.082).

Some studies have determined a difference in survival rates among molecular subtypes in locally advanced breast cancer [14,15]. Sorlie et al. [15] described prognosis on the basis of intrinsic subtype. The basal-like and HER2-enriched subtypes exhibited the poorest prognosis, with both shorter time to progression and lower OS. Patients with the luminal A subtype had significantly better prognosis compared with all other groups. The luminal B subtype exhibited an intermediate outcome. Results in locally advanced breast cancer are to date similar to those of early breast cancer. In contrast to the literature, molecular subtypes made no positive or negative contribution to disease outcome in our study. The prognostic effect of subtypes in IBC may not resemble early stage breast cancer,-showing that different biology may play a role in this rare subtype. The fact that our study was retrospective and included a rather low patient numbers may have affected our analytical results.

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