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Basal-Like Breast Cancer; Clinicopathological, Molecular, and Prognostic Features

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ABSTRACT

Background: Molecular classification of breast tumors has identified the basal-like subtype, with high heterogeneity and very poor prognosis. These tumors are mainly triple negative, characterized by the expression of basal markers CK5/6 and EGFR. In this study, we sought to investigate the features, outcome, and therapeutic modalities of basal-like breast cancers (BLBC).

Methods: We retrospectively identified 90 BLBC patients diagnosed at the Department of Surgical Oncology of Salah Azaiez Institute between January 2009 and December 2013.

Results: The mean age of our patients was 50 years, and 15.5% had a family history of breast cancer. The mean tumor size was 43.8 mm. Histological examination revealed invasive ductal carcinoma in 88.9% of the cases, metaplastic carcinoma in 5.6%, and medullary carcinoma and adenoid cystic carcinoma in 2.2%. BLBC was most often associated with a high tumor grade (55.3% had a grade 3 tumor) and a high Ki-67 proliferative index. Vascular invasion was found in 31.1% of the cases. Regarding lymph node involvement, 42.9% had positive lymph nodes and 7.9% featured distant metastases. Surgical treatment was provided for 85 patients. It consisted of conservative surgery in 40 cases and radical surgery in 45 cases. Neoadjuvant chemotherapy was administrated to 23 patients, with a 13% complete pathologic response. The rates of overall survival and disease-free survival at 3 years for localized BLBC were 74.4% and 75.9%, respectively.

Conclusion: BLBCs are aggressive tumors associated with poor prognosis. Thus, to identify novel prognostic factors and therapeutic targets, prospective studies should investigate the epidemiological and evolutive profile of these tumors.

Introduction

Breast cancer is the most common cancer and the second leading cause of death in women globally.[1] Human breast tumors can be classified at the molecular level, with each molecular subtype being characterized by distinctive gene signatures and clinical outcomes.[2] However, as standard microarray-based transcriptional profiling is not currently feasible in the clinic, immunohisto-chemistry provides a more practical approach to determining various subtypes of breast cancer by identifying protein products of the signature genes.[3,4]

The various molecular subtypes of breast cancer include luminal A and B, marked by overexpression of estrogen receptor (ER) and its targets in the luminal epithelial layer of the mammary gland; human epidermal growth factor receptor 2 (HER2/ErbB2)-positive subtype, characterized by

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high expression of the HER2 oncogene; and triple-negative subtype, defined by negative expression of genes coding for estrogen, progesterone, or HER2.[2]

A subset of triple-negative cancers, distinguished by expression of genes characteristic of the outer or basally located epithelial layer of the mammary gland such as cytokeratin (CK) 5 and 17 and the epidermal growth factor receptor (EGFR/HER1), is classified as basal-like breast cancer (BLBC).5 BLBC is associated with an unfavorable clinical profile with a high risk of early metastatic relapse. Furthermore, currently there is no targeted treatment for BLBC, and the only validated systemic therapy is chemotherapy. Despite the use of recent patterns of chemotherapy, the prognosis remains poor, representing a challenge in clinical practice.[3]

The aim of our study was to determine the clinicopathological, therapeutic, and prognostic features associated with this type of breast cancer in the Tunisian population.

Methods

Study population

In a retrospective cohort study, we reviewed a total of 4120 breast cancer cases with complete immunohistochemical analysis registered in Salah Azaiez Institute of Cancer between January 2009 and December 2013. Only triple-negative breast cancer (TNBC) cases were eligible for inclusion in the study. Cases were excluded if there was no expression of basal markers (CK5/6), the patient was deceased, or had lost her eyesight.

Variables

The epidemiological, clinicopathological, therapeutic, and evolutive data were analyzed. The basal-like tumors in our study were defined by the absence of ER and PR expression, and the lack of high HER2 expression (a HER2 score of ≤ 2, with negative FISH testing).[2] Cancer staging was carried out based on the TNM system. In patients who had undergone upfront surgical treatment, cancer staging was based on pathological findings; however, for cases receiving neoadjuvant chemotherapy, clinical and radiologic staging was performed.

Tumors were graded using the Scarff-Bloom-Richardson (SBR) histological system. Sataloff and Chevalier's pathological classification was chosen as the primary end point in the assessment of histological response in both the mammary gland and axillary lymph nodes.

Overall survival (OS) was defined as the interval between the date of diagnosis and either death or the date of the last follow-up. The other end point considered was disease-free survival (DFS), defined as the length of time from the date of diagnosis to the date of the first signs of progress confirmed by the investigator in the medical record, the date of death, or date of most recent news when the patient was censored.

Statistical analyses

The statistical analysis was performed using SPSS 21.0. Descriptive statistics (frequencies for qualitative variables and minimum, maximum, mean and SD for quantitative variables) were used to summarize clinical data and demographics of the patients. Estimations of the OS and FDS functions S (t) at 3 and 5 years were performed according to the Kaplan-Meier analysis and the log-rank test with stratification of our study population into 2 groups: localized and metastatic disease.

Results

Clinicopathological characteristics

Of the 4120 cases reviewed, 300 (11.3%) were TNBC, of which 90 (30%) expressed basal-like markers on immunohistochemistry and therefore were included in the study.

The frequencies of risk factors for breast cancer in our study sample are shown in Table 1. The median age at diagnosis was 50 years (range: 24-91 years; <40 years = 21%, 40-59 years = 21%, >60 years = 58%).

Forty-four patients were menopausal (48.9%). Fourteen patients reported having at least one first- or second-degree relative with breast cancer. The identification of BRCA mutation was not performed in any patient.

Table 2 illustrates the main clinicopathological characteristics of the study population. Combined mammography and ultrasound showed abnormalities in 97.5% of patients, of whom 72.5% had lesions that were highly suspicious of malignancy (BI-RADS category 5). Only 2.5% were known to be probably benign lesions (BI-RADS 3) and were then reclassified.

As for disease stage, 10.1% were classified as stage I, 53.9% stage II, 28.1% stage III, and 7.9% (n = 8) stage IV at first diagnosis. Almost half of the patients (51.1%) had a T2 tumor.

The metastases were especially visceral in the first position. Bone metastases accounted for 25%.

The majority of patients (85.6%) had an infiltrating ductal carcinoma, 2.2% had medullary carcinoma, 5.6% had metaplastic carcinoma and others histologic subtypes were identified in 6.6% of cases. Tumors were poorly differentiated and had high proliferation indexes, with 47 (55.3%) cases being grade 3 and 33 (44.7%) cases being grade II, with a mean Ki-67 index of 49%. Regarding lymph node involvement, 42.9% of patients had positive lymph nodes at initial diagnosis, and a lymphovascular invasion was found in 31.1% of cases.

Based on the immunohistochemical study, all the tumors had a triple-negative basal-like phenotype defined by lack of expression of the ER, PR, and

Table 1. Risk factors for breast cancer

Parameters		%
Menarche (y)	< 11	12.4
	≥ 11	84.6
Age at first pregnancy (y)	< 30	87
	≥ 30	13
Parity	Nulliparous	5.1
	Primiparous	8.9
	Multiparous	86.1
Hormonal contraception	No	47.8
	Yes	52.2
Breast feeding	No	46.7
	Yes	53.3
Menopausal status	No	51.1
	Yes	48.9
Family history (n = 14)	First-degree relatives	71.5
	Second-degree relatives	28.5
	Ovarian cancer	0
	Other cancers	3.3
BMI (kg/m²)	< 25	30.8
Mean BMI = 30.32	≥ 25	69.2

Table 2. Clinical and histopathological characteristics (N = 90)

Parameters		%
Presentation	Breast mass	72.2
	Axillary adenopathy	8.9
	Pain	10
	Nipple retraction	4.5
	Screen-detected	1.1
Localization	Left	54.4
	Right	43.3
	Bilateral	2.2
Tumor size (mm)	≤ 30	45.6
Mean size=43.87	> 30	54.4
T category	Tx	1.1
	T0	0
	T1	13.3
	T2	51.1
	T3	18.9
	T4b	10
	T4d	5.6
Metastasis(n = 8)	Lung	75
	Liver	75
	Bone	25
	Brain	50
Histologic subtype	IDC	88.9
	Metaplastic	5.6
	Medullar	2.2
	Adenoid cystic	2.2
	Papillary	1.1
Lymph node status	N0	57.1
	N+ (1-3)	17.9
	N+ (4-9)	11.9
	N+ (> 10)	13.1
Capsular rupture	No	74.1
	Yes	25.9
Necrosis	No	44.7
	Yes	55.3
Intraductal component	No	67.8
	Yes	32.2
Ki-67 (%)	≤ 14	13.6
	> 14	86.4

HER2 with positive staining for CK 5/6. FISH testing was needed in 12 cases to confirm the HER2 status, and we found a positive expression of androgen receptor only in 5 cases.

Treatment details and outcomes

As for treatment modalities, 85 (94.4%) patients received surgery, of whom 40 had conservative surgery (tumorectomy with axillary lymph node) and 45 received radical mastectomy with axillary lymph node dissection (Patey type mastectomy). Histological margins were clear in all patients with local disease.

Of 68 patients who had received adjuvant chemotherapy, 17 (25%) had anthracycline-based chemotherapy, and 35 (51.5%) had anthracycline followed by taxane. The 8 patients with metastatic disease had received an anthracycline-based regimen as the first-line for patient with metastatic diseases.

Radiation therapy was indicated in 69 nonmetastatic patients. Palliative radiotherapy was delivered in 2 patients with painful bone metastasis.

After a median follow-up of 49 months, 12 of the 82 nonmetastatic patients experienced locoregional relapse and 19 patients had a metastatic recurrence. The maximum of recurrence occurred between the first and second year after diagnosis, with a median of 21 months, and 24 patients died.

Six patients of the 8 with metastatic disease at diagnosis experienced progression, and two patients responded to palliative treatment with tumoral stability and then progression. All the metastatic cases died with a median survival of 12.5 months (range 7-20).Of the 23 patients who had advanced tumors or inflammatory breast cancer, 19 had received anthracycline and 4 had received anthracycline plus taxane neoadjuvant chemotherapy. Only 3 (13%) patients had a pathologic complete response (pCR) following neoadjuvant chemotherapy according to Sataloff and Chevalier's classification.

OS at 3 and 5 years were respectively 74.4% and 61.9% (Figure 1). After exclusion of patients diagnosed at a metastatic stage, OS raised to 81.9% at 3 years and 67.2% at 5 years (Figure 2). DFS rate for patients with localized disease was 75.9% at 3 years and 67% at 5 years (Figure 3).

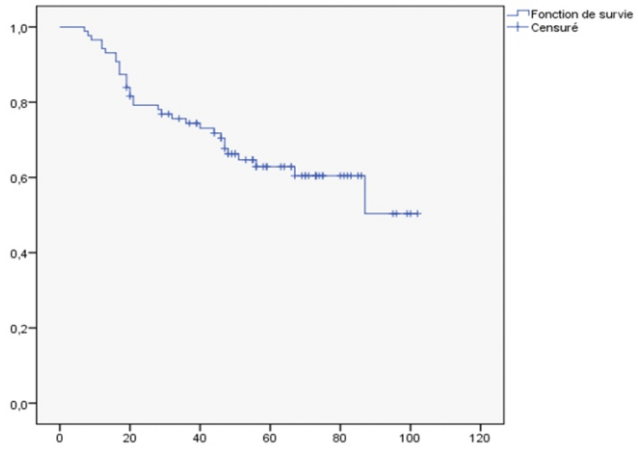

Fig 3. Overall survival of the cases

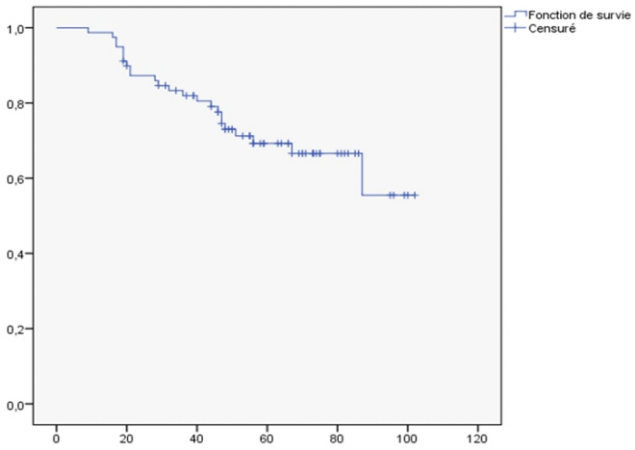

Fig 2. Overall survival after the exclusion of patients with metastatic disease

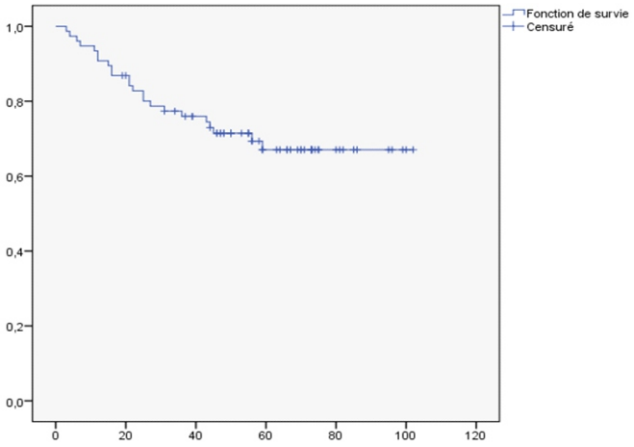

Fig 3. Disease-free survival for patients without metastatic disease

Discussion

We analyzed the epidemiological, clinical, and therapeutic characteristics of BLBC in a sample of Tunisian patients. The demographic and clinical features of our sample were, to a large extent, consistent with the literature.[6-9] The frequency of TNBC reported in the present work (11.3%) agrees with the previous reports (10%-17%).[7] In the Chinese population, approximately 12.9% of breast cancers are TNBC.[10]

In our work, however, the basal-like phenotype represented only 30% of TNBC, which is not in accordance with the literature. In fact, 80% of TNBC have a basal-like phenotype (TN-BL) and the remaining 20% are defined as TN non–basal-like (TN–non-BL) tumors.[11] BLBCs were reported to present at a younger age compared with other subtypes (53 vs 58 years).[7] The median age at diagnosis (50 years) in our study was younger than the average age mostly reported in the US population but close to the median age in Hispanic patients.[6,9,12]

More than half of the subjects in our study (59%) were 40 to 59 years old, suggesting that there might be factors predisposing towards the development of this disease. BLBC occurs more frequently in premenopausal women compared with other breast cancer subtypes.[13] In the current study, patients were premenopausal in 51.1% of cases. We found a 71.5% rate of family history of breast cancer in our cases. Unfortunately, data regarding BRCA1/2 gene mutations were not available. Given that 20% of BLBC had mutations in BRCA in the literature, the basal-like type may be used as a criterion for genetic screening to improve the prognosis of this aggressive molecular subtype through a diagnosis at an early stage and the sensitivity of BRCA1-mutant TN-BLBC to PARP inhibitors.[3,14,15]

Clinically, BLBC patients presented with large tumors with a mean tumor size of 43.87 mm and a high rate of nodal involvement (42.9%). Studies suggest that lower incidence of microcalcifications and peritumoral ductal carcinoma in situ may represent typical mammographic characteristics of BLBC.[16,17] Because of its more aggressive biology, BLBC often manifests itself as an interval cancer (detected within 12 months after a normal screening mammogram).[18] Histologically, basal-like tumors in our study were characterized by a high frequency of ductal histology (88.9%), greater histological grade (55.3%), and lymphovascular invasion (31.1%), which are in accordance with the literature.[3,5,19,20]

Currently, there is no approved targeted therapy available for BLBC. Both adjuvant treatment and palliative therapy are limited to chemotherapy. TNBC generally has higher pCR rates than non-TNBC, and TNBC patients achieving pCR have better survival compared with TNBC patients who do not achieve pCR.[21] The higher rate of response to neoadjuvant chemotherapy may be due to the typically high tumor grade and mitotic index of BLBC.[3,22] However, it seems that only TN non-BLBC tumors achieve a pCR.[14] In fact, in our series, pCR rate was 13% after neoadjuvant chemotherapy based on the classification of Sataloff and Chevalier.

Prognosis of BLBC remains pejorative compared with other subtypes. TN-BL tumors usually display aggressive metastatic behavior.[10] These tumors respond to conventional chemotherapy but recur more frequently than hormone receptor–positive, luminal subtypes and have a high mortality rate.[7] In our series, 3- and 5-year survival rates were 81.9% and 67.2%, respectively. These results are similar to those reported by Liedtke et al. in 1118 patients over a 20-year period (1985-2004).[23] BLBC is also associated with a higher risk of relapse when compared with other molecular subtypes, especially during the first 2-3 years of follow-up.[24] Dent et al. reported that the risk of recurrence in BLBC patients peaked 1 to 3 years from the date of diagnosis.[7] In the study of Luedtke et al., DFS rates at 1 and 3 years were 81% and 63%, respectively, for BLBC in localized stages compared with 90% and 76% for other molecular subgroups.[25] In our study population, DFS rates at 3 and 5 years were 75.9% and 67%, respectively.

In the metastatic setting, the prognosis is extremely worse. It represented an aggressive entity associated with very rapid progression and mortality. The most common sites for BLBC metastases are the lungs, liver, and central nervous system.[26]

Research suggests that cell cycle and DNA damage response are highly activated in BLBC and that tumor cells are results of defects in the homologous recombination repair system. Therefore, they are vulnerable to platinum salts or PARP inhibitors.[14,27] However, we have to wait for the outcome of several current clinical studies in order to define the correct strategy for the management of BLBC.[28-30]

In conclusion, we found that BLBC characteristics in Tunisian patients were consistent with the literature in terms of age at diagnosis, tumor grade, stage at diagnosis, and recurrence. BLBC is associated with poor prognosis and a high incidence of early metastatic recurrence.

Moreover, currently there is no targeted therapy available for this subtype of breast cancer. Therefore, novel molecular targets and tumor response to various treatments are open avenues of investigation. Also, since BLBC is perplexingly heterogeneous, research should strive to identify novel prognostic markers to aid in improving disease management in this population.

Conflict of Interest

None.

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