RESEARCH ARTICLE

Triple Negative Breast Cancer at the University Hospital Mohammed VI – Oujda

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Abstract

Introduction: The triple-negative breast cancer (TNBC), defined by the absence of receptors to oestrogen and progesterone and no histochemical expression of human epidermal receptor -2, is associated with a particularly aggressive behavior. The aim of our study was to determine the clinico-pathological, therapeutic and prognostic features associated with this type of breast cancer in Morocco. **Methods:** A cohort retrospective study, spread over 3 years, was conducted of 116 breast cancer patients, diagnosed between January 2009 and December 2011 at the Regional Center of Oncology. Epidemiological, clinical, histological and therapeutic data were analyzed. Survival curves at 3 years were estimated by Kaplan-Meier analysis with use of the log-rank test. **Results:** The proportion of triple-negative breast cancer in our series was 13.2%. The average age was 46.5 years and 20,7% had a previous history of familial breast cancer. Some 56,9% of tumors were greater than 3 cm in diameter. infiltrating ductal carcinoma being the histological type in the majority of cases (75.9%). TNBC was most often associated with a high grade, grade III accounting for 50.9%. Vascular invasion was found in 58.6% of cases. Regarding lymph node involvement, 42.2% had positive lymph nodes and 15.5% featured distant metastases. Neoadjuvant chemotherapy was administrated to 20% of patients with a 23.5% complete pathologic response. The rates for overall survival and disease-free-survival at 3 years for localized stages were 70 and 55.6%, respectively. With metastatic lesions, the figures were 27.5% and 10.3% respectively. **Conclusion:** The TNBC is correlated with a poor prognosis with a high mortality and early relapse requiring identification of new target therapies and markers for prediction of tumoral response to various treatments.

Keywords: Triple-negative- breast cancer- prognosis- survival outcomes

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Introduction

Breast cancer is a major public health problem. In terms of incidence, it represents the first cancer among the different cancer sites in women in the worldwide, approximately one million cases of breast cancer cases are diagnosed annually (23% of all new cancer cases) (Ferlay et al,2008). Breast cancer appears recently as a complex disease characterized by the accumulation of multiple molecular alterations that give each tumor an own phenotype and evolutionary potential. Recently, five distinct gene expression profile-based "intrinsic" subtypes were identified by c DNA microarray analysis. Luminal A (ER+ and/or progesterone receptor positive PR+, HER2−,low Ki67), luminal B (ER+ and/or PR+, HER2+ (or HER2- with high Ki67)), basal-like (ER−, PR−, HER2−, cytokeratin 5/6 positive, and/or HER1+), HER2-like (ER−, PR−, an HER2+), and unclassified (negative for all 5 markers) (Perou et al,2000/Sorlie et al,2001)

«Triple negative» breast cancer, which is characterised by the absence of receptors to oestrogen, progesterone and no histochemical expression of HER-2 growth factor, represents 10 - 17% of all breast cancers (Anders et al,2009). This subtype of breast cancer is associated with an unfavorable clinical profile with a high risk of early metastatic relapse. Furthermore, "triple negative" has currently no targeted treatment and the only validated systemic therapy is chemotherapy. Despite the use of recent patterns of chemotherapy, the prognosis remains poor. Therefore it represents a challenge in clinical practice (Stockmans et al,2008).

The aim of our study was to determine the clinico-pathological, therapeutic and prognostic features associated with this type of breast cancer in the oriental area.

Materials and Methods

Patients

After reviewing data of the Regional Center of oncology Hassan II - Oujda (CRO), a total of 876 breast cancer cases with complete immunohistochemical analysis was registered between January 2009 and December 2011. In this retrospective cohort study we recruited 116 Triple-negative breast cancer patients diagnosed in this

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period. We excluded from the study non triple-negative breast cancer and patients who died or lost before starting treatment. The epidemiological, clinico-pathological, therapeutic and evolutive data were analyzed.

Methods

The triple-negative tumors in our study were defined by an association of RE at 0%, RP at 0%, and HER-2 not overexpressed, a score of HER-2 at 0, 1 or 2 with CISH or FISH negative. The histological classification was based on the TNM classification 2002 modified in 2003. Histological tumor grading was performed using the Scarff Bloom and Richardson (SBR) histological system. Sataloff classification was chosen as primary endpoint to assess histological response in both the mammary gland and axillary lymph nodes.

OS was defined as the length of time from the date of diagnosis until either the date of death (from any cause) or the date of last follow-up. DFS was determined as the length of time from the date of diagnosis of this disease to the date of the first signs of progress confirmed by the investigator in the medical record, or the date of death or date of latest news when the patient is censored.

The statistical analysis was performed by SPSS 21.0 software. Descriptive of clinical data were expressed in percentages for the qualitative variables and median or mean ± standard deviation for the quantitative variables, the minimum and maximum were also presented. An estimation of the global and free disease survival functions S (t) at 3 years was performed according to the Kaplan-Meier analysis and the log-rank test to estimate the outcome, with stratification of our study population into 2 groups: localized and metastatic disease.

Results

Clinical characteristics

Among 876 patients diagnosed with breast cancer, one hundred sixteen (13.2%) were identified as triple negative. The median age at diagnosis was 46.5 years and was ranging from 26 to 87 years. Eighty five patients (73 %) were non-menopausal. Tweenty four patients (20.7%) had a family history of breast cancer. The identification BRCA mutation was not performed in any patient.

The overwhelming majority of patients (75.9 %) had an infiltrating ductal carcinoma, carcinoma, 6.9% had medullar carcinoma, 6% had infiltrating lobular carcinoma and others histologic subtypes were identified in 11.2% of cases. Fifty nine cases (50.9%) were grade III Scarff-Bloom-Richardson (SBR), 48 patients(41.4%) were grade II and nine (7.7%) were grade I.

Regarding lymph node involvement, 56.2 % of patients had positive lymph nodes at initial diagnosis and a lymphovascular invasion was found in 58.6 % of cases. For the AJCC staging 3.4% were classified stage I, 33.6% stage IIA, 19% stage IIB, 12.1% stage IIIA, 10.4% stage IIIB, 6% stage IIIC and 15.5% were metastatic at first diagnosis. The metastases were especially visceral in first position with : liver metastases in 28.1% and lung in 28.1% of cases. While bone metastases accounted for 15.7% (Table 1).

Treatment details and outcomes

For treatment modalities, One hundred and five

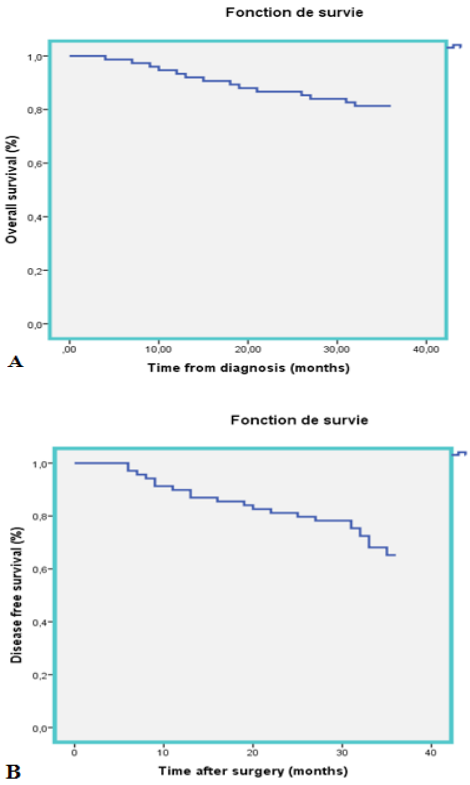

Figure 1. (A) Overall Survival at 3 Years for Non Metastatic Patients, (B) Disease Free Survival at 3 Years for Non Metastatic Patients.

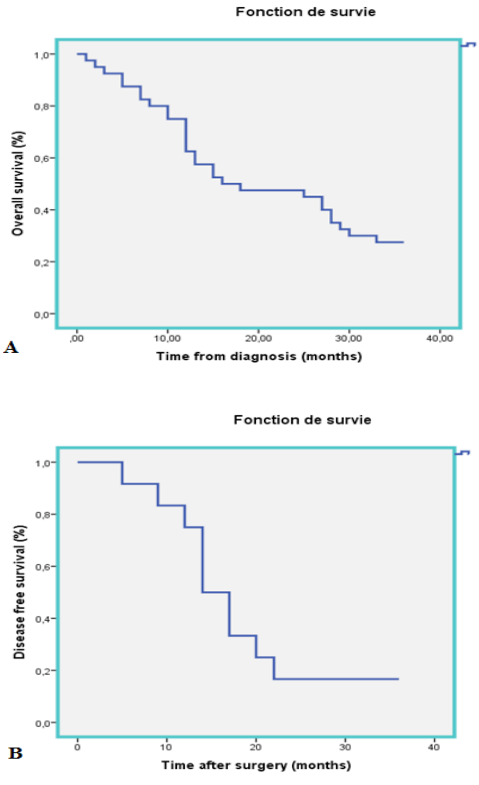

Figure 2. (A) Overall Survival at 3 Years for Metastatic Patients, (B) Disease Free Survival at 3 Years for Metastatic Patients.

Table 1. Description of the Characteristics in the Population Study

Characteristics	%
Median age	46.5
TNBC	13.2
Histological type	
Invasive ductal carcinomas	75.9
Medullar carcinomas	6.9
Invasive lobular carcinomas	6.0
Others	11.2
Grade SBR	
I	1.7
II	41.4
III	50.9
Vascular invasion	58.6
Positive lymph nodes	56.2
Distant metastases	15.5
AJCC staging	
Stage I	3.4
Stage IIA	33.6
Stage IIB	19.0
Stage IIIA	12.1
Stage IIIB	10.4
Stage IIIC	6.0
Stage IV	15.5
Site of metastases	
Liver	28.1
Lung	28.1
Bone	15.7
Brain	15.7
Others	12.4

patients received surgery (90.5%). Twenty sex patients (24.8%) had conservative surgery (tumorectomy with axillary lymph nodes). The remaining patients (75.2%) received radical mastectomy with axillary lymph nodes dissection (Patey type mastectomy) (Table 2). All patients with local disease, who were operated, received optimal surgery with free histological margins.

Twenty three patients with advanced tumors or inflammatory breast cancer have received neoadjuvant chemotherapy before surgery (Table 2). Eight patients (34.8%) had Anthracycline based chemotherapy and fifteen patients (65.2%) received Anthracycline and taxane based protocol. 23.5% of patients had complete response to neoadjuvant chemotherapy according to Sataloff classification (Table 2).

From 75 patients how received adjuvant chemotherapy, 36 patients (48%) had Anthracycline based chemotherapy, 39 patients (52%) had sequential Anthracycline and taxane (Table 2). Eighteen patients with metastatic disease received anthracycline-based regimen in the first line metastatic chemotherapy.

At last follow up, nine patients (9.1% %) experienced local relapse, twenty five patients (25.5%) had metastatic

Table 2. Treatment Modalities and Outcomes

	%
Surgery	
Radical mastectomy	75.2
Conservative surgery	24.8
Chemotherapy	
Neoadjuvant chemotherapy	20.0
Adjuvant chemotherapyPalliative	64.5
chemotherapy	15.5
pCR	23.5
Outcomes	
OS at 3 years	
Localized stages	70.0
Metastatic stage	27.5
DFS at 3 years	
Localized stages	55.6
Metastatic stage	10.3

progression and 29 patients (30%) died. Among 18 patients with metastatic disease at diagnosis, fifteen patients (83%) experienced progression, Two patients (11.5%) had tumoral stability and one patient (5.5%) had partial response.

Three years disease-free survival for patients with localized disease was 55.6 % and the overall 3 years survival was 70 % (Figure 1A,B). Patients diagnosed in a metastatic stage had shorter survival rates than those diagnosed at early stage, OS and DFS at 3 years were 27.5 and 10.3% respectively (Figure 2A,B).

Discussion

This study conducted at the regional centre of oncology Hassan II – Oujda analyzed the epidemiological, clinical, and therapeutic characteristics of TNBC in Moroccan population in Eastern Region. Most of demographic and clinical features of our study group are in accordance with previous findings in the literature (Rais et al, 2012/ Akasbai et al,2011/ Derkaoui et al,2016).

The frequency of TN breast cancer reported in the present work (13.2 %) is consistent with literature data (10-17 %) (Reis-Filho et al,2008). In the Chinese population, approximately 12.9% of breast cancers are TNBC (SU et al,2011). However, in the US, the prevalence of TNBC is about 16% and this difference is explained by the higher prevalence of TNBC in African-American women and Hispanic.

TNBC are associated with a younger age at presentation, having a mean age of 53 years old, compared to 58 years old for other subgroups in a study reported by Dent et al., (2007). In our study population, the median age at diagnosis (46 years) was younger than the average age mostly reported in the United States but may be comparable to the median age in Hispanic triple negative breast cancer patients and in the series conducted in others Moroccan oncology institutes (Reis et al., 2012/ Akasbai et al., 2011/ Derkaoui et al., 2016). Seventeen

(14.6%) patients had an age ≤ 35 years old suggesting that there might be factors that may predispose them to development of this disease. TNBC occurs more frequently in premenopausal women compared with other breast cancer subtypes. In the current study, the majority of our patients were non menopausal (73 %).

This study found 20.7% of family history of breast cancer. Unfortunately, the research of a BRCA1/2 gene mutation was not performed due to its non availability. Given that in the literature 20% of TN breast cancers had mutations of BRCA (Gonzalez et al,2011), the triple - negative type may be used as a criterion for genetic screening (Wrong-Brown et al,2015) to improve the prognosis of this aggressive molecular subtype through a diagnosis at an early stage and the sensitivity of TN breast cancer mutated BRCA1 to PARP inhibitors (Anders et al,2009/ Fong et al,2009).

Clinically, TN patients presented large tumors (towo thirds were > 3 cm) with a high rate pf nodal involvement (42.2%). Histologically, TN tumors are characterized by high frequency of ductal histology (75.9%), greater histological grade (50.9%) and lympho-vascular invasion (58.6%). These results are in accordance with literature data. (Akasbai et al,2011/ Darkaoui et al,2016/ Dent et al., 2007/ Hu et al, 2006/ Liu et al, 2008/ Nofech-mozes, 2009/ Parise et al., 2009/ Reddy et al., 2011/ Zhao et al., 2009).

TNBC constitute a heterogeneous subtype of breast cancer that have a poor clinical outcome. Althrough no approved targeted therapy is available for TNBCs. Both adjuvant treatment and palliative therapy is limited to chemotherapy (Bianchini et al., 2016). TNBC has typically higher rates of chemosensitivity compared with hormone receptor positive breast cancer. It was demonstrated in previous reports (Liedtke et al., 2008) that patients with TNBC have generally higher pathologic complete response (pCR) rates than non-TNBC, and also had better survival compared to TNBC patients who don't achieve pCR. pCR rate in our series was 23.5 % after neoadjuvant chemotherapy , based on the classification of Sataloff. This result is similar to that observed in several other studies (Akasbai et al., 2011/ Darkaoui et al., 2016/ Liedtke et al., 2008/ Wu et al., 2014/ Zhao et al., 2009).

Prognosis for TN cancers remains pejorative comparatively to other subtypes. TNBC tend to exhibit aggressive metastatic behavior (Prat et al., 2014). These tumors respond to conventional chemotherapy but relapse more frequently than hormone receptor positive, luminal subtypes and have a high mortality rate (Rais et al., 2012). According to Dent and al (42.2% against 28%) with a shorter median survival (4.2 years against 6 years) (Dent et al., 2007). In our series, OS was 90 % and 70 % at 1 and 3 years respectively. These results are similar to those described by the study conducted in Houston Texas by Liedtka and al in 1118 patients over a 20 year period (1985-2004): 90 % and 74 % at 1 and 3 years respectively (iedtke et al., 2008).

TN breast cancer is also associated to a higher risk of relapse than other molecular type, especially during the first 2-3 years of follow up (Frères et al., 2010/ Zhang et al., 2014). Dent and al reports that the pattern of distant recurrence was strikingly different between cancer sub groups (Dent et al., 2009) . In patients with triple negative breast cancer, the risk of any recurrence rose sharply from date of diagnosis, peaked 1 to 3 years, and dropped quickly thereafter (Geiger et al., 2011). According Liedtka and al, DFS at 1 and 3 years were 81 and 63% for TNBC in localized stages against 90 and 76 % for other molecular subgroups (Liedtke et al., 2008). In our study population, DFS at 1 and 3 years were 83.3% and 55.6 % respectively.

In metastatic setting, the prognostic is extremely worse. It represented an aggressive entity associated with mortality and very high progression according to the literature data (Arpino et al., 2015/ Wrong-Brown et al., 2015). The 3-year mortality rate for the metastatic stage, in our series, was 72.5 % with a median survival of 16 months. Likewise, the progression occurs early and often (more than 50 % in 1 year and almost 90% in 3 years).

The main barrier in improving survival and developing targeted therapy for patients with TNBC is its molecular heterogeneity (Sung et al., 2016). Several studies revealed that TNBC could be classified into four major subtypes with unique biological pathways for each subtype : basal-like, mesenchymal, immunomodulatory (IM) and luminal androgen receptor (LAR) (Lehmannet al., 2011/ Jézéquel et al., 2015)

Basal-like cancer comprised a large proportion of cases of TNBC. In this subtype, cell cycle and DNA damage response are highly activated, and tumor cells are defects in the homologous recombination repair system (Walkins et al., 2014). Therefore, they are vulnerable to platinum salts or PARP inhibitors that lead to DNA cross-link stand breaks (Hu et al., 2015/ Tutt et al., 2015/ O'shaughnessy et al., 2014). Mesenchymal subtype is characterized by up-regulated gene signatures associated with cell differentiation and growth factor signaling. Various therapeutic approaches have been evaluated to treat this subgroup, such as mTOR inhibitors, given that these cancer cells have activated PI3K/AKT signaling and Eribulin mesylate, may be an option for those tumors by targeting the epithelial to mesenchymal transition (EMT) pathway (Yoshida et al., 2014) . In immunomodulatory subtype, with enriched immune cell process, better treatment outcome have been achieved with cytotoxic chemotherapy (Burstein et al., 2015). Currently, it is unclear if immune checkpoint blockade could be an effective therapeutic approach for this immunomodulatory subtype. In the luminal androgen receptor subtype, the biological pathways involving hormone regulation and estrogen/androgen metabolism are highly expressed. Luminal androgen blockade seems to be an effective targeted therapy for LAR tumors (Gucalp et al, 2013/ Traina et al., 2015).

The classification of TNBC based on genomic data is necessary to deliver optimizing therapies and improve the management of patients with TNBC.

Our results suggest that most TNBC characteristics in Moroccan patients are in accordance with literature data, especially concerning young age at diagnosis, high grade tumors, advanced stage at diagnosis, and short time to relapse(Carey et al., 2007/ Rakha et al., 2007/ Rakha et al., 2008). This subtype carries a poor prognosis and a high incidence of early metastatic recurrence. Furthermore, no

target therapy can be defined up to now in this subtype (Frères et al., 2010). Thus, identification of new target therapy and prediction of tumoral response to various treatments could help in the global understanding of patients affected by this particularly aggressive type of breast cancer.

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