

Inflammatory breast cancer in 210 patients: A retrospective study on epidemiological, anatomico-clinical features and therapeutic results

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Abstract. To report epidemiological and anatomico-clinical features within a retrospective series of inflammatory breast cancer and to evaluate prognostic factors. This retrospective study included 210 Tunisian patients presenting a clinically diagnosed IBC, treated at the Institute Salah Azaiez (ISA) of Tunis, Tunisia, from 2008 to 2013. We collected data on epidemiology, anatomico-clinical and biological features and histologic response to neoadjuvant therapy. Overall and disease-free survivals were calculated by Kaplan-Meier method and compared by log-rank tests and Cox's models were used to identify prognostic factors impacting survival. The 210 IBC patients had a median age of 42 years (24-62) and 15% of them were aged less than 35 years. Mean age at menarche was 13 years and 45% had their 1st childbirth before 23 years. On histology, grades III represented 42% of cases, hormone receptors were negative in 59%, HER2 over-expressed in 32, 25% of our IBC cases had a triple negative profile and Ki-67 was >20% in 53% of cases. High pathological grade III was significantly correlated to TN subtype (58%) (Fisher's exact test, $P=7.5 \times 10^{-3}$). Further, high Ki-67 expression (>20%) was evident in the TN subtype (84%) (Fisher's exact

test, $P=3.7 \times 10^{-4}$). After neoadjuvant therapy (and trastuzumab in 88 and 69% of HER2+ patients, respectively), we observed 49% of objective clinical responses and 35% of pathological complete response (pCR) and >3 axillary lymph nodes were invaded on a resected tumor in 55% of cases. Overall survival (OS) was associated with age at menarche (Wald-test, $P=2.2 \times 10^{-2}$) and metastases at diagnosis (Wald-test, $P=2.4 \times 10^{-2}$). Reaching a pCR was correlated with a better metastasis-free survival (MFS), (Fisher's exact test, $P=3.6 \times 10^{-2}$).

Introduction

Inflammatory Breast Cancer (IBC) is a particular and aggressive variety of breast cancers (BC), with a high metastatic potential. IBC is a rare form of breast cancer representing 2% of BC in Europe and USA lower than that (5-10%) in North Africa and Tunisia (1-3). Diagnosis is based on strict clinical criteria's and this entity is classified as a T4d tumor according to the TNM-UICC (4). IBC is a rapidly evolutive disease, with clinical signs, occurring in less than six months presented by edema, erythema, breast enlargement and 'peau d'orange' (3). Despite advances obtained through a multidisciplinary approach by combining neoadjuvant chemo and/or targeted therapy-mastectomy and loco-regional radiotherapy, prognosis remains poor, with 5-years overall and disease-free survival <50% compared to ~70% for 'neglected' T4b non-inflammatory breast cancers (non-IBCs) (5).

This retrospective study aimed to report the epidemiologic, anatomico-clinical and therapeutic features and to evaluate the role of prognostic factors within an extensive series of 210 Tunisian patients with IBC treated from 2008 to 2013.

Materials and methods

Patients and samples. We collected 210 cases of IBC, treated between 2008 and 2013 at Salah Azaiez Institute (ISA) in

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Tunis, Tunisia. Main inclusion criteria were female sex, with clinically defined and pathologically confirmed IBC (T4d), written informed consent, available formaldehyde-fixed and paraffin-embedded pre-therapeutic diagnostic tumor sample, and comprehensive clinic-pathological data. These features included: Age at diagnosis, TNM stage, pathological plus immunohistochemical data such as histologic type and grade, pathological tumor size, pathological complete response, axillary lymph node status of Estrogen (ER)/Progesterone (PR) receptors, HER2 and Ki-67 status, treatment and clinical outcome. The molecular subtypes of tumors were defined according to immunohistochemistry (IHC). The study was approved by our institutional ethics committee at Salah Azaiez Institute.

Immunohistochemistry analysis. IHC staining of the paraffin blocks was routinely carried out for an immune-peroxidase assay for ER, PR and HER2 (Novocastra, Laboratories, Ltd., Newcastle upon Tyne, UK). The 4 μ m thick tissue sections were cleared in xylene, rehydrated in ethanol and rinsed in distilled water. The slides were then incubated with specific primary antibodies for 30 min at room temperature and the reaction revealed through incubation with hydrogen-peroxide and a chromogen agent diaminobenzidine for 10 min and counterstained with hematoxylin. The slides were then dehydrated and mounted for local pathologists to evaluate the IHC staining of sections from paraffin. Only the nuclear reactivity was taken into account for steroid hormone receptors (HR) to define the presence or absence of ER, PR in <5% of the neoplastic cells. Tumor scores of 0 or 1+ were considered to be HER2 negative (HER2-) whereas those scoring 3+ with strong complete membrane staining were considered to be HER2 positive (HER2+). The tumors with an IHC score of HER2 2+ were assayed with colorimetric *in situ* hybridization (CISH) using (HER2 probe kit; ZytoDot SPEC Molecular Diagnostics, Bremerhaven, Germany). CISH was scored on a standard quantitative scale in which less than six copies of the HER2 gene are classified as negative. The molecular subtypes of tumors were based on ER, PR and HER2 IHC statuses and included luminal A or B (ER+/PR+/HER2-), luminal B HER2+ (ER+/PR+/HER2+), HER2+ (ER-/PR-/HER2+), and triple negative (ER-/PR-/HER2-). The immunohistochemistry detection of Ki-67 (1/200 Novocastra, incubation 1 h at pH9) was carried out as previously described (6).

The revelation was performed using the Dako Flex system (Dako, Agilent Technologies, Inc., Santa Clara, CA, USA) in DAB. Sections counterstained with hematoxylin were independently evaluated by light microscopy by two experienced breast pathologists. Immunoreactivities were scored mainly by measuring the percentage of positive tumor cells, from 0% for the undetectable level to 100% for total homogeneous staining.

Statistical analysis. Data were summarized by numbers and percentages for categorical variables, and median and range for continuous variables. Correlations between tumor groups and clinicopathological features were analyzed using the two-sample t-test or the Fisher's exact test when appropriate. Follow-up was calculated from the date of diagnosis to the date of last news for event-free patients. Metastasis-free survival (MFS) was calculated from the date of diagnosis until the date of first distant relapse. Overall survival (OS) was calculated

from the date of diagnosis until the date of breast cancer-related death. Univariate prognostic analyses for OS and MFS were done using Cox regression analysis (Wald test). All statistical tests were two-sided at the 5% level of significance. Analyses were performed by the survival package (version 2.30) in the R software (version 2.9.1; www.cran.r-project.org/).

Results

IBC epidemiological and clinicopathological features. We analyzed the clinicopathological features about our series of 210 IBC patients with known receptor status treated from 2008 and 2013 at the Salah Azaiez Institute of Tunis are listed in Table I. Their mean age was relatively young at 42 years (24-62) and 15% were younger than 35 years. Mean age at menarche was 13 years. Mean age at first childbirth was at 23 years in 45% of cases and 54% of patients never received oral contraception. On histology, 42% of tumors were grade SBR III, 59% were HR-negative and 32% overexpressed HER2. IHC subtypes were HR-negative/HER2-positive in 27%; HR-positive/HER2-negative in 43%, HR-positive/HER2-positive in 5% and TN in 25% (Fig. 1) while Ki-67 rate higher than 20% was in 53% of cases. Neoadjuvant treatment (NAT) consisted in the sequential protocol (anthracyclines-taxanes in 88%) and 69% of HER2+ cases received trastuzumab. We observed after NAT, 49% of objective clinical responses and 35% of pCR, and most patients (55%) had more than three axillary lymph nodes invaded.

Correlation of clinical outcomes. In Table I, the four subgroups did not differ significantly in age, mean age at menarche, mean age at first birth before 23 years, or contraception status. There were no differences by subtype in clinical node status, lymphatic involvement. However, high pathological grade III was significantly correlated to TN subtype (58%) (Fisher's exact test, $P=7.5 \times 10^{-3}$). Further, high Ki-67 expression (>20%) was evident in the TN subtype (84%) (Fisher's exact test, $P=3.7 \times 10^{-4}$). We found no differences in the distribution of neoadjuvant regimens, clinical response or pCR among the four groups. In term of pCR rate, we observed that the obtention of pCR was correlated with a better MFS (Fisher's exact test, $P=3.6 \times 10^{-2}$). We didn't find any anatomoclinical parameter correlated with pCR (Table II). On univariate analysis concerning 154 patients, poor OS was correlated with younger age at menarche [Wald-test, $P=2.2 \times 10^{-2}$, HR=1.97 (1.10-3.55)] and initial metastases [(Wald-test, $P=2.4 \times 10^{-2}$, HR=17.2 (2.73-108)]. No correlation was found with the other clinicopathological factors or with the four subgroups (Table III). For MFS, univariate analysis concerned 160 non-metastatic (M0) patients at diagnosis and a better MFS was observed in the presence of an objective clinical response to NAT [Wald-test, $P=2.3 \times 10^{-2}$, HR=0.28 (0.10-0.84)] and tended to be associated with the presence of pCR [Wald-test, $P=5.4 \times 10^{-2}$, HR=0.23 (0.05-1.03)]. None correlation, good or poor, was found between a poor MFS and the other clinicopathological factors or the four subtypes (Table IV).

Discussion

We have reported here clinical and biological data from a large cohort of 210 Tunisian patients with IBC treated

Table I. Epidemiological and clinicopathological characteristics of patients (2008-2013).

Characteristics	N=210	HR/HER2 status				P-value
		HR-/HER2+	HR+/HER2-	HR+/HER2+	TN	
Age, years, mean (range)	42 (24-62)	42 (27-62)	42 (24-61)	41.5 (31-51)	42 (28-60)	0.64
<35	32 (15%)	6 (12%)	12 (14%)	2 (25%)	11 (22%)	0.36
≥35	175 (85%)	46 (88%)	71 (86%)	6 (75%)	38 (78%)	
First menarche, mean year (range)	13 (9-18)	13 (10-18)	13 (9-18)	12 (11-15)	13 (10-16)	0.47
First child, years						
<23	68 (45%)	16 (40%)	30 (50%)	3 (50%)	16 (43%)	0.79
≥23	84 (55%)	24 (60%)	30 (50%)	3 (50%)	21 (57%)	
Contraception						
No	97 (54%)	29 (63%)	43 (57%)	4 (50%)	16 (39%)	0.13
Yes	82 (46%)	17 (37%)	32 (43%)	4 (50%)	25 (61%)	
Pathological type						
Ductal	209 (100%)	52 (98%)	83 (100%)	9 (100%)	49 (100%)	0.57
Mixed	1 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	
Pathological grade						
I-II	100 (58%)	24 (52%)	50 (68%)	5 (100%)	18 (42%)	7.50x10 ⁻³
III	73 (42%)	22 (48%)	24 (32%)	0 (0%)	25 (58%)	
HR						
Negative	114 (59%)	53 (100%)	12 (14%)	0 (0%)	49 (100%)	<1.0x10 ⁻⁶
Positive	80 (41%)	0 (0%)	71 (86%)	9 (100%)	0 (0%)	
HER2						
Negative	133 (68%)	0 (0%)	83 (100%)	0 (0%)	49 (100%)	<1.0x10 ⁻⁶
Positive	64 (32%)	53 (100%)	0 (0%)	9 (100%)	0 (0%)	
Ki67, %						
<20	51 (47%)	15 (44%)	30 (65%)	2 (67%)	4 (16%)	3.70x10 ⁻⁴
≥20	57 (53%)	19 (56%)	16 (35%)	1 (33%)	21 (84%)	
Nodal involvement						
≤3 nodes	66 (45%)	22 (61%)	23 (38%)	3 (50%)	14 (38%)	0.12
>3 nodes	80 (55%)	14 (39%)	37 (62%)	3 (50%)	23 (62%)	
TNM						
N0	10 (5%)	1 (2%)	3 (4%)	0 (0%)	3 (6%)	0.68
N1-3	198 (95%)	52 (98%)	79 (96%)	9 (100%)	46 (94%)	
TNM						
M0x	184 (88%)	45 (85%)	73 (88%)	8 (89%)	46 (94%)	0.5
M1	25 (12%)	8 (15%)	10 (12%)	1 (11%)	3 (6%)	
Neoadjuvant treatment						
No	203 (12%)	8 (15%)	8 (11%)	1 (11%)	4 (8%)	0.6
Yes	179 (88%)	45 (85%)	63 (89%)	8 (89%)	45 (92%)	
Trastuzumab (of HER2+ patients)						
No	20 (31%)	16 (30%)	0 (0%)	2 (22%)	0 (0%)	1
Yes	45 (69%)	37 (70%)	0 (0%)	7 (78%)	0 (0%)	
Clinical response						
No	67 (51%)	20 (57%)	28 (51%)	3 (60%)	14 (48%)	0.89
Yes	64 (49%)	15 (43%)	27 (49%)	2 (40%)	15 (52%)	
Pathological complete response						
No	66 (65%)	18 (67%)	28 (60%)	4 (80%)	13 (68%)	0.79
Yes	36 (35%)	9 (33%)	19 (40%)	1 (20%)	6 (32%)	

Table I. Continued.

Characteristics	N=210	HR/HER2 status				P-value
		HR-/HER2+	HR+/HER2-	HR+/HER2+	TN	
Molecular subtypes						
HR-/HER2+	53 (27%)					
HR+/HER2-	83 (43%)					
HR+/HER2+	9 (5%)					
TN	49 (25%)					

HR, hormonal receptor; HER2, human epidermal growth factor receptor 2; TNM, tumor-nodes-metastasis; TN, triple negative.

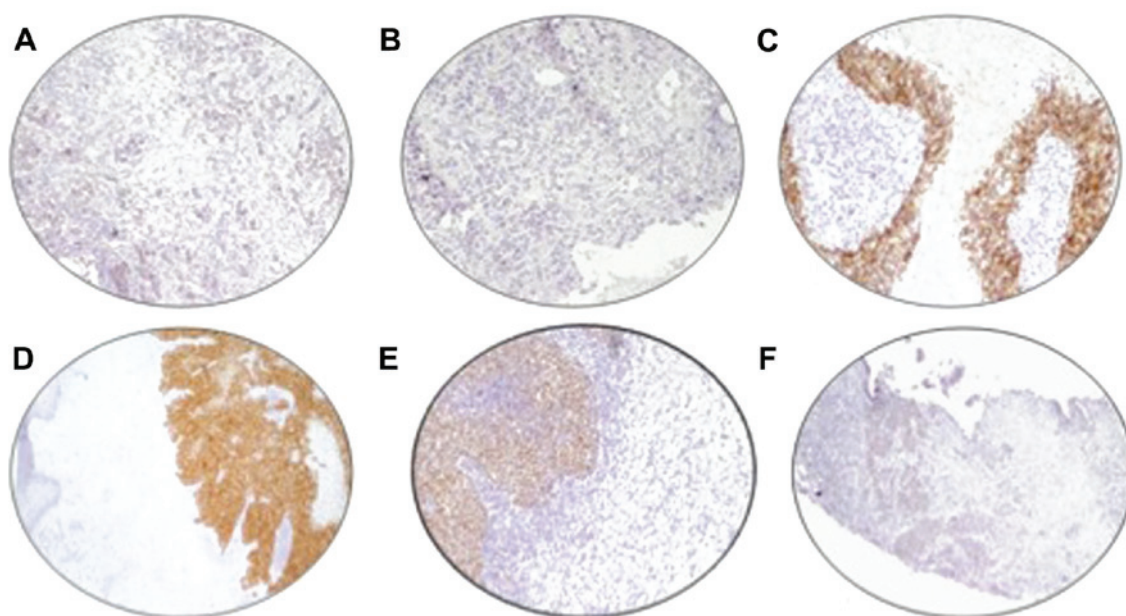


Figure 1. Immunohistochemistry in inflammatory breast cancer. (A and B) Absence of expression of ER and PR in IBC tumor cases. (C) Strong expression of HER2 in IBC cases (Score 3). (D and E) Expression of ER and PR in 100% of tumors cells in IBC cases. (F) Absence of expression of HER2 in IBC cases (magnification, x200). ER, estrogen receptor; PR, progesterone receptor; IBC, inflammatory breast cancer; HER2, human epidermal growth factor receptor 2.

from 2008 to 2013 and classified as T4d by using stringent diagnosis criteria, treated at the Salah Azaiez Institute of Tunis, Tunisia, a comprehensive center, having a huge clinical expertise in the field of IBC for >50 years (7,8). The clinical IBC entity represents 5-7% of BCs in Tunisia and its frequency was readjusted by applying more strict diagnosis criteria, compared to the higher (30-55% of BCs) reported in the seventies by Mourali team (1,8,9). In North Africa, Algeria, Morocco and Tunisia constitute a cluster with high IBC incidence compared to occidental countries, where this entity account for <2% of BCs (7,10,11). A correct diagnosis of IBC is crucial and should be based on an amnesic evolution of symptoms in less than 3 months, combined with the presence of local inflammatory and/or regional, i.e., erythema, edema, skin thickness ('peau d'orange'), involving more than 1/3 of breast (3). It is essential to differentiate IBC from the locally advanced non-IBC (LABC) and neglected BC that occur in older patients (>70 years), with evolution within six months or more and a frequent delay in consultation and

diagnosis. This confusion between IBC and LABC remains the reported studies from occidental countries, wherein IBC series, the average age is ten years or more, higher than that observed in Tunisia, over 55 years (12). In the Surveillance, Epidemiology and End Results (SEER) series (12), including a retrospective cohort collected from 1992-2002, the older age reported for patients is probably biased by the absence of documented diagnostic reviews and the inclusion of elderly patients probably presenting a higher enrichment in LABCs than IBC entities (13). The same age difference between occidental and North African series, exceeding ten years for mean age at IBC diagnosis (55 vs. 42 years) is observed in the series from the MD Anderson Cancer Center and those we studied (per the M.D Anderson IBC Registry) (7). Most IBC epidemiologic and risk factors data were previously reported in Tunisian, US and French studies (7,8,14,15). Retrospective data suggest as risk factors, a young age (<12 years old) at 1st menarche and first birth between 20-23-year-old (7,8,14,16). A frequent association between IBC, pregnancy and a

Table II. Pathological complete response and clinicopathological features.

Characteristics	pCR		P-value
	No	Yes	
Age, mean year (range)	42 (28-61)	42 (24-60)	0.99
Age, <35 years (%)	17	19	0.79
First menarche, mean year (range)	13 (9-18)	13 (10-18)	0.93
First child, <23 years (%)	49	52	1.00
Contraception, no (%)	39	39	1.00
Pathological type, ductal (%)	98	100	1.00
Pathological grade, III (%)	41	52	0.37
HR, negative (%)	52	66	0.29
HER2, positive (%)	35	31	0.67
Ki67, ≥20% (%)	36	52	0.27
TNM, N1-3 (%)	94	91	0.35
TNM, M0x (%)	94	92	0.70
5-year MFS, % (IC ₉₅)	37 (15-91)	48 (12-100)	3.6x10 ⁻²

pCR, pathological complete response; HR, hormonal receptor; HER2, human epidermal growth factor receptor 2; N, nodes; M, metastasis; MFS, metastasis free survival.

Table III. Univariate prognostic analysis for overall survival.

Characteristics	Univariate analysis		
	N	HR (95% CI)	P-value
Age	153	1.00 (0.92-1.10)	0.93
Age, <35 vs. ≥35 years	153	1.30 (0.15-11.2)	0.81
First menarche	140	1.97 (1.10-3.55)	2.2x10 ⁻²
First child, <23 vs. ≥23 years	115	1.77 (0.29-10.8)	0.54
Contraception, yes vs. no	134	3.59 (0.40-32.3)	0.25
Pathological type, ductal vs. other	154	0.00 (0.00-Inf)	1.00
Pathological grade, III vs. I-II	132	0.65 (0.10-4.18)	0.65
HR, positive vs. negative	147	0.37 (0.04-3.16)	0.36
HER2, positive vs. negative	148	1.13 (0.20-6.25)	0.89
Molecular subtypes			
HR-/HER2+ vs. HR+/HER2-	147	1.42 (0.20-10.1)	0.98
HR+/HER2+ vs. HR+/HER2-		0.00 (0.00-Inf)	
TN vs. HR+/HER2-		0.98 (0.13-7.14)	
Ki67, ≥20% vs. <20%	84	0.31 (0.03-3.53)	0.34
TNM, N1-3 vs. N0	153	9.6E+06 (0-Inf)	1.00
TNM, M1 vs. M0x	154	17.2 (2.73-108)	2.4x10 ⁻²
Clinical response, yes vs. no	104	0.00 (0.00-Inf)	1.00
pCR, yes vs. no	78	1.40 (0.09-22.5)	0.81

Concerned 154 patients with an available survival information. HR, hormonal receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; N, nodes; M, metastasis; pCR, pathological complete response; HR, hazard ratio; CI, confidence interval.

prolonged period of breastfeeding, exceeding 24 months was also reported (17). In our series, mean age at menarche has occurred at 13 year-old, and first childbirth was before 23 years in 45% of cases.

In our series, we found that clinical IBC aggressiveness is associated, compared to 'classical BC' with a higher frequency of HR-negative, HER2+ and TN subtypes (59, 32 and 25% of cases, respectively). Such data are in agreement with those reported

Table IV. Univariate prognostic analyses for metastasis-free survival.

Characteristics	Univariate analysis		
	N	HR (95% CI)	P-value
Age	160	0.98 (0.94-1.02)	0.32
Age, <35 vs. ≥35 years	160	0.85 (0.37-1.97)	0.70
First menarche	145	1.07 (0.89-1.28)	0.49
First child, <23 vs. ≥23 years	120	1.81 (0.84-3.94)	0.13
Contraception, yes vs. no	142	1.07 (0.50-2.29)	0.86
Pathological type, ductal vs. other	161	0.00 (0.00-Inf)	1.00
Pathological grade, III vs. I-II	143	1.27 (0.62-2.57)	0.51
HR, positive vs. negative	154	1.11 (0.54-2.30)	0.77
HER2, positive vs. negative	155	0.75 (0.33-1.67)	0.48
Molecular subtypes			
HR-/HER2+ vs. HR+/HER2-	154	0.83 (0.33-2.11)	0.89
HR+/HER2+ vs. HR+/HER2-		0.74 (0.09-5.79)	
TN vs. HR+/HER2-		1.17 (0.51-2.69)	
Ki67, ≥20 vs. <20%	89	1.87 (0.63-5.54)	0.26
TNM, N1-3 vs. N0	160	1.52 (0.21-11.3)	0.681
TNM, M1 vs. M0x	-	-	-
Clinical response, yes vs. no	110	0.28 (0.10-0.84)	2.3x10 ⁻²
pCR, yes vs. no	89	0.23 (0.05-1.03)	5.4x10 ⁻²

Concerned 160 non-metastatic (M0) patients at diagnosis. HR, hormonal receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative; N, nodes; M, metastasis; pCR, pathological complete response; HR, hazard ratio; CI, confidence interval.

in previous studies (18,19) where high HER2 positive and TN frequencies (>30 and >20%, respectively) confer a bad prognosis to IBC, despite a higher rate of clinical and histological response to chemo and targeted therapy. IBC aggressiveness is also confirmed in our series, by an increased average Ki-67 expression (>20%), a nuclear non-histone protein present at low levels in quiescent cells but increased in proliferating cells (20,21). Masuda *et al* (22) showed that there was no significant difference in clinical outcomes in IBC between ER/PR-positive/HER2-positive, ER/PR-positive/HER2-negative, and ER/PR-negative/HER2-positive subtypes. In our series, TN subtype was associated with a high pathological grade (III) comparatively to the other subtypes. In a retrospective study of 240 patients, treated at the MD Anderson Cancer Center in six prospective trials between 1973 and 2000, a 25% pCR rate was observed after FEC-paclitaxel vs. 10% after FEC alone (23,24). In the same study of Cristofanilli *et al* (24), pCR was shown to be a strong predictor for prognosis and a better DFS tended to be associated with the presence of pCR ($P=6 \times 10^{-2}$). The same was concluded in our study with 35% of pCR in patients receiving paclitaxel plus anthracycline-containing regimen and was found associated with a better MFS ($P=3 \times 10^{-2}$).

Histologic grades and involvement of axillary nodes are, like in 'classical BC', others important prognostic factors, for the risk of recurrence and/or overall and disease-free survival (25,26).

Multimodality therapy with systemic neoadjuvant chemotherapy and/or targeted therapy, followed by loco-regional surgery and radiotherapy, became the standard approach and improved IBC survival (27). Following previous studies,

we also observed that for IBC management in Tunisia, the introduction of taxanes and trastuzumab in the neoadjuvant setting improves the prognosis of IBC. The introduction of taxanes showed benefit in metastatic breast cancer (11,22) and the administration of biological therapy with the monoclonal antibody trastuzumab was recommended for a patient with HER2-positive disease (22). While anthracycline- and taxane-containing regimens are most commonly prescribed, the optimal chemotherapy regimen and sequence of agents have yet to be defined (28). Multimodality treatment is the standard treatment for IBC, and induction of chemotherapy followed by surgery and radiotherapy seems to be the best sequence.

To our knowledge, our study is the first to examine IBC by clinicopathological characteristics and by subtypes based on hormonal and HER2 status in a large series of patients from one institution in a short period of 5 years with the same protocol treatment notably the introduction of target therapy. The limits of our study were the retrospective nature and associated biases such as missing data with 20% of patients lost for follow-up and the insufficiency of the number of patients per subtype for analysis, resulting in limited statistical power.

In conclusion, our study confirms, the younger age of Tunisian IBC patients, compared to US and European series, the poor prognosis histo and immunohistochemical features with the predominance of HR-, HER2+ and TN subtypes. These characteristics could explain the poor OS and MFS observed lower than 50 and 40%, respectively, despite the multidisciplinary approach used for combined medical and

loco-regional treatment. Identify new therapeutic targets to treat IBCs more efficiently constitutes a priority and a real hope for a patient.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MaM conceived the project. MaM, NM, KR, AG and SA contributed by providing the data, and conceived and designed experiments. MaM, PF and FB analyzed the data. MaM and HB wrote the manuscript. HB, NM, DB, MC, AG and MoM revised the manuscript critically for important intellectual content, and MC, DB and MoM gave final approval of the version to be published.

Ethics approval and consent to participate

The present study was approved by the Institutional Ethics Committee of Institut Salah Azaiez (approval no. 1646).

Patient consent for publication

Patients gave their informed consent for being included in the hospital breast cancer database for research purpose and publication.

Competing interests

The authors declare that they have no competing interests.

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