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Review

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Inflammatory Breast Cancer: A Literature Review

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Abstract

The multidisciplinary management of inflammatory breast cancer (IBC), which is the most aggressive form of breast cancer due to its rapid proliferation, has changed over the past three decades thanks to advances in medical treatments that represent the basis of treatment, without eliminating the use of locoregional treatments including surgery and radiotherapy in the localized stages. The molecular profile determination of IBC allows the orientation towards new targeted therapeutic strategies with an impact on survival.

Keywords: Inflammatory breast cancer; Treatment; Molecular profile

Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive clinicopathological entity of breast cancer. It represents 1% to 6% of all cases of breast cancer [1]. The first description of IBC in the scientific literature was published in 1814 by Sir Charles Bell [2], then in 1938 the terms "true IBC" and "primary IBC" were coined to distinguish what is now considered "IBC" and "secondary IBC". Secondary IBC was defined by secondary changes in the breast or recurrence of breast cancer [3]. The incidence of IBC varies considerably in different regions around the world. Studies have shown that IBC is more common in North Africa than in other parts of the world; the most recent estimates suggest that it represents 5% to 7% of all breast cancers in Tunisia [4], 4% to 5 % in Morocco [5], while in Egypt it has a rate of 11% [6]. IBC is also characterized by rapid progression and higher metastatic potential [2]. The 5-year survival of patients with this cancer type is low compared to other breast cancers [7]. However, the combinations of neoadjuvant chemotherapy, surgery and radiotherapy led to an improvement in prognosis. Optimal management of IBC requires coordination between oncologists, surgeons and radiation therapists [2]. The present study aims to provide an update on clinical, molecular and therapeutic specificities of IBC.

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Literature Search

The reviewed studies were identified through PubMed, Google Scholar and Science Direct research using the combination of the following terms for both French and English languages: inflammatory breast cancer; breast cancer; neoadjuvant chemotherapy; clinical presentation, molecular profile and treatment. For each study, abstracts was read and included based on its relevance and had to meet the following criteria: 1) To be focused on IBC; 2) To consider new biomarkers of IBC; 3) To be majorly based on the recent studies.

Accordingly, selected studies were then read and evaluated for inclusion. Only studies on breast cancer survivor, behavior or quality of life were included. Given that this pathology is rare, references of the selected studies were also reviewed and considered for inclusion. At the end, only 50 articles and abstracts were included in the examination.

What Are IBC's Risk Factors?

Currently, there are no established risk factors for IBC. However, many epidemiological studies clarify the characteristics of IBC that have been studied. The most important suspected risk factors associated with this disease are: black race, body mass index (BMI), age and region [8]. In fact, African-American women have an IBC incidence at least 50% higher than Caucasian [9]. Also, high BMI and young age at the emergence of this disease have been identified as risk factors [8]. Additionally, North African countries have reported a higher percentage of IBC cases than other regions. Historical reports from Tunisia had recorded the highest incidence in the word with 50% of newly diagnosed cases of breast cancer [10]. The use of a more uniform approach in classification criteria had led to a better distinction between IBC and neglected locally advanced breast cancer. The estimated incidence in this region is now comprised between 5% and 10% [4]. Also, some recent reports suggested that the westernization of the population habits had played a role of the change observed of the global profile of breast cancer in North Africa.

IBC Diagnosis Criteria

At present, there are no definitive molecular or pathological

Table 1. Comparison Between Studies Concerning Molecular Classification of Inflammatory Breast Cancer Subtypes [15-19]

	Francois et al 2005 [15] (%)	Nabila et al 2011 [16] (%)	Neyran et al 2015 [17] (%)	Tina et al 2016 [18] (%)	Sarah et al 2017 [19] (%)
Dermal lymphatic emboli					
Present	70	-	-	-	-
Absent	30	-	-	-	-
Type					
Ductal	89	88	84.9	86	81.26
Lobular/other	11	11.9	11.9	14	18.75
Grade					
I/II	35	63.3	29.5	30	12.5
III	65	36.7	53.6	70	81.5
Subtypes					
Luminal		72.3	52.5	30	
Triple negative		17.7	20.5	26	31.25
HER2		9.9	24.4	44	18.75

diagnosis criteria for IBC. Therefore, the diagnosis is entirely based on clinical symptoms such as the rapid onset of signs like erythema and edema of the breast skin (orange peel), i.e. the possibility of misleading between IBC and benign bacterial infections such as mastitis is high, that is why it is important to note that IBC is not usually associated with symptoms of infection such as fever [11].

Clinical criteria

According to the American Joint Committee on Cancer, The New Edition (seventh) AJCC Staging System for Breast Cancer, the signs and symptoms required for IBC diagnosis are erythema occupying at least one-third of the breast, edema and/or orange peel of the breast, and/or a warm breast. A palpable mass is present in only one-third of cases. The onset of these signs and symptoms should be rapid; the length of the time taken during its initial presentation should be 3 months [12]. These criteria are important to distinguish the skin changes of IBC (T4d) from the skin changes associated with a neglected noninflammatory breast tumor (T4a-c).

Pathological criteria

IBC is not considered as a specific histological subtype of breast carcinomas, and it has no specific diagnostic pathological criteria. Most IBC are ductal carcinoma and had a high histological nuclear grade [13]. About 17 % to 30% of IBC cases are triple negative and 18% to 44% are epidermal growth factor receptor 2 (HER2) positive [14] (Table 1, [15-19]). The combination of histopathological breast data with the characteristic clinical features may confirm the diagnosis of IBC. Dermal lymphatic emboli are present in approximately 75% of cases. There is no direct correlation between the presence, number, or size of emboli and the degree of redness of the skin in patients with IBC [20]. Although cutaneous pathological evidence of nodal invasion is not considered as a definitive diagnostic endpoint for IBC, skin biopsy is recommended in case of suspicion as an aid to diagnosis, and the absence of dermal emboli does not exclude the diagnosis [21].

Molecular criteria

Studies have suggested that IBC does not have a specific molecular signature. Recently, they have identified *in vivo* and *in vitro* genes that can contribute to the aggressive phenotype of IBC (Table 2) [15].

In addition, authors have reported that cell proliferation genes are more strongly associated with IBC than non-IBC; and those genes for tumor processes, including the signaling pathway associated with inflammation, cellular transformation, and angiogenesis, are altered more in IBC than in non-IBC [22]. About 80% of IBC tissue samples are characterized

Table 2. The Genes Associated to IBC Phenotype

Cluster	Genes
Estrogen receptor (ER)	*ESR1*, *GATA3*, *XBP1*, *HNF3A*, *MUC1* and *CCND1*
ERBB2	*ERBB2* and *GRB7*
Basal	*KRT5* and *TRIM29*

by a loss of WNT1-inducible-signaling proteins 3 pathway (WISP3) which are cysteine-rich proteins and which play a role in inhibiting the invasive potential and the angiogenesis of IBC cells in tissue cultures and animal models [23]. Furthermore, lymphovascular emboli of IBC are characterized by overexpression of a number of genes, such as homologues of the C- guanosine triphosphatase family (*RhoC-GTPase*) and *E-cadherin* [23, 24]. IBC cells are characterized by overexpression of *E-cadherin*, which is essential for cell adhesion, tumor emboli formation, and progression of metastasis which implies poor prognosis [25, 26]. In addition, *RhoC-GTPase* is overexpressed in 90% of IBC tumors compared to 38% of non-IBC tumors. Indeed, *RhoC-GTPase* plays a critical role in the metastatic behavior of IBC by increasing all aspects of metastatic processes such as motility and cell invasion, cytoskeletal assembly, and cell adhesion [26]. However, all the above mentioned markers do not distinguish IBC from non-IBC and fail to explain the specific pathophysiology of IBC. The latter had a significantly higher expression of *Ki-67* and genes associated with metabolic pathways and lipid signaling [27]. An *in vitro* study revealed that epithelial-mesenchymal transition (EMT) is associated with IBC cell line cell migration and invasion [28], and much emphasis has been placed on determining the role of EMT in tumor progression and metastasis in IBC [29]. Other studies have reported that the epidermal growth factor receptor (EGFR) that is involved in the pathway of tumor growth and IBC metastasis through EMT and EGFR expression is an independent factor in prognosis [30].

Radiology in IBC

Significant advances in imaging techniques have improved the diagnosis and classification of IBC, therefore, in women with suspected IBC, imaging the primary breast tumor helps to facilitate diagnosis, biopsy, evaluate the response to treatment but also to provide screening of the contralateral breast [12, 31]. It is well documented that 20% to 30% of newly diagnosed IBC women have distant metastases at the time of diagnosis; imaging may also be useful in identifying these distant metastases [32].

Mammography is the current standard imaging. The optimal compression can be limited by the pain related to breast's inflammation. As in other types of breast cancer, mammography can reveal several changes such as skin thickening, stromal infiltration, architectural disorganization or diffuse increase in density. The tumor mass is absent in 25% of cases [33].

Ultrasound also provides valuable information about regional lymph nodes, including axillary nodes and supraclavicular nodes [34].

Breast magnetic resonance imaging (MRI), has the highest sensitivity in the detection of primary mammary parenchymal lesions and global skin abnormalities. It's also helpful to guide skin biopsies. On MRI, the thickening of the skin is visible in 90% to 100% of patients with IBC; thus, MRI can be a useful tool for differentiating patients with IBC from patients with locally advanced (non-IBC) cancer. A study from the University of Texas MD Anderson Cancer demonstrated that for IBC, breast MRI identifies all breast parenchymal lesions, while mammography identifies 80% of breast parenchymal lesions and ultrasound identifies 95% of lesions of the mammary parenchyma [35]. Because of its high sensitivity, MRI is highly recommended in patients suspected of IBC and is a useful method for monitoring the response to chemotherapy (Fig. 1).

Treatment

Historically IBC was treated by surgery and/or radiotherapy. The 5-year overall survivals were under 5% [36]. Before 1950, the median survival for patients treated by mastectomy was 19 months, none of the patients survived to 5 years [37]. The use of definitive radiotherapy without surgery showed a 5-year survival rate without recurrence and overall survival rate of 17% and 28%, respectively. The combination of surgery and radiotherapy leads to the improvement of overall survival [38]. The introduction of systemic chemotherapy showed additional survival benefit. The trimodal therapy including chemotherapy, surgery and radiotherapy became the standard of care of IBC. In December 2008, The First International Conference on Inflammatory Breast Cancer developed guidelines for the management of IBC [39].

For metastatic disease, the treatment is based on chemotherapy with/without target therapy. Surgery and radiotherapy are used only to control palliative symptoms (Fig. 2).

Chemotherapy

Due to the rarity of the disease, there is no prospective randomized clinical trial for IBC. Available data come from retrospective series, centers experiences and cohorts in randomized trials. In a study from MD Anderson with 178 IBC patients, anthracycline-based chemotherapy followed by local treatment with irradiation, with or without mastectomy led to an improvement of overall survival rate at 5 years to 40% and 10 years survival to 33% [40]. The integration of taxanes into chemotherapy has shown efficacy in the neoadjuvant treatment of IBC. In a cohort study of 68 patients with IBC in two prospective randomized trials, treatment with either three cycles of FEC (cyclophosphamide, epirubicin and 5-fluorouracil), then taxanes followed by surgery, adjuvant therapy, and radiotherapy have resulted in overall 5-year survival rate of 44% and 10 years survival of 32% [41]. The standard of care in neoadjuvant is a sequential regimen using anthracyclines then taxanes.

Targeted therapy

In IBC, HER2 is overexpressed in 36% to 60% of IBC cases [42]. For the treatment of localized breast cancer, only monoclonal antibodies for HER-2 have been shown to be efficacious. In the NOAH study, which includes IBC patients, the addition of trastuzumab to systemic therapy significantly improved the pathological complete response (pCR) rates (38% versus 19%, P = 0.001) and event-free survival (3-year event-

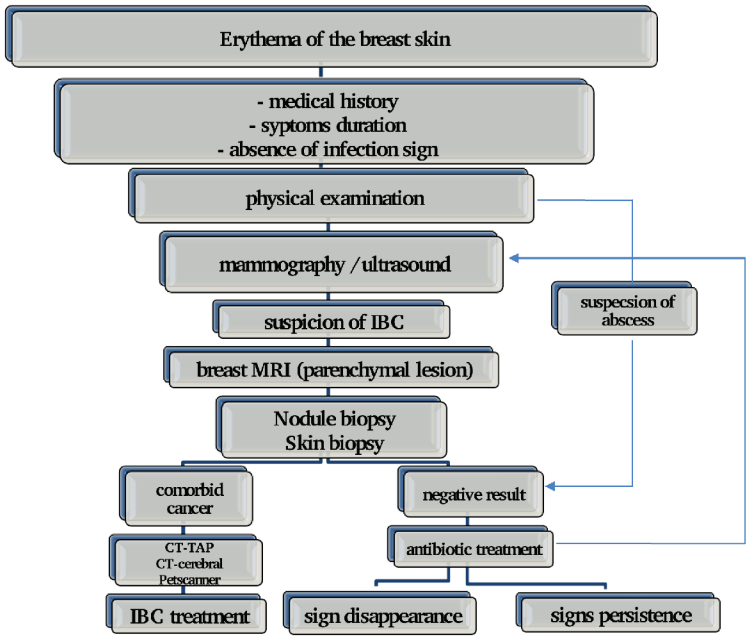

Figure 1. Approach upon IBC diagnosis.

free survival 71% versus 56%, HR 0.59, P = 0.013) [43]. The use of double blocking with trastuzumab and pertuzumab in the neoadjuvant sitting had improved the rate of pCR. In the NeoSphere and TRYPHAENA trials the pCR rate was 45.8% and 50.7% respectively [44, 45]. The studies with lapatinib, a tyrosine kinase inhibitor of EGFR and HER-2, failed to demonstrated efficacy [46]. Moreover, the anti-angiogenic therapies (bevacizumab and semaxanib) have shown only modest clinical effect in the clinical trials [47].

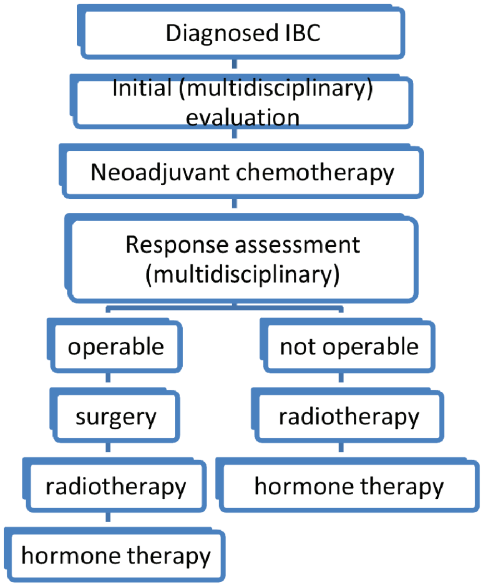

Figure 2. Diagram of therapeutic strategy of inflammatory breast cancers.

Surgery

Surgery plays an important role in the multimodal treatment of IBC. The standard procedure is a radical mastectomy with axillary dissection. The involvement of axillary lymph nodes is noted in 55% to 85% in IBC at the time of diagnosis [48]. The purpose of the surgery must be complete resection of the residual disease. Conservative surgery and sentinel lymph node biopsy must be avoided [49]. Several studies have demonstrated that pCR predicts of higher survival as well as good local control [50]. In the metastatic disease, surgery is indicated only for uncontrolled hemorrhage.

Radiotherapy

The standard approach for patients with IBC after mastectomy is radiotherapy. There are no specific doses for IBC. To evaluate the most effective radiation dose effect, 32 patients who were treated with radiotherapy twice a day at a total dose of 60 Gy were compared with the results for the 39 patients treated twice daily for a total dose of 66 Gy. A better rate of locoregional control was achieved in the high-dose group than in the standard-dose group (84% vs. 58% at 5 years, 77% vs. 58% at 10 years) [51]. Short-term and long-term analyses of toxic reactions to this treatment were examined, the higher risk of developing late complications was observed in the high-dose group than in the standard-dose group (29% vs. 15%, respectively). This approach is not yet validated [52].

Preoperative radiotherapy trials have shown that the rate of complications is higher in patients who receive preoperative radiotherapy and the risk of postoperative complications is dose-dependent [53]. In MD Anderson preoperative radio-

therapy trials evaluating local 5-year control and non-distant metastasis-free survival for 42 patients with IBC, the rates were 75% and 20%, respectively, and eight patients survived without distant metastasis for more than 40 months (unpublished data). However, the higher rate of complications has been reported in patients who received preoperative radiation. Preoperative concomitant chemoradiotherapy is not indicated in breast cancer as in other cancers [54].

Conclusions

The diagnosis of IBC remains above all a clinical diagnosis supported by a histological evidence of infiltrating carcinoma, and the therapeutic approach can only be multidisciplinary. The ability to identify new targeted therapies allows us to control the aggressive phenotype of IBC. Molecular biology and genomics are very likely to play an important role in the diagnosis and management of IBC.

Conflict of Interest

The authors have no conflict of interest to declare.

Author Contributions

All authors have been involved in the process of writing and have approved the final manuscript.

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