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Review

# Inflammatory breast cancer and chest wall disease: The oncologist perspective

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ABSTRACT

Chest wall inflammatory and lymphangitic breast cancer represents a clinical spectrum and a model disease. Inflammation and the immune response have a role in the natural history of this special clinical presentation. Preclinical models and biomarker studies suggest that inflammatory breast cancer comprises a more important role for the tumour microenvironment, including immune cell infiltration and vasculogenesis, especially lympho-angiogenesis. Across this clinical continuum of the chest wall disease there is an important role of the inflammation cascade. The activation of mature dendritic cells (DCs) through toll like receptors (TLRs) or by inflammatory cytokines converts immature DCs into mature DCs that present specific antigen to T cells, thereby activating them. Maturation of DCs is accompanied by co-stimulatory molecules and secretion of inflammatory cytokines polarizing lymphocytic, macrophages and fibroblast infiltration. It is unknown whether immune cells associated to the IBC microenvironment play a role in this scenario to transiently promote epithelial to mesenchymal transition (EMT) in these cells. Immune and microenvirnment factors can induce phenotypic, morphological, and functional changes in breast cancer cells. We can hypothesize that similar inflammatory conditions in vivo may support both the rapid metastasis and tight tumor emboli that are characteristic of chest wall disease and that targeted anti-inflammatory therapy may play a role in this patient population. The current review will review biological and clinical data of this special condition.



## Introduction

Inflammatory breast cancer (IBC) is an uncommon entity that affects about 2.0–2.5% of women diagnosed with breast cancer [1]. The clinical presentation consists of diffuse erythema, rapid enlargement of the breast, skin ridging, and a characteristic “peau d'orange” appearance of the skin secondary to dermal lymphatic involvement [2,3]. Overall survival is shorter than with non-IBC [4,5]. Many patients relapse and progress locally to a lymphangitic spread to chest wall and to metastatic disease. Lymphangitic breast cancer (LBC) is pathologically characterized by high vascularity, skin lymphatic vessels infiltration and increased micro vessel density because of high expression of angiogenic factors [3]. Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis and is involved in endothelial and tumor cell growth and motility and blood vessel permeability [6]. Extensive vascular involvement of LBC makes this tumor especially amenable to antiangiogenic treatment. Use of bevacizumab, a VEGF-targeting monoclonal antibody, resulted in improved progression-free survival and response in patients with advanced breast cancer in several randomized phase 3 trials [7–12].

## Epidemiologic features

Inflammatory breast cancer is the most aggressive entity of breast cancer and comprises 2.5% of all breast cancers [1]. The median overall survival among women with IBC is less than 4 years even with multimodality treatment options. However, an increasing survival in recent years has been noted with improvement of chemotherapeutical management [2]. The incidence of IBC appears to be increasing, particularly among Caucasian women. Women with IBC typically present at a younger age than non IBC [2]. Four large population-based studies have reported a higher incidence in young African-American women, and they had a worse survival compared to Caucasian women. The cause of racial

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disparities has not yet been elucidated [2–5]. It has been noted that Hispanic women had the youngest mean age of onset (50.5 years) compared with 55.2 years for African-American women and 58.1 years for Caucasian women [2]. Data on risk factors is limited: a high body mass index (BMI) is positively associated with a diagnosis of IBC compared to non IBC [2]. Several other risk factors have shown some indication of being associated with the diagnosis of IBC (e.g. younger age at live first birth), but further studies are warranted [2]. In contrast, higher level of education was associated with reduced risk of ER-positive IBC, more so than for non-inflammatory breast cancer. Advanced age at first birth was associated with reduced risk of ER-negative IBC. Several studies have reported that IBC constitutes a larger proportion of breast cancers in low income countries than Western countries [13,14]. Managing IBC in low income countries poses a different set of challenges including access to screening, stage at presentation, adequacy of multidisciplinary management and availability of therapeutic interventions [15].

## Biological features of disease

IBC is characterized by less hormone receptor expression compared to non-inflammatory breast cancer (NIBC), which has been associated with a more aggressive clinical course and decreased survival [16,17]. Up to 83% of IBC tumors lack estrogen receptor (ER) expression compared with other forms of locally advanced breast cancers which are mostly ER positive [18]. Analysis of 2000 patients with IBC from the California Cancer Registry has shown that expression of ER and PR was lower among IBC patient cases compared to both non-T4 carcinomas (56% ER, 45% PR versus 80% ER, 68% PR) and in patients with locally advanced breast cancer (67% ER, 54% PR) [18]. Despite a decreased estrogen receptor expression in IBC, hormone production might still play a role. GPR30-expression (a seven-transmembrane receptor belonging to the G-protein coupled receptor family and regulates cellular and physiological responsiveness to estrogen) was found in 69% of patients with IBC which was not interdependently expressed with ER. Therefore, estrogen signaling may be active in ER-negative IBC patients [19]. Subsequently, it may be possible to exploit new potential therapies through non-classical estrogen-dependent pathways despite the lack of detectable ER. Specific GPR30 antagonists (G15 and G36) have shown to inhibit estrogen-stimulated proliferation of uterine epithelial cells in vivo. Further assessment of the effects and mechanisms of action of both agents in IBC cell lines and tumor xenografts is yet to be conducted [20,21].

## Epidermal growth factor receptors

The epidermal growth factor receptor-family plays an important role in cell proliferation, survival, migration and differentiation and consists of four members: epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2, 3 and 4 (HER2, HER3 and HER4) [22]. EGFR overexpression was detected in 30% of patients with IBC and found to be associated with a significantly worse 5-year overall survival rate compared to EGFR-negative IBC. Furthermore, EGFR-expression was associated with increased risk of IBC recurrence [22]. In an IBC xenograft model, erlotinib (an EGFR tyrosine kinase inhibitor) inhibited IBC tumor growth and inhibited spontaneous lung metastasis. These results suggest that the EGFR pathway is involved in tumor growth and metastasis of IBC and thereby potentially represents an effective therapeutic target [23]. Human epidermal growth factor receptor-2 (HER2) is a transmembrane receptor tyrosine kinase and is involved in signal transduction pathways leading to cell growth and differentiation [24]. Overexpression of HER2 in breast cancer is associated with increased aggressiveness and higher recurrence rates and higher mortality [25]. IBC patient cases were noted to have a higher proportion of HER2-positive patient cases compared with non-T4 patients and compared with LABC [26]. Despite the association with advanced tumor stage, HER2-positive status is not an independent adverse prognostic factor for survival among IBC patient cases [26]. The NOAH-trial aimed to assess event-free survival in patients with HER2-positive locally advanced or inflammatory breast cancer, respectively 144 and 77 patients, receiving neoadjuvant chemotherapy with or without 1 year of trastuzumab. The addition of neoadjuvant and adjuvant trastuzumab to neoadjuvant chemotherapy showed a significantly improved event-free survival in patients with HER2-positive breast cancer (3-year event-free survival of 71% study) and a significantly improved pathological response in both breast tissue and axillary lymph nodes [21]. When trastuzumab is administered in the neoadjuvant setting only, with an average of 20 weeks preoperative administration, patients with IBC continue to have a high risk of locoregional recurrence and, relatively early recurrence in the brain even when pathological complete response is reached [26]. However, it should be noted that no comparison with NIBC was made and that current standard is 1-year duration of trastuzumab treatment, rather than 20 weeks only. Lapatinib is a dual inhibitor of the EGFR and HER2 receptor tyrosine kinases. Lapatinib induces tumor delayed cell growth or apoptosis in EGFR- or HER2-dependent tumor cell lines or xenografts [11]. A phase II trial was performed to investigate the neoadjuvant administration of lapatinib in combination with paclitaxel [27]. Patients were assigned to cohorts A (HER2-overexpressing [HER2+] ± EGFR) or B (HER2−/EGFR+). The primary endpoint was pathologic response, which was evaluated at the time of surgical resection at the completion of 12 weeks of lapatinib/paclitaxel combination therapy and was defined according to evidence of residual invasive tumor, including residual tumor in the axillary lymph nodes. The HER2-negative/EGFR-positive cohort had been terminated because of lack of efficacy observed in another trial with IBC patients with HER2-negative/EGFR-positive tumors. Secondary endpoints included safety and tolerability of lapatinib and paclitaxel combination [26]. A neoadjuvant treatment regimen of daily lapatinib monotherapy for 14 days, followed by combination therapy with daily oral lapatinib and weekly paclitaxel for 12 weeks had a combined clinical response rate of 78.1% in IBC patients with HER2 overexpressing tumors without unexpected toxicity [28]. The impact on DFS and OS of neoadjuvant administration of lapatinib has to be evaluated in future clinical trials. Remarkably, HER3 has been identified as a potential marker of drug sensitivity in lapatinib therapy [29]. Phosphorylated HER3 predicted response to lapatinib and tumors coexpressing phosphorylated HER2 and HER3 were more likely to respond [29]. As a prognostic marker, expression of HER3 has been associated with reduced breast cancer specific survival [30]. A more complete picture of the role of HER3 as a therapeutic target or potential marker in IBC is yet to emerge. HER3 lacks a tyrosine kinase domain, therefore other potential targets than the tyrosine kinase domain have to be addressed. Several ligands, such as the neuregulins and heregulin, bind HER3 [31,32]. Blocking heregulin expression inhibits tumorigenicity and metastasis of breast cancer cells [33]. HER3 ligands could thereby be potential therapeutic targets in IBC.

## Tumor suppressor genes and oncogenes

Tumor suppressor p53 is a transcription factor that regulates the cell cycle. Alteration or inactivation of p53 by mutation can lead to cancer development [33]. Higher levels of dysregulated p53 expression have been detected in IBC compared with other locally advanced breast cancers, however not statistically significant: 53% versus 36% ($p = 0.19$) [34]. In a study of 24 patients it was shown

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