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Inflammatory breast cancer: An overview

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Contents

Abstract

Inflammatory breast cancer (IBC) is the most aggressive entity of breast cancer. Management involves coordination of multidisciplinary management and usually includes neoadjuvant chemotherapy, ablative surgery if a tumor-free resection margin is expected and locoregional radiotherapy. This multimodal therapeutic approach has significantly improved patient survival. However, the median overall survival among women with IBC is still poor. By elucidating the biologic characteristics of IBC, new treatment options may become available. We performed a comprehensive review of the English-language literature on IBC through computerized literature searches. The objective of the current review is to present an overview of the literature related to the biology, imaging and multidisciplinary treatment of inflammatory breast cancer.

Keywords: Inflammatory breast cancer; Molecular characteristics; Treatment; Surgery

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1. Introduction

Inflammatory breast cancer (IBC) is a rare subtype of locally advanced breast cancer according to the tumor-node-metastasis (TNM) breast cancer staging system. IBC is classified as T4d and clinically characterized by diffuse in duration of the skin with an erysipeloid edge, usually with no underlying mass (Fig. 1) [1]. The objective of the current review is to present an overview of the literature related to the biology, imaging and multidisciplinary treatment of inflammatory breast cancer.

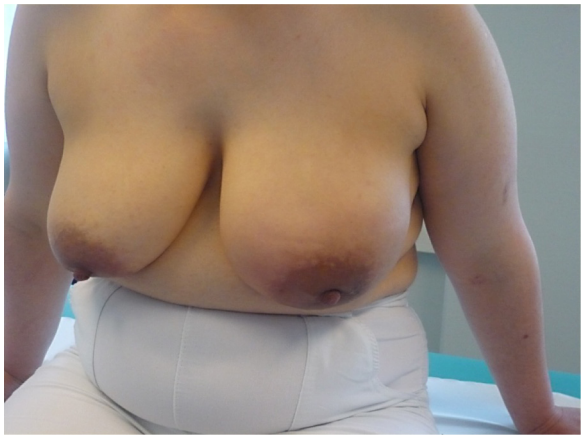

Fig. 1. 46-year old women presenting with swelling and erythema of the left breast, caused by inflammatory breast cancer.

2. Methods

The PubMed database was searched using the following terms (Fig. 2): "inflammatory breast cancer" successively complemented with "epidemiology" and "risk factors", "MRI" and "PET/CT", "chemotherapy", "surgery", "radiotherapy", "hormone receptors", "epidermal growth factor receptors", "tumor suppressor genes", "(lymph) angiogenesis" with the limits English, Publication Date from 1980/01/01, Humans, abstract available. We augmented this computerized literature search by manually reviewing the reference lists of included studies to identify additional relevant articles. We discarded duplicate publications. Filtered on title and abstract, we analyzed the manuscripts and articles were eligible when they reported a series of patients presenting with inflammatory breast cancer or when an overview concerning a specific subject with regard to inflammatory

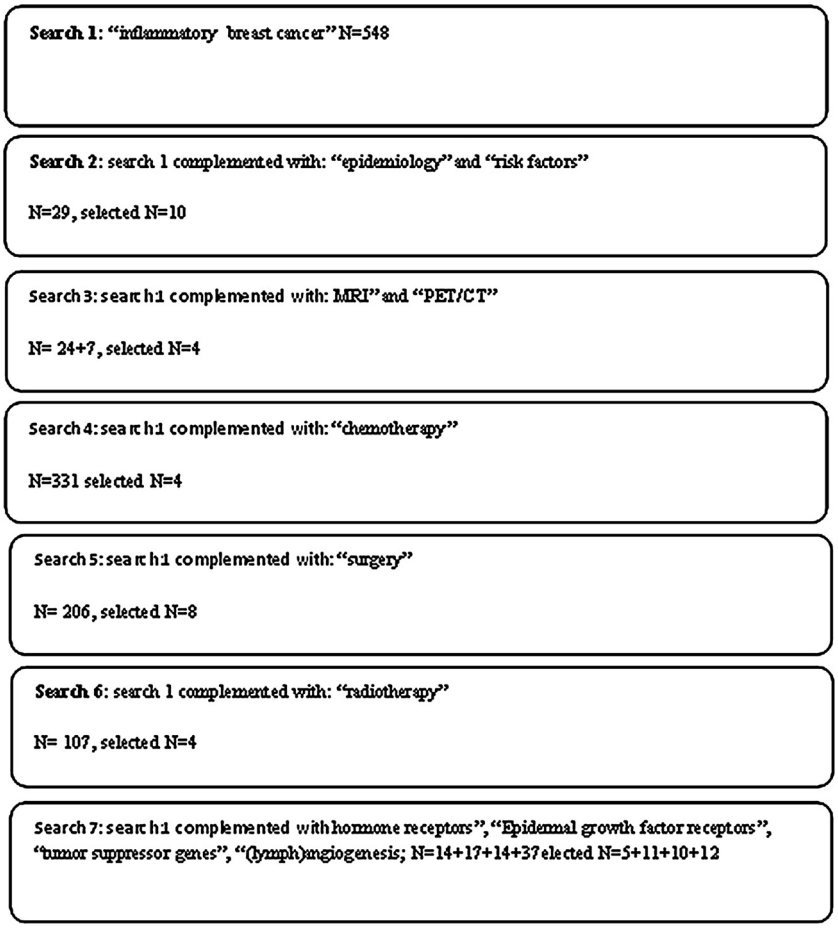

Fig. 2. Flowchart of literature search.

breast cancer was given. Hereafter, we prepared our manuscript with the most recent trials and/or most quoted articles which were found by cross referencing, to provide a comprehensive overview of inflammatory breast cancer.

3. Clinical and pathological characteristics of inflammatory breast cancer

A differentiation between primary and secondary inflammatory breast cancer has to be made. By primary inflammatory breast cancer, we refer to the development of breast carcinoma in a previously normal breast. The term secondary inflammatory breast carcinoma is given to the development of inflammatory skin changes associated with invasive breast carcinoma in a breast that already had cancer or there was carcinoma in the chest wall that developed after a mastectomy for non-inflammatory breast carcinoma [2].

Several conditions can mimic the clinical presentation of IBC. Nonpuerperal bacterial mastitis may be confused with IBC, leading to potentially preventable delays in diagnosis and treatment [3]. The skin changes in IBC are caused by tumor emboli within the dermal lymphatics, and – contrary to the suggestion evoked by the nomenclature – not by infiltration of inflammatory cells. Although microscopical detection of tumor emboli in dermal lymphatic vessels is supportive of the diagnosis, it is not required. Furthermore, dermal lymphatic invasion without typical clinical findings is not sufficient for a diagnosis of IBC [4].

4. Epidemiologic features

Inflammatory breast cancer is the most aggressive entity of breast cancer and comprises 2.5% of all breast cancers [5]. 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 [6]. The incidence of IBC appears to be increasing, particularly among Caucasian women. Women with IBC typically present at a younger age than NIBC [7]. 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 disparities has not yet been elucidated [5,8–10]. 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 [10].

Data on risk factors is limited: a high body mass index (BMI) is positively associated with a diagnosis of IBC compared to NIBC [11]. 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 [7]. 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 [11]. See Table 1.

Table 1
Risk factors for inflammatory breast cancer.

Younger age at menarche and at the time of first live birth compared to non-IBC
Premenopausal state (higher proportion of IBC patients were premenopausal than their non-IBC)
Ethnicity (independent predictor of elevated risk for breast cancer mortality)
Socioeconomic status (independent predictors of advanced stage at diagnosis in breast cancer)
Body mass index

Several studies have reported that IBC constitutes a larger proportion of breast cancers in low income countries than Western countries [12,13]. 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 [14].

5. Diagnosis and staging of inflammatory breast cancer

An appropriate initial work-up of IBC should consist of history and physical examination followed by diagnostic evaluation. Patients with IBC typically present with pain and a rapidly progressing, tender, firm, and enlarged breast. The skin over the breast is reddened, warm, and thickened, termed '*peau d'orange*'. Mammography may show an obvious tumor mass, a large area of calcification, and/or parenchymal distortion. Mammography also may show skin thickening over the breast, with or without a breast mass [15]. Advances in imaging techniques such as ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT) have improved the diagnosis and staging of IBC [16]. Sonography has shown to be a useful localizing tool in the biopsy of patients with identifiable masses and for evaluation of the regional nodes. Furthermore, primary breast lesions are more frequently visible on sonography than on mammography [17]. MRI has a high sensitivity for demonstrating parenchymal breast lesions and skin thickening and enhancement (Fig. 3). Therefore, MRI also may help in guiding skin punch biopsies.

The diagnosis can be made by core biopsy if a breast mass is present. A full thickness skin biopsy should also be obtained if IBC is suspected, since a hallmark of this disease is dermal lymphatic invasion by tumor cells. For women with palpable or suspicious regional lymph nodes, an ultrasound with guided fine needle aspiration (FNA) and/or a core needle biopsy will be performed in order to make a more accurate determination of the tumor stage [18].

Because of a high rate of metastases at presentation in IBC patients (approximately 30%), an accurate initial staging is

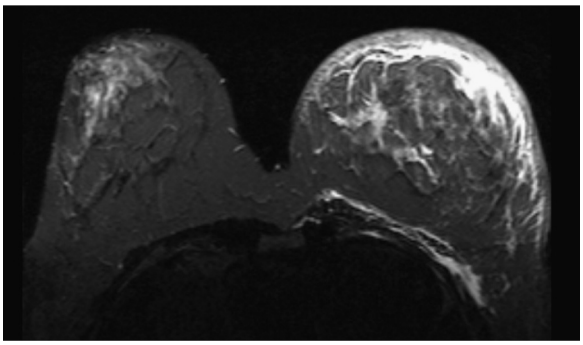

Fig. 3. MRI of a 44-year old woman with left inflammatory breast cancer, showing extensive skin thickening.

Table 2
Chemotherapeutic agents for the treatment of inflammatory breast cancer.

Anthracyclines
–Doxorubicin
–Epirubicin
Taxanes
–Paclitaxel
–Docetaxel
Alkalating agents
–Cyclofosfamide
Pyrimidine analog
–Fluorouracil

crucial to plan adequate systemic and locoregional treatment [17]. Staging workup includes chest X-ray, bone scintigraphy, and abdominal ultrasound. PET/CT has shown to be accurate at demonstrating loco-regional disease and distant metastases. Furthermore, it has the potential to replace the current staging studies, allowing a single hospital visit and decreased imaging time. Further studies are still being undertaken to evaluate the value of PET/CT for incorporation in the standard clinical work up [17].

The current management of non-metastatic IBC includes neoadjuvant chemotherapy, ablative surgery if a tumor-free resection margin is expected (in case of axillary lymph node involvement combined with lymph node dissection), and locoregional radiotherapy but also periadjuvant trastuzumab and adjuvant hormone therapy in case of HER2 or ER/PR positive tumors respectively. This multimodal therapeutic approach has significantly improved patient survival in recent years which might, in part, be explained by more targeted therapy becoming available [5,19–21]. Nevertheless, IBC still has a poor outcome, with a median disease-free survival of less than 2.5 years and an overall survival of 30–40% at 5 years [2].

6. Systemic neoadjuvant chemotherapy

Anthracycline- and taxane-based adjuvant chemotherapy regimens are widely used for neoadjuvant chemotherapy and are particularly effective in IBC. See Table 2. Sixty-eight patients with IBC received treatment three courses of neoadjuvant chemotherapy with cyclophosphamide, doxorubicin, 5-fluorouracil (5-FU) (CAF) or cyclophosphamide, epirubicin, 5-FU (CEF) followed by surgery and six adjuvant courses of CAF or CEF alternated with cyclophosphamide, methotrexate, 5-FU. Radiation therapy was administered at the end of adjuvant treatment. In this study, the reported 5- and 10-year disease-free survival rates were 29% and 20%, respectively, and overall survival rates were reported to be 44% and 32%, respectively. This analysis confirms significant long-term survival benefit from combined-modality therapy for patients with IBC [22]. Comparable to NIBC, integration of taxanes into combination chemotherapy has shown efficacy in the neoadjuvant treatment of IBC. A review of 240 patients (treated in 6 different clinical trials) displayed an improved progression free survival and overall survival by adding paclitaxel to anthracycline-based regimens, especially in patients with ER-negative IBC [23,24]. These results were superior to outcomes reported before the introduction of anthracycline and taxane containing primary systemic treatment. Patients with IBC and HER2 overexpression should receive HER2-targeted therapy in conjunction with neoadjuvant chemotherapy as was reported in the NOAH trial which will be discussed further down [21].

7. Surgery

Historically, patients with IBC treated by surgery alone had a very poor prognosis, thus IBC was considered to be a contraindication for surgical intervention. At present, primary systemic chemotherapy is considered the first choice of treatment aiming at downsizing the tumor followed by mastectomy combined with axillary lymph node dissection when indicated. Reports on the use of sentinel lymph node biopsy in patients with IBC have demonstrated that it is not reliable in axillary staging [25]. Also, after neoadjuvant chemotherapy false-negative rates are considered to be unacceptably high [26].

Mastectomy is usually performed 2–3 weeks after completion of chemotherapy. The degree of the initial response to chemotherapy predicts for local control, overall survival, and disease-free survival [27]. Even in patients with excellent clinical response, it can be challenging to determine the extent of surgical resection since in IBC the extent of disease may be underestimated in 60% of patients [28].

An aggressive surgical approach, practically always consisting of mastectomy, may be justified with the goal of a negative surgical margin since achievement of local control is associated with an improved overall outcome [29].

A retrospective series based on 232 patients suggested an improvement in locoregional control in patients treated by surgery. All patients received primary chemotherapy followed by either exclusive radiotherapy (118 patients, 51%) or surgery with or without radiotherapy (114 patients, 49%) and the addition of surgery was associated with a significant improvement in locoregional disease control but with no

significant difference in overall survival rate or disease-free interval [30].

Despite a clinical response to treatment, residual disease may still be present in the affected skin of the involved breast. Breast conserving therapy has a higher probability of incomplete margins than mastectomy. Therefore, a mastectomy is recommended in patients with IBC and it is not recommended to perform a lumpectomy in patients with IBC outside the context of a clinical trial [25].

Oncoplastic surgery is possible for women with IBC who have undergone a modified radical mastectomy. Modern techniques for breast reconstruction after mastectomy provide excellent cosmetic results and can have a significant positive effect on self-image and quality of life.

However, the timing of the reconstruction in this cohort is controversial. Limited data suggests reasonable success with no outcome differences when immediate reconstruction was compared with delayed reconstruction [31,32]. Moreover, the presence of a reconstructed breast limits radiation coverage and may also compromise coverage of the internal mammary lymph nodes [33].

Candidates for surgery should typically have all evidence of skin inflammation resolved in response to primary chemotherapy.

8. Radiotherapy

Radiation therapy (RT) to the thoracic wall, including ipsilateral axillary, infraclavicular, and supraclavicular lymph nodes, is generally recommended for women with IBC. Although a survival benefit for postmastectomy RT has not been proven in patients with IBC, the improvement in locoregional control makes RT an important modality in the treatment protocol [18]. Radiation fractionation schedules may vary, but usually cumulative doses above 50 gray (Gy) are applied. In a dose-escalation study, twice-daily postmastectomy RT to a total dose of 66 Gy in 39 patients with IBC was compared to 32 patients treated twice daily to a cumulative dose of 60 Gy. Patients treated with 66 gray total dose had significantly improved 5-year locoregional control (84 versus 58%) and a nonsignificant increase in disease free survival compared to patients treated with 60 Gy [34,35]. The benefit of an increased dose appeared highest in cases at high risk of recurrence: a poor response to chemotherapy, patients with close or positive surgical margins, patients with four or more positive lymph nodes after neoadjuvant chemotherapy, and patients under 45 years old. Importantly, excellent locoregional control rates were achieved with a dose of 60 Gy dose for patients without any of these features [35]. In 2012, a study reported long-term outcome of a monocentric clinical trial combining primary chemotherapy (CT) with a schedule of anthracycline-based CT and an alternating split-course of radiotherapy (RT*CT) without surgery. With a median follow-up of 20 years in 82% of patients local control was achieved. The 10- and 20-year local relapse rates were 26% and 33%, respectively. The 10- and 20-year overall survival rates were 39% and 19%, respectively. This combined regimen allowed good long-term local control without the use of surgery. These survival rates were similar to those obtained with conventional regimens (primary chemotherapy, total mastectomy, and adjuvant radiotherapy) [36].

Since IBC continues to be an entity with a poor prognosis, this approach, safely combining preoperative or postoperative radiation therapy and systemic treatments, should be reassessed when suitable targeted agents are available. Among patients with HER2-positive disease, trastuzumab may be administered concomitantly with radiation therapy [21].

9. Molecular characteristics

9.1. Hormone receptors

Current hormone receptors determinants available in daily practice include the estrogen – (ER) and the progestron receptor (PR). 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 [37,38].

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 [39]. 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).

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-proteincoupled 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 [40]. 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 [41,42].

9.2. 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) [43].

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 [38]. 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 [44].

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 [45]. Overexpression of HER2 in breast cancer is associated with increased aggressiveness and higher recurrence rates and higher mortality [46]. IBC patient cases were noted to have a higher proportion of HER2-positive patient cases compared with non-T4 patients and compared with LABC [37]. Despite the association with advanced tumor stage, HER2-positive status is not an independent adverse prognostic factor for survival among IBC patient cases [37,47].

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 [48]. 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 [49]. A phase II trial was performed to investigate the neoadjuvant administration of lapatinib in combination with paclitaxel [50].

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 [51]. 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 [50]. 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 [51]. Phosphorylated HER3 predicted response to lapatinib and tumors coexpressing phosphorylated HER2 and HER3 were more likely to respond [51]. As a prognostic marker, expression of HER3 has been associated with reduced breast cancer specific survival [52]. 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 [53,54]. Blocking heregulin expression inhibits tumorigenicity and metastasis of breast cancer cells [55]. HER3 ligands could thereby be potential therapeutic targets in IBC.

9.3. 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 [56]. 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% ($p = 0.19$) [57].

In a study of 24 patients it was shown that patients with IBC with a p53 gene mutation and nuclear overexpression of p53 protein have an 8.6-fold higher risk of death compared with patients that had neither mutation nor protein overexpression. Moreover, an important prognostic interaction with ER expression was observed. Patients who were both ER-negative and had nuclear p53 overexpression had a 17.9-fold higher risk of death, compared to 2.8-fold for women with tumors that had p53 nuclear overexpression alone [56].

Analysis of 95 patients with IBC has shown that patients with IBC who do not have dysfunctional p53 protein expression (p53 negative) have a better prognosis compared to p53-positive IBC when treated with optimal systemic and locoregional treatments. All recurrences and deaths in this study, 28 and 26 respectively, occurred in the group of nuclear p53-positive tumors [58].

As p53 status seems to have an important influence on outcome, the results of the INGN-201-bioengineer construct are eagerly awaited. INGN-201 is an adenoviral vector

that carries the normal p53 gene under the control of the cytomegalovirus (CMV) promoter. INGN-201-mediated p53 expression induces apoptosis and/or inhibition of proliferation in vitro in cancer cell lines from numerous tumor types, with almost no effects on normal cells [59]. INGN-201 was investigated in combination with Docetaxel and Doxorubicin in locally advanced breast cancer [60]. Unfortunately, no results are known and patients with IBC were excluded. However, the higher levels of expression of p53 IBC cancer may justify the use of INGN-201 in future IBC trials.

Another potential target might be anaplastic lymphoma kinase (ALK) genetic abnormalities. ALK is a receptor tyrosine kinase (RTK) within the insulin receptor superfamily and there has been evidence for the activation of ALK pathway activation in pre-clinical models of IBC [60,61]. Crizotinib, a small molecule ALK inhibitor, showed promising results in non-small cell lung cancer patients with ALK genetic abnormalities compared with standard second line chemotherapy [62]. Crizotinib arrested growth of IBC cells in culture and activated the cell death pathway [61]. Based on these results, IBC patients are being screened for ALK genetic abnormalities and, if eligible, included in clinical trials with ALK inhibitors [63].

9.4. (Lymph) angiogenic factors

The dependence of solid tumors on blood supply for their ability to grow and metastasize is nowadays an established concept in tumor biology. Tumor angiogenesis, the sprouting of new capillaries from existing vessels, is the result of a complex and precise balance between proangiogenic and antiangiogenic factors, and is essential to the growth of primary and metastatic tumors beyond the diameter of 1–2 mm^3. A variety of endogenous factors associated with angiogenesis induction have been studied extensively, including vascular endothelial growth factors (VEGF) and basic fibroblast growth factors (bFGF). Recently, endogenous inhibitors of angiogenesis gained more attention.

At time of diagnosis, most patients with IBC have axillary lymph node involvement [64]. Lymphatic metastases can occur by invasion of pre-existing lymph vessels, and by tumor-induced lymph angiogenesis in which VEGF also plays an important role [65]. Therefore, it might be an interesting molecular mechanism to target in the prevention of axillary involvement.

Molecular and histomorphometric studies of human IBC samples have provided evidence of increased angiogenesis and lymphangiogenesis in IBC. Significant increased intratumoral microvessel density was observed in IBC patients compared to NIBC. Thereby indicating IBC as a highly vascular disease with an enlarged intratumoral vascular area [57]. Furthermore, a positive correlation between the expression of carbonic anhydrase IX (an endogenous hypoxia marker) and endothelial cell proliferation was found. However, expression of CA IX was significantly less frequent in IBC than in NIBC with early metastasis. There was a significant positive correlation between the expression of CA IX and endothelial cell proliferation in IBC, implying that the angiogenesis is partly hypoxia driven. However, the higher endothelial cell proliferation in IBC and the less frequent expression of CA IX in IBC versus NIBC points at a role for other factors than hypoxia in stimulating angiogenesis [66].

Molecular evidence of increased angiogenesis was provided by elevated mRNA expression of angiogenic factors and their receptors which were quantified by real-time reverse transcriptase polymerase chain reaction (RT-PCR). Among others, expression of TIE-1 and TIE-2 (cell surface proteins of endothelial cells), which have been described in angiogenesis, are elevated [67]. Histomorphometric evidence of lymphangiogenesis appeared from a study comparing samples from 29 patients with IBC with 56 samples from patients with NIBC. A higher lymphatic endothelial cell proliferation in IBC was demonstrated and a larger relative tumor area occupied by lymph vessels compared to NIBC [68].

As previously noted, VEGF is involved in both angiogenesis and lymphangiogenesis and elevated levels of VEGF, are found to be highly expressed in IBC [2,67].

It was observed that intra-tumoral VEGF-C and VEGF-D mRNA were significantly more expressed in IBC than in patients with non-inflammatory disease [67]. VEGF-C has shown to be associated with increased lymph vessel density and lymph node involvement in invasive breast cancer [69]. VEGF-D can induce both tumor angiogenesis and lymphangiogenesis and promotes the lymphatic spread of tumors [65].

By real-time quantitative reverse transcriptase-PCR, levels of mRNA of tumor angiogenesis and lymphangiogenesis-related factors (e.g. VEGF) were measured in 16 patients with IBC and 20 patients with non-inflammatory breast cancer. No significant difference in expression level of angiogenic VEGF-A in inflammatory breast cancer was found when compared with non-inflammatory breast cancer. However, its receptor (vascular endothelial growth factor receptor 2) was significantly up-regulated in IBC versus non-inflammatory breast cancer. VEGFR2 is predominantly expressed in endothelial cells and its activation results in a mitogenic and migratory response. Most functions of VEGF are mediated through this receptor [70]. Furthermore, it was demonstrated that tumor stromal VEGF-A expression is a valuable prognostic indicator of breast cancer specific survival and disease free survival at diagnosis and can therefore potentially be used to stratify IBC patients into low-risk and high-risk groups for death and relapses [71]. In a retrospective analysis, IBC samples were compared to normal breast tissue from reduction mammoplasty patients. Significantly lower epithelial VEGF-A immunostaining was found in IBC tumor cells than in normal breast tissues, cytoplasmic VEGF-R1 and nuclear VEGF-R2 levels were slightly higher, and cytoplasmic VEGF-R2 levels were significantly higher ($P = 0.04$). Sixty-two percent of IBC tumors had high stromal VEGF-A expression. Stromal VEGF-A levels predicted breast cancer specific survival (BCSS) and DFS in

IBC patients with estrogen receptor-positive ($P < 0.01$ for both), progesterone receptor-positive ($P = 0.04$ and $P = 0.03$), HER2+ ($P = 0.04$ and $P = 0.03$), and lymph node involvement ($P < 0.01$ for both). Tumor stromal VEGF-A was identified as an independent predictor of poor BCSS (hazard ratio [HR]: 5.0; 95% CI: 2.0–12.3; $P < 0.01$) and DFS (HR: 4.2; 95% CI: 1.7–10.3; $P < 0.01$). This might indicate that tumor stromal VEGF-A expression is a valuable prognostic indicator of BCSS and DFS at diagnosis and can therefore be used to stratify IBC patients into low-risk and high-risk groups for death and relapses. High levels of tumor stromal VEGF-A may be useful for identifying IBC patients who will benefit from anti-angiogenic treatment.

Due to the displayed highly angiogenic features, patients with IBC might benefit from anti-angiogenic agents that target VEGF [2]. Bevacuzimab is a monoclonal antibody to VEGF and has been shown to inhibit VEGF-receptor activation, specifically VEGF-A [2,67].

However, bevacizumab's indication to treat locally recurrent or metastatic HER2-negative breast cancer has been removed by the Food and Drug Administration (FDA). It stated that no trial in breast cancer using bevacizumab provides evidence of direct clinical benefit and that only modest effects on primarily radiographic outcomes were demonstrated. These modest indirect measures of clinical benefit must be weighed against a marked increase in clinically serious adverse events (gastrointestinal perforations, hemorrhage, surgery and wound healing complications) and therapy-related deaths. Deaths attributed to bevacizumab ranged between 0.8 and 1.2% as released by the Food and Drug administration [72].

Despite these concerns involving treatment of breast cancer with bevacizumab, there may still be an indication for a subgroup of patients. For example, since IBC is more angiogenic than non-inflammatory breast cancer and has significantly higher levels of VEGF-expression, bevacizumab treatment may be useful in IBC patients [67]. Some hints for efficacy of bevacizumab in IBC have been suggested in small clinical studies. The first study demonstrated a significant decrease of 66.7% in phosphorylated VEGFR-2 in 21 patients with inflammatory and locally advanced breast cancer (one patient had NIBC since the study briefly was open to NIBC patients) which were treated with one cycle of bevacuzimab, followed by six cycles of bevacizumab with doxorubicin and docetaxel. However, clinical benefit in terms of DFS and OS has not been determined [73]. In another study, twenty patients with IBC and one with locally advanced breast cancer, received one cycle of bevacizumab followed by six cycles of bevacizumab with docetaxel-doxorubicin before surgery. Angiogenic markers were measured at baseline before bevacizumab, after bevacizumab and after bevacizumab plus chemotherapy. VEGF-A was higher at baseline in the responders than non-responders, demonstrating a trend toward association with response. Moreover, baseline CD31 and platelet derived growth factor (PDGFR) beta were significantly associated with response to bevacizumab. Patients with IBC with higher tumor gene expression of VEGF-A, CD-31 and PDGFR-beta were more likely to benefit from treatment with bevacizumab with chemotherapy [74].

In a phase 2, multicentre, open-label, single-arm, non-comparative trial patients with histologically confirmed HER2-positive non-metastatic IBC were enrolled to assess efficacy and safety of neoadjuvant bevacizumab combined with trastuzumab and chemotherapy. Primary endpoint was pathological complete response. Before surgery, patients were treated with fluorouracil, epirubicin, cyclophosphamide, and bevacizumab (cycles 1–4) and docetaxel, bevacizumab, and trastuzumab (cycles 5–8) in 3-week cycles. After surgery, patients received adjuvant radiotherapy, trastuzumab, and bevacizumab. After neoadjuvant therapy, 33 of 52 patients had a pathological complete response. Furthermore, this treatment regimen seemed to be well tolerated [75].

Before potential incorporation of bevacizumab in the multimodality treatment of IBC, predictive markers have to be selected for identifying patients with IBC who may benefit from bevacizumab or related therapies. VEGF-A might be used to stratify IBC patients into low-risk and high-risk groups for death and relapses. High levels of tumor stromal VEGF-A may be useful for identifying IBC patients who will benefit from anti-angiogenic treatment. See Table 3 for a brief summary of molecular targets in IBC.

Table 3
Potential molecular targets in inflammatory breast cancer.

-HER2-positive
○Trastuzumab
-Hormone receptors
○Tamoxifen or an aromatase inhibitor
○GPR 30 antagonists
-Epidermal growth factor receptors
○Lapatinib
-P53
○INGN-201
-Anaplastic lymphoma kinase
○Crizotonib
-VEGF
○Bevacizumab

10. Conclusion

This overview of the literature shows that inflammatory breast cancer has several different characteristics which determine the aggressive biology of this disease compared to non-inflammatory breast cancer. Locoregional therapies like surgery and radiation therapy have shown to improve local recurrence, without significance on overall survival. Since the consistent use of neoadjuvant chemotherapy, overall survival increased [20]. However, new and additional agents are necessary to improve the standard treatment since it remains a disease with a dismal prognosis.

Molecular subtyping has identified several specific characteristics of IBC compared to non-inflammatory breast cancer and has enabled the identification of new therapeutic targets to regulate the aggressive nature of IBC.

Breast cancer treatment will be increasingly based on molecular profiling of tumors rather than on histology alone. There is paucity of data from large-scale, prospective, multicenter, randomized trials because of the low incidence of inflammatory breast cancer and the optimal chemotherapeutic regimens, in combination with targeted treatments, are yet to be defined. Future trials to evaluate targeted agents are necessary to improve survival for patients with this aggressive form of breast cancer.

Conflict of interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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