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HOT TOPICS IN BREAST CANCER (K HUNT, SECTION EDITOR)

Inflammatory Breast Cancer: Diagnostic, Molecular and Therapeutic Considerations

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Abstract

Purpose of Review Inflammatory breast cancer (IBC) is an aggressive type of breast cancer with poor prognosis. Treatment for non-metastatic disease is neoadjuvant chemotherapy followed by mastectomy and radiation. IBC diagnosis is primarily a clinical diagnosis, which can lead to misdiagnosis and delayed management. In addition, there are no molecular criteria for diagnosis or therapeutic regimens developed specifically for IBC. We aimed to discuss recent developments in IBC, including diagnosis, molecular mechanisms, and treatment.

Recent Findings Recently, the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) breast cancer staging system has defined the diagnostic features of IBC. Current molecular characterization of IBC has not revealed a unique signature or marker for diagnosis; however, this work sheds light on the pathophysiology of IBC and provides potential therapeutic targets.

Summary The prognosis of IBC remains poor, although the survival is improved significantly with trimodal management. To date, a consensus on diagnosis and prospective trials specifically designed for IBC therapy are lacking. Standardized criteria incorporating clinical, pathologic, and molecular criteria remains an unmet need. Recent consensus recommendations regarding diagnosis and management are reviewed with a view towards evolving molecular characterization, potential targets, and current clinical trials.

Keywords Inflammatory breast cancer · Neoadjuvant therapy · Modified radical mastectomy · Radiation therapy · Targeted therapy

Introduction

Inflammatory breast cancer (IBC) is rare and is the most aggressive form of breast cancer. IBC accounts for up to 6% of breast cancer cases annually in the USA but accounts for about 10% of breast cancer deaths [1, 2••]. Clinical presentation is usually profound with rapid and diffuse skin changes including erythema, edema, and peau d'orange. Also common is lymph node involvement and/or distant metastases at diagnosis [3]. Wecsler et al. demonstrated that positive nodal status was associated with a significant decrease in overall survival (OS) [4]. Race, body mass index, age, and region of the country are defined as important suspected risk factors. IBC has a tendency to affect younger women with a median age of 57 years at diagnosis. There is also a higher incidence rate in African Americans compared with Caucasians [5–8]. Biomarker expression in IBC shows improved survival with hormone receptor positive disease and worse survival in those with triple negative disease (TNBC) [9••]. Currently, IBC has no definitive molecular or histological diagnostic criterion and its diagnosis is primarily based on clinical symptoms such as the rapid onset of erythema and edema involving at least one-third of breast skin often without a clinically evident breast mass. The disease is by definition T4d, which stages all non-metastatic patients as stage III. For non-metastatic disease, the 5-year OS is historically 40–50%, however in the modern era is reported to be as high as 68%, reflecting advances in

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treatment [10••]. Despite these improvements in survival, prognosis for IBC remains poor when compared to non-IBC [11]. Although no molecular markers are specific to IBC, further molecular characterization of IBC is ongoing [12, 13]. These preclinical studies offer insights into the unique tumor biology of IBC and the potential to develop novel therapeutic strategies.

Trimodal therapy includes neoadjuvant chemotherapy, modified radical mastectomy, and locoregional radiation and has been shown to improve OS. However, IBC has lower OS despite the use of multimodal therapy when compared to locally advanced non-IBC, with a 5-year survival rate of 62% versus 81% [3, 11]. Multidisciplinary coordination between medical, surgical, and radiation oncology is required for optimal management.

Clinical Presentation

Common symptoms of IBC are breast redness, pain, or a rapidly enlarging breast mass [3]. Erythema involving at least one-third of the breast is a hallmark of IBC, although the redness may come and go. The breast may be swollen, enlarged, and hard or heavy. There is usually widespread involvement of the lymphatic system during the initial presentation of IBC, with tumor-driven lymphangiogenesis and tumor emboli causing lymphatic blockage [5]. Extensive nodal involvement is present in the majority of IBC, and distant metastases are present in approximately 36% of patients at the time of diagnosis [3]. Fluid buildup leads to warmth, thickening, erythema or discoloration, and pitting of the superficial skin; this constellation of symptoms is termed peau d'orange with the skin resembling an orange peel [5, 14]. The nipple can also be involved, and presentation can range from inversion, scaling, and blistering [6]. Some of these symptoms are similar to those seen with mastitis. Unlike IBC, however, mastitis is often associated with fever and is easily treated with antibiotics. Any persistent breast changes should warrant early investigation with imaging and/or biopsy. IBC differs from non-IBC in that a breast mass may not be present on exam; however, diffuse skin involvement is a common presentation.

Diagnosis

In 2011, Dawood et al. published an international expert panel consensus-based diagnostic criteria of IBC [15]. Criteria included the rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass; duration of history no more than 6 months; erythema occupying at least one-third of the breast; and pathologic confirmation of invasive carcinoma [15]. Dermal lymphatic emboli are present in about 75% of IBC cases but the absence of dermal emboli does not exclude the diagnosis [16].

According to the 2017 American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) breast cancer staging system, IBC is characterized by diffuse erythema and edema (peau d'orange) involving one-third or more of the skin of the breast. Current diagnostic criteria are still based on clinical presentation and lack definitive histopathologic and molecular criteria. A full-thickness skin punch biopsy of the affected area can help confirm the diagnosis. Tissue diagnosis via punch biopsy or core biopsy demonstrating carcinoma of the breast is required before initiating chemotherapy treatment. Delayed or misdiagnosis of IBC can compromise outcomes in this aggressive disease; therefore, early and accurate diagnosis is critical.

Imaging

At present, there are no radiographic findings that are specific for IBC. Mammography is currently the imaging modality of choice for patients with suspected IBC. Skin thickening, stromal infiltration, and trabecular distortion are subtle early findings in IBC. Ultrasonography is useful for guiding core biopsy of a primary breast lesion (mass or non-mass lesion) and fine needle aspiration or core biopsy of axillary and supraclavicular lymph nodes. Breast magnetic resonance imaging (MRI) can identify almost all (> 90%) parenchymal lesions and skin changes, and it has the highest sensitivity in detecting breast parenchymal lesion compared to mammography and ultrasound [17]. Therefore, MRI is recommended to demonstrate the extent of disease, including ipsilateral and contralateral skin involvement. An expert panel also recommends medical photography to document findings required for diagnosis and to inform members of the multidisciplinary team who may not meet the patient until resolution of skin findings [10••].

About one-third of women with newly diagnosed IBC have distant metastasis at the time of diagnosis and systemic staging is indicated for all newly diagnosed cases of IBC. Positron emission computed tomography (PET/CT) may be particularly beneficial in IBC as it provides both cross sectional imaging and functional imaging based on metabolism. In a retrospective study of IBC and locally advanced breast cancer, PET/CT detected metastatic disease in 46% of IBC cases and N3 nodal involvement in 90%. This study also showed PET/CT outperformed conventional imaging for bone metastases, distant lymph nodes, and liver metastases, whereas CT was more sensitive for lung metastases (98.3% vs. 97.4%) [18]. Decrease in SUV may be associated with increased survival in IBC patients undergoing neoadjuvant chemotherapy [19]. These retrospective studies should be confirmed prospectively but suggest that PET/CT can alter staging and management.

CT scan of the chest, abdomen, and pelvis and a bone scan to evaluate for bony metastasis are an appropriate alternative [15]. Routine brain imaging is not recommended for IBC in the absence of symptoms.

Molecular Biomarkers and Targeted Approaches

Currently, no molecular criteria have been established to differentiate IBC from non-IBC. Due to the rarity of the disease, most observational biomarker cohort studies are limited by small sample size [20]. Rarity of cases compounded by the high degree of heterogeneity has made an IBC-specific molecular signature difficult to identify [20–22]. The World IBC Consortium classified 137 IBCs compared to 252 non-IBCs by gene expression profiling. Differentially activated pathways included 8 pathways more activated in IBC (CTNB, HER2, MYC, RAS, INFα, INFγ, TNFα, and VEGF), and 4 pathways attenuated in IBC (ER, PR, p53, and TGFβ). Although most of these differences were driven by differential molecular subtype distribution, an IBC-specific 79-gene signature based on this data was found to be prognostic of distant metastasis-free survival in a non-IBC series [23].

Next generation sequencing (NGS) technologies, epigenetic analysis, microRNA expression profiling, and reverse-phase protein lysate arrays have been used to define the molecular characteristics of IBC and potential targetable strategies [21, 24–29]. Additional preclinical and clinical studies are required to evaluate whether biomarker-based targeted therapies may be beneficial to IBC patients.

Classic Biomarkers: Hormone Receptors and Human Epidermal Growth Factor Receptor 2 (HER2)

IBC has lower rates of hormone receptor expression and higher rates of human epidermal growth factor receptor (HER2) positivity and TNBC compared to non-IBC [30, 31]. Similar to non-IBC, patients with estrogen receptor-negative IBC have a shorter disease-free survival and poorer prognosis than patients with estrogen receptor-positive IBC [11]. Approximately 40% of IBCs have amplified HER2 and appear to have equivalent or marginally better prognosis compared with HER2-negative IBC [31, 32]. About 17 to 30% of IBCs are TNBC [33, 34] and survival is poor for TNBC (5-year OS, 37% for triple-negative IBC vs. 60% for other biologic subtypes) [35•]. In metastatic TNBC, OS for IBC is 15.2 months compared to 21–31 months for non-IBC [36]. Molecular subtyping of IBC has shown that although all the subtypes in non-IBC are represented in IBC, incidence differs. The World IBC Consortium reported lower prevalence of luminal A and higher prevalence of ErbB2+ subtypes in IBC versus non-IBC; luminal A subtype 19% versus 42%; $p < 0.001$ and the ErbB2+ subtype 22% versus 9%; $p < 0.001$ [23]. Multiple smaller data sets have reported higher incidence of the basal-like subtype in IBC [13, 37]. Although these biomarkers do not differentiate IBC from non-IBC, the higher incidence of basal-like IBC and lower incidence of luminal A-type IBC are associated with poor outcomes.

Epidermal Growth Factor Receptor (EGFR)

EGFR overexpression has been associated with cancer cell survival and metastasis [38]. EGFR is overexpressed in 18% of breast cancers, and up to 50% of IBCs have amplification of EGFR which is associated with poor prognosis [39, 40]. Preclinical studies demonstrated that suppression of EGFR signaling controls breast cancer tumor growth by enhancing apoptosis and suppressing cancer stem cells [41, 42]. Further study in IBC cells demonstrated targeting the EGFR pathway can shift the phenotype of IBC cells from mesenchymal to epithelial and also inhibited tumor growth and metastatic progression [43]. Therefore, EGFR is a rational target for IBC treatment. Lapatinib, a multi-tyrosine kinase inhibitor of HER2 and EGFR was evaluated in a phase 2 study of HER2-overexpressing relapsed or refractory IBC with a reported 39% response rate [44]. In the neoadjuvant setting, panitumumab, an anti-EGFR monoclonal antibody, combined with nab-paclitaxel and carboplatin has been studied in a phase 2 clinical trial. Preliminary data showed improved pathological complete response (pCR) rate of 44% in HER2-negative and triple negative IBC [45]; while, pCR rate was < 25% in IBC patients treated with combination anthracycline and taxane neoadjuvant chemotherapy [46]. However, recently, a phase 2 study of panitumumab along with nab-paclitaxel and carboplatin for patients with primary HER2-negative IBC reported pCR rates of 28%, 42% in triple-negative IBC, and 14% hormone receptor–positive/HER2-negative IBC. Panitumumab-associated side effects include neutropenia with the most frequent non-hematologic adverse event (AE) being skin rash [45]. This combination of panitumumab and chemotherapy showed the highest pCR rate ever reported in triple-negative IBC. Due to the positive impact of EGFR-targeted therapy for triple negative-IBC patients, a randomized phase 2 study (NCT02876107) is underway to definitively determine the role of panitumumab in triple negative-IBC and to further validate predictive biomarkers. Another randomized phase 2 study is also ongoing to define the role and safety of panitumumab in patients with HER2-negative IBC (NCT01036087).

RhoC GTPase

RhoC GTPase, a transforming oncogene, is a member of the Ras superfamily of small GTP-binding proteins. It is involved in cytoskeletal reorganization which partially recapitulates the

IBC phenotype such as tumor emboli formation and progression of metastasis via promoting cell adhesion, motility, and release of angiogenic cytokines such as vascular endothelial growth factor [47, 48]. Van Golden et al. showed > 90% of IBCs overexpressed *RhoC GTPase.* Farnesyl transferase inhibitors (FTIs) were used to reverse the RhoC-induced phenotype, manifested by a significant decrease in anchorage-independent growth, motility, and invasion in IBC cell lines [49, 50]. Similarly, Kaushal et al. showed that antiRhoC siRNA led to decreased invasion, motility, and migration of aggressive breast cancer cell lines [44]. Statins (HMG-CoA reductase inhibitors) may inhibit RhoC GTPase and, in a hypothesis generating retrospective study, hydrophilic statin use in patients with primary IBC was associated with improved PFS [51].

Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) Pathway

The *interleukin 6-JAK-STAT* pathway has been implicated in tumor differentiation, proliferation, apoptosis, increased sensitivity to cytotoxic agents, angiogenesis, recruitment of immune cells, and metastasis in human malignancies [52]. *JAK2* was found to be significantly activated in IBC (95%) compared to non-IBC (20%) with relatively higher levels of *STAT3* in IBC (55%) compared to non-IBC (7.7%) [53]. The pattern of JAK/STAT in treated non-IBC was found to rise after treatment indicating that the activation of the *JAK/STAT* pathway could be associated with treatment resistance. Inhibition of this pathway is a developing therapeutic strategy.

Ruxolitinib, a selective JAK1/2 inhibitor has been studied as monotherapy in IBC. Stover et al. conducted a non-randomized phase 2 study to evaluate the safety and efficacy of ruxolitinib in patients with refractory, metastatic triple-negative breast cancer. Pharmacodynamic analysis pre- and post-therapy suggested on-target activity, including a significant decrease in activated STAT3 positive cells and downregulation of *JAK–STAT* target genes. However, none of the 21 patients had objective response and the study was closed to further accrual. Ruxolitinib was well-tolerated with infrequent grade 3 or higher toxicities. The most common toxicity was fatigue. Unfortunately, ruxolitinib, as a single agent, did not meet the primary efficacy endpoint in refractory IBC despite on-target activity. At present, study of combination ruxolitinib with neoadjuvant chemotherapy in triple negative IBC is ongoing in one phase 1/2 and one phase 2 clinical trials (NCT02041429, NCT02876302).

Matriptase and c-MET

Matriptase is an epithelial-specific member of the type II transmembrane serine protease family and its dysregulation is associated with different cancers. Matriptase upregulates c-MET oncogene signaling by activating its ligand hepatocyte growth factor (HGF). Zoratti et al. demonstrated correlation of matriptase and c-MET expression in IBC patient samples with 95% of samples expressing matriptase and 77% expressing both matriptase and c-MET consistent with co-localization. In IBC cells, abrogation of matriptase expression decreased HGF activation and subsequent c-MET signaling resulting in impaired proliferation and invasion of IBC cells [54]. Inhibition of matriptase is a potential targeted therapy for IBC.

E-Cadherin

IBC is known to have higher rates of angiogenesis, lymphoangiogenesis, and dermal lymphatic emboli when compared to non-IBC. E-cadherin is a transmembrane adhesion protein that is highly expressed in IBC. Kleer et al. showed that E-cadherin was expressed in all IBC samples and tumor emboli uniformly while in non-IBC, E-cadherin expression was found in only 68% [55]. E-cadherin (which is a tumor suppressor in some breast cancers) is overexpressed in IBC and contributes to the aggressive lymphovascular emboli characteristic to IBC [56, 57]. Tomlinson et al. hypothesized that it is the expression of E-cadherin that uniquely promotes tumor progression in IBC [57]. Alpaugh et al. demonstrated that together with E-cadherin overexpression, decreased sialyl-Lewis X/A carbohydrate ligand-binding epitopes on its overexpressed MUC1 synergistically led to tumor emboli in IBC [58].

Angiogenesis

IBC is characterized by markers of angiogenesis including endothelial cell proliferation and vessel density [59]. In a genome-wide expression profiling study of 37 IBC patient samples compared to 44 non-IBC, overexpression of genes belonging to a vascular cluster was identified. In another study, real-time quantitative RT-PCR for > 500 genes associated with angiogenesis and inflammation was performed on 36 IBC patient samples. In the 27 dysregulated genes identified in IBC, one-third were related to angiogenesis [60]. Based on this vascular profile, antiangiogenic therapies are a potential therapeutic target in IBC. It should be noted that combination of an antiangiogenesis agent, SU546 with anthracycline reported unfavorable cardiac toxicity [59, 61].

.Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A) inhibits vascular permeability and induces apoptosis in tumor cells. It was administered in IBC with conventional chemotherapy in the neoadjuvant setting in the BEVERLY-1 AND-2 trials [62]. The BEVERLY-1 (UCBG-0802) trial was a phase 2, single-arm trial, aimed to assess the addition of bevacizumab to neoadjuvant and adjuvant chemotherapy in the treatment of patients with HER2-negative inflammatory

breast cancer. After neoadjuvant therapy, 19% (19/100 patients; $p = 0.16$) of patients achieved a pCR according to centralized review. Overall response rate (ORR) of chemotherapy with bevacizumab was 67% compared to the control arm (ORR 81%). The most frequent grade 3–4 events during the neoadjuvant phase were neutropenia (89%) and proteinuria (7%) during the adjuvant phase. The authors concluded that bevacizumab did not provide clinical benefit to patients with non-metastatic HER2-negative IBC [63•].

The BEVERLY-2 trial was designed to evaluate neoadjuvant bevacizumab combined with trastuzumab and chemotherapy in patients with primary HER2-positive IBC [64]. The pCR rate was 63.5% (33/52 patients) after neoadjuvant therapy. The most common AEs were asthenia and nausea, both 69%. However, the pCR rate was comparable to a previously published report of 62.5% pCR when trastuzumab was added to preoperative chemotherapy [65]. Taken together, bevacizumab failed to show additional advantage in improving pCR rates in IBC. One hypothesis is that IBC has high expression of non-VEGF angiogenic factors which cannot be sufficiently blocked by bevacizumab alone [25].

Multi-tyrosine kinase inhibitors (TKIs) such as sorafenib and sunitinib have been studied in IBC cell lines, demonstrating inhibition of IBC cell proliferation [66]. Pazopanib is another TKI-targeting VEGF receptors 1-3, platelet-derived growth factor receptors-α/-β. Cristofanilli et al. reported a phase 2, multi-arm study evaluating lapatinib, pazopanib, or the combination in patients with relapsed HER2-positive IBC [67]. Cohort 1 was closed due to the high-grade diarrhea observed with this combination in another study (VEG20007). In Cohort 2, 1000 mg lapatinib and 400 mg pazopanib were administrated in combination. The lapatinib-pazopanib combination was associated with a higher ORR (47% lapatinib alone, 31% pazopanib alone, and 58% for the combination) but no increase in PFS (16.0 weeks lapatinib alone, 11.4 weeks pazopanib alone and 16.0 weeks for the combination). Rates of grade ≥ 3 AEs were similar with pazopanib alone (46%) and the combination treatment (50%); however, more dose reductions and treatment delays were observed in the combination group. Development of a safe and potent multi-targeted TKI agent remains an area of need in IBC.

Current Treatment Approaches

Systemic Therapy

Chemotherapy

Neoadjuvant chemotherapy including anthracycline, cyclophosphamide, and sequential taxane is the standard approach for HER2-negative IBC. In a large study of 178 IBC patients, upfront anthracycline plus cyclophosphamide (AC) followed by weekly paclitaxel resulted in a 5-year OS rate of 40% and 10-year OS of 33% [68]. Dose-dense delivery of chemotherapy (DD-CT) has been shown in a meta-analysis to decrease the risk of recurrence and breast cancer mortality for early stage breast cancer patients [69]. However, its role in IBC is less clear. In a phase 3 study of DD-CT in high-risk breast cancer, DD-CT was shown to increase rates of pCR (18% vs. 10%) but did not translate to DFS benefit in the IBC subgroup [15, 70]. In TNBC, the addition of carboplatin to taxane (with sequential AC) chemotherapy has been reported to improve pCR rates; however, with limited long-term data (none specific to IBC), the adoption of this strategy remains in question [71–73]. At present, ongoing neoadjuvant trials include carboplatin and nab-paclitaxel in patients with locally advanced or inflammatory TNBC (NCT01525966) and eribulin followed by doxorubicin and cyclophosphamide (AC) chemotherapy for participants with HER2-negative IBC (NCT02623972).

Subsequent therapy in the adjuvant setting does not diverge significantly from non-IBC and is generally tailored to a high-risk strategy. The CREATE-X study showed addition of six to eight cycles of capecitabine to standard adjuvant therapy increased the disease-free and OS in HER2-negative non-IBC with the magnitude of benefit in TNBC [74].

For metastatic disease, the treatment strategy mirrors that of non-IBC without any regimens specific to IBC. Clinical trials should be considered, including phase 1 trials if appropriate (Table 1), particularly for patients with chemotherapy resistant IBC. Palliative use of surgery and radiation is also appropriate in select cases.

Hormonal Therapy

Hormonal agents should be used for estrogen receptor-positive IBC with consideration for intensified endocrine therapy with ovarian function suppression in premenopausal women given higher risk disease [75, 76]. For postmenopausal patients, adjuvant endocrine therapy with aromatase inhibitor extended beyond 5 years should be considered.

HER2 Targeted Therapy

Forty to 60% of IBC cases are HER2 amplified [77]. The addition of HER2-directed agents is appropriate for IBC tumors that are HER2 amplified in both the neoadjuvant and adjuvant settings. In the NOAH trial, a subgroup analysis for IBC showed trastuzumab added to neoadjuvant chemotherapy improved the pCR rate to 48%, 5-year event-free survival to 64%, and 5-year OS to 74% [78]. Further advances in HER2-directed therapy such as dual HER2 inhibition [79], TDM-1 or ado-trastuzumab emtansine (in patients without pCR to neoadjuvant HER2-based therapy) [80], and extended adjuvant therapy with neratinib [81] may apply to the IBC population.

Table 1 Currently enrolling IBC-focused clinical trials

Clinical trial.gov identification no.	Phase of study	Agent(s)	Phase of treatment	Status	Title
NCT01894451	1	89Zr-bevacizumab	Neoadjuvant	Active, not recruiting	Pilot Study of Zirconium-89 Bevacizumab Positron Emission Tomography for Imaging Angiogenesis in Patients with Inflammatory Breast Carcinoma Receiving Preoperative Chemotherapy
NCT02041429	½	Ruxolitinib	Neoadjuvant	Active, not recruiting	Phase II Study of Combination Ruxolitinib (INCB018242) with Preoperative Chemotherapy for Triple Negative Inflammatory Breast Cancer Following Completion of a Phase I Combination Study in Recurrent/Metastatic Breast Cancer
NCT02876302	2	Ruxolitinib	Neoadjuvant	Recruiting	Phase II Study of Combination Ruxolitinib (INCB018424) with Preoperative Chemotherapy For Triple Negative Inflammatory Breast Cancer
NCT01036087	2	Panitumumab	Neoadjuvant	Active, not recruiting	Phase II Study of Panitumumab, Nab-paclitaxel, and Carboplatin for Patients with Primary Inflammatory Breast Cancer (IBC) Without HER2 Overexpression
NCT02876107	2	Panitumumab	Neoadjuvant	Recruiting	A Randomized Phase II Study of Neoadjuvant Carboplatin/Paclitaxel (CT) Versus Panitumumab/Carboplatin/Paclitaxel (PaCT) Followed by Anthracycline-Containing Regimen for Newly Diagnosed Primary Triple-Negative Inflammatory Breast Cancer
NCT03598257	2	Radiation therapy ± olaparib	Adjuvant	Recruiting	A Phase II Randomized Trial of Olaparib (NSC-747856) Administered Concurrently With Radiotherapy Versus Radiotherapy Alone for Inflammatory Breast Cancer
NCT03742986	2	Nivolumab	Neoadjuvant	Recruiting	Phase II Trial of Nivolumab with Chemotherapy as Neoadjuvant Treatment in Inflammatory Breast Cancer (IBC)
NCT03515798	2	Pembrolizumab	Neoadjuvant	Recruiting	A Prospective Multicenter Open-label, Randomized Phase II Study of Pembrolizumab in Combination with Neoadjuvant (F)EC-Paclitaxel Regimen in HER2-Negative Inflammatory Breast Cancer.
NCT02971748	2	Pembrolizumab	Adjuvant	Recruiting	A Phase II Study of Anti-PD-1 (Pembrolizumab) in Combination With Hormonal Therapy During or After Radiation in Patients with Hormone Receptor (HR)-Positive Localized Inflammatory Breast Cancer (IBC) Who Did Not Achieve a Pathological Complete Response (pCR) to Neoadjuvant Chemotherapy
NCT02411656	2	Pembrolizumab	Metastatic/recurrent	Recruiting	A Phase II Study of Anti-PD-1 (MK-3475) Therapy in Patients With Metastatic Inflammatory Breast Cancer (IBC) or Non-IBC Triple Negative Breast Cancer (TNBC) Who Have Achieved Clinical Response or Stable Disease to Prior Chemotherapy
NCT03202316	2	Atezolizumab, Cobimetinib, and Eribulin	Metastatic/recurrent	Recruiting	A Phase II Study of Triple Combination of Atezolizumab + Cobimetinib + Eribulin (ACE) in Patients with Recurrent/Metastatic Inflammatory Breast Cancer
NCT01796197	2	Paclitaxel, trastuzumab and pertuzumab	Neoadjuvant	Active, not recruiting	Phase II Trial of Paclitaxel Combined with Trastuzumab and Pertuzumab as Pre-Operative Therapy for Inflammatory Breast Cancer
NCT02132949	2	Pertuzumab and trastuzumab	Neoadjuvant	Active, not recruiting	A Multicenter, Multinational, Phase II Study to Evaluate Perjeta in Combination with Herceptin and Standard Neoadjuvant Anthracycline-Based Chemotherapy in Patients With HER2-Positive, Locally Advanced, Inflammatory, or Early-Stage Breast Cancer
NCT02623972	2	Eribulin	Neoadjuvant	Recruiting	A Phase 2 Study of Eribulin Followed by Doxorubicin and Cyclophosphamide as Preoperative Therapy for HER2-negative Inflammatory Breast Cancer
NCT01525966	2	Carboplatin and nab-paclitaxel	Neoadjuvant	Active, not recruiting	Phase II Trial of Neoadjuvant Chemotherapy with Carboplatin and NAB-Paclitaxel in Patients with Locally Advanced and Inflammatory Triple Negative Breast Cancer

Accessed on August 4th 2019 at www.clinicaltrials.gov

Surgery

Several studies have shown the improvement of both 5-year OS rate (46%) and DFS rate (40%) with surgical intervention compared with 5-year OS of 31% and DFS rate of 21% without surgical intervention [82]. Mastectomy including the overlying skin has been shown to improve local control, disease-free survival, and cancer-specific survival in IBC compared with radiation and chemotherapy or radiation alone in case series [83, 84]. Skin-sparing mastectomy and breast conserving therapy (BCT) are generally contraindicated for women with IBC given high rates of local recurrence (67% in the BCT group vs. 15% in the mastectomy group) that have been reported [85]. However, a small prospective cohort study of BCT in patients with IBC and good response to neoadjuvant chemotherapy showed excellent 5-year actuarial survival. They also noted that most locoregional recurrence was associated with widespread metastatic disease [86]. In the era of trimodal therapy for nonmetastatic IBC, the 2-year rate of locoregional recurrence was reported at 3.2% demonstrating rates similar to non-IBC [87]. Over 50% of IBC cases have axillary lymph node involvement at diagnosis; therefore, total mastectomy along with axillary dissection is recommended [88]. Sentinel lymph node dissection is also contraindicated given the high false-negative rates reported in IBC [89]. Breast reconstruction should be deferred until at least 6 months after the completion of radiation therapy.

Radiation Therapy

Postoperative radiation therapy (RT) is recommended for all patients with IBC for improved locoregional control. RT should cover the chest wall, axilla, supra- and infraclavicular nodes, and internal mammary nodes. Although the most effective dose of radiotherapy is debated, most experts advocate a total of 60 Gy dose with chest wall boost, and 66 Gy can be used as an alternative option for high-risk patients with poor response to preoperative systemic treatment, positive or close surgical margins, four or more positive nodes following preoperative systemic treatment, or age < 45 years with a proportionally increased toxicity [90, 91]. A retrospective study by Bristol et al. reported improved locoregional control with a total post-mastectomy chest wall dose of 66 Gy compared to 60 Gy for high-risk IBC cases (patients with less than a partial response to chemotherapy; positive, close, or unknown margins; or age < 45 years [90]. Locoregional RT can be administered in patients who remain inoperable after chemotherapy [92]. In a retrospective review of 87 cases, 22 patients received preoperative radiation with intent to achieve resectability. Only 12 of these patients received surgery and patients who did not receive surgery had poor outcomes with 9 of 10 dying from their disease [93].

Clinical Trials and Other Targeted Strategies

The development of specialized treatment strategies for IBC is an ongoing area of unmet need. Challenges arise due to the heterogeneous nature of IBC and its rarity. A few targeted strategies based on molecular markers were discussed previously. Further targeted strategies via PARP inhibition and immune checkpoint inhibition are reviewed here. Clinical trials for IBC are sorely needed, and trials that are active or currently enrolling at the time of this review are listed below (Table 1).

PARP Inhibitors

BRCA1 and *BRCA2*, two DNA repair genes, are critical for the survival and normal function of breast cancer cells. Breast cancer cells with BRCA1/2 mutations adapt and become reliant on other DNA repair mechanisms such as the PARP (poly ADP-ribose polymerase) enzyme, which repairs single-strand DNA breaks. Olaparib inhibits the PARP enzyme, which when combined with BRCA1 or BRCA2 mutation, renders cells susceptible to DNA damage ultimately resulting in cell death, a phenomenon termed synthetic lethality. Single-agent olaparib has been approved in germline BRCA1/2-mutated, HER2-negative (HR-positive or triple-negative) breast cancer [94]. Currently, radiation in combination with olaparib is being studied in a phase 2 randomized trial for IBC (NCT03598257). The rationale for this study is that PARP inhibitors induce sensitization to the DNA damage induced by radiation. About 300 participants will be recruited to assess whether radiation therapy together with olaparib may work better in treating patients with IBC than radiation therapy alone. Of note, a prior phase 1 study reported concerning toxicity with a similar PARP inhibitor/radiation combination. In the TBCRC 024 phase 1 study of concurrent veliparib (PARP inhibitor) with chest wall and nodal radiation for inflammatory or locoregionally recurrent breast cancer, rates of any grade 3 toxicity were 10% at year 1, but 46.7% at year 3 underscoring the need for long-term toxicity follow-up in trials of radiosensitizing agents [95].

Immunotherapy

Although not reviewed here, immune characterization of IBC is rapidly developing. Programmed cell death-ligand 1 (PD-L1) is overexpressed in some tumors to maintain immunosuppression in the microenvironment and allow for tumor progression. In IBC tumor cells, PD-L1 expression is reported at 0–36%. PD-L1 expression appears to be higher in peritumoral immune cells (40–66%), and may have prognostic or predictive value [96•]. Bertucci et al. found that PD-L1 expression predicted for pathologic response to neoadjuvant anthracycline-based chemotherapy, but was not predictive for metastasis-free or OS [97]. PD-L1 targeting has been

clinically successful in many tumor types and its potential in IBC is promising.

In March 2019, the Food and Drug Administration (FDA) granted an accelerated approval for the PD-L1 inhibitor atezolizumab, a fully humanized monoclonal antibody of IgG1 isotype against the PD-L1 protein, in combination with chemotherapy for the initial treatment of locally advanced or metastatic triple-negative breast cancers that are positive for PD-L1. Accelerated approval was based on results from the phase 3 IMpassion130 clinical trial, which compared atezolizumab plus nab-paclitaxel with placebo plus nab-paclitaxel as the first-line treatment for patients with triple-negative breast cancer [98]. Among the 369 patients with PD-L1-positive tumors, atezolizumab plus chemotherapy improved median progression-free survival (PFS) to 7.4 months from 4.8 months for those who received placebo plus chemotherapy. The ORR was 53% in the atezolizumab group versus 33% for the placebo group. The median OS was 25.0 months and 15.5 months, respectively. The most common side effects in the atezolizumab group included hair loss, peripheral neuropathy, cough, fever, fatigue, neutropenia, nausea, and hypothyroidism. AEs that led to the discontinuation of any agent occurred in 15.9% of the combination group versus 8.2% in the chemotherapy only group. Atezolizumab is the first immunotherapy agent approved in breast cancer. Given one-third of IBCs express PD-L1, immunotherapy is an attractive strategy for treatment. The MEK inhibitor cobimetinib increases PD-L1 expression; thus, atezolizumab and cobimetinib may act synergistically in IBC. Based on this hypothesis, a phase 2 study of atezolizumab, cobimetinib, and eribulin in patients with recurrent or metastatic IBC is currently enrolling (NCT03202316).

Pembrolizumab, a PD-1-directed monoclonal antibody, was investigated in patients with metastatic TNBC (mTNBC). In the phase 2 KEYNOTE-086 trial (NCT02447003), in cohort A, the PD-1 inhibitor elicited a 4.7% ORR in patients with heavily pretreated mTNBC; median PFS was 2.0 months, and median OS was 9.0 months. Treatment-related AEs occurred in 60.6% patients, including 12.9% with grade 3 or 4 AEs [99]. In cohort B, pembrolizumab as first-line therapy was evaluated in patients with PD-L1-positive mTNBC with ORR of 21.4% and disease control rate of 23.8%. The median duration of response was 10.4 months, the median PFS was 2.1 months, and the median OS was 18.0 months [100]. Pembrolizumab monotherapy had a manageable safety profile and showed durable antitumor activity as first-line and pretreated mTNBC. Clinical trials are ongoing to evaluate pembrolizumab in IBC in the neoadjuvant, adjuvant, and metastatic settings (NCT03515798, NCT02971748, NCT02411656). Another anti-PD-1 monoclonal antibody, nivolumab, is also under investigation with a single-arm open-label multicenter phase 2 study of nivolumab with neoadjuvant chemotherapy in patients with non-metastatic IBC (NCT03742986).

Conclusions

Inflammatory breast cancer is a rare and highly aggressive subtype of breast cancer that requires immediate and aggressive treatment. Early diagnosis is paramount to timely initiation of therapy with multimodal therapy including neoadjuvant chemotherapy, surgery, and radiation therapy resulting in the best long-term outcomes for non-metastatic disease. If available, IBC patients should be treated in centers with open clinical trials since standard of care treatments leave room for improvement.

Molecular subtyping may help define IBC as a clinical entity, reveal mechanisms of pathology, and identify targets for therapy. Despite advances in the treatment of IBC, overall survival is still poor compared with non-IBC. Future investigation seeks to define pathognomonic molecular signatures, test novel treatment modalities, and identify biomarkers of response. Immunotherapy is one promising and rapidly developing strategy; however, more studies are necessary to understand the immunity specific to IBC and evaluate the determinants of response to immune-based therapy. Owing to the rarity of IBC and its poor prognosis, clinical trials specifically designed for this unmet need should be prioritized.

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Compliance with Ethical Standards

Conflict of Interest Irene Kang reports personal fees from Puma Biotechnology and from Pfizer outside the submitted work. Julie Lang reports grants from ANGLE Parsortix and personal fees from Genomic Health outside the submitted work. Grace Li and Justin Tiulim declare no conflicts of interest relevant to this manuscript.

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- • Of importance
- •• Of major importance

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