What Progress Have We Made in Managing Inflammatory Breast Cancer?

By Shaheenah Dawood, MBBCH, MRCP (UK) [4] and Massimo Cristofanilli, MD [5]

Inflammatory breast cancer (IBC) is a rare and aggressive form of the disease. It is diagnosed based on clinical signs of a rapidly enlarging, tender, erythematous, edematous breast that often presents without an underlying breast mass. IBC historically was considered a uniformly fatal disease. With the advent of multimodality treatments including primary systemic chemotherapy, surgery, and radiation therapy, approximately one-third of women diagnosed with IBC will become long-term survivors. This review examines the limitations of the current definition of IBC, explores our current understanding of the biology of IBC, and reviews the many exciting advances in locoregional and systemic treatment of IBC.

Inflammatory breast cancer (IBC), a term first coined by Lee and Tannenbaum in 1924,[1] is an aggressive form of breast cancer that accounts for approximately 1% to 6% of all cases in the United States.[2] Over the years, various clinical definitions have been used to describe IBC. The most widely used is the definition introduced by the American Joint Committee on Cancer, which states that IBC "is a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying palpable mass."[3]

Two varieties of IBC have been identified in the literature. Primary IBC refers to a de novo presentation in which IBC develops in a previously otherwise normal breast. Secondary IBC is a term used to describe a situation where a previously diagnosed noninflammatory invasive breast cancer acquires inflammatory features or when an inflammatory recurrence occurs at the site of a mastectomy for a noninflammatory breast cancer. For the purposes of this review, we will use the term IBC to mean primary IBC.

Epidemiology

IBC is a rare distinct epidemiologic form of locally advanced breast cancer. In a recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database, Hance et al[4] assessed data from 180,224 histologically confirmed invasive breast cancer patients between the years 1988 to 2000. They found that women with IBC comprised approximately 2% of all breast cancer cases in this population, tended to present at a younger age, and were more likely to have metastatic disease at presentation. Patients with IBC also had a shorter survival (median: 2.9 years) than women with noninflammatory breast cancer, accounting for 7% of all breast cancer-specific deaths. Due to the rarity of IBC, few epidemiologic studies have addressed the etiology of IBC and most are retrospective. Factors such as age at menarche, menopausal status, smoking, and alcohol consumption have not been consistently associated with IBC.[5,6] In a small retrospective study by Chang et al,[6] high body mass index (BMI > 26.65 kg/m²) was associated with an increased risk for IBC compared to non-IBC patients (odds ratio = 2.40, 95% confidence interval = 1.05-5.73). These observations require further prospective validation before determining their value.

Clinical Characteristics and Classification of IBC

FIGURE 1

Left Inflammatory Breast Cancer
Unlike other forms of invasive breast cancer that usually present with a painless mass, IBC is associated with a variety of clinical presentations, making the diagnosis somewhat difficult. In 1956, Haagensen[7] recognized this problem and established a set of clinical diagnostic criteria that are still in use. Clinical characteristics of IBC (Table 1) include a painful, tender, rapidly enlarging breast, and edema and erythema of the skin of the breast (Figure 1). More often than not, a breast mass is not palpable. Other changes associated with IBC include a "peau d'orange" (skin of an orange) appearance of the overlying skin of the breast,[8] reflecting the exaggerated appearance of hair follicle pits that occur secondary to skin edema. Flattening, crusting, and retraction of the nipple can also occur as the disease progresses.[2]

**TABLE 1**

<table>
<thead>
<tr>
<th>Clinical Characteristics of Inflammatory Breast Cancer</th>
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<tr>
<td>Pain and tenderness</td>
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<td>Diffuse warmth and erythema</td>
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<tr>
<td>Edema and enlargement of the breast</td>
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<tr>
<td>Rapid enlargement of the breast</td>
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<tr>
<td>Sensation of heavier breast</td>
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<tr>
<td>Diffuse firmness on palpation</td>
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<tr>
<td>Peau d'orange and ridging</td>
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<tr>
<td>Thick skin with or without palpable mass</td>
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Unfortunately, most of the clinical characteristics associated with IBC are nonspecific, resulting in a significant number of cases that are initially diagnosed as mastitis or breast abscess. This leads to delays in appropriate investigation and, together with the rapid rate of disease progression (usually less than 2 months) that is pathognomonic of IBC, a significant proportion of patients present with advanced disease. Supporting studies have shown that the involvement of ipsilateral axillary and supraclavicular lymph nodes is common, with up to one-third of patients also presenting with distant metastases at the time of diagnosis.[1,2,4,9] According to the American Joint Committee on Cancer, IBC is classified as a T4d tumor, thus classifying all IBC patients as stage IIIB, IIIC, or IV, depending on nodal status and the presence of distant metastases.[3]

**Molecular Biology of IBC**

The designation of "inflammatory" in IBC derives from breast skin changes that resemble an acute inflammatory process. However, a true state of inflammation is not present in IBC. The skin changes are secondary to invasion of the dermal lymphatic vessels by tumor emboli,[1,2] which is a typical pathologic feature described in IBC. These emboli are believed to obstruct lymphatic drainage, thereby contributing to the observed clinical signs of erythema and edema.

**TABLE 2**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Expression</th>
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<tr>
<td>HER2[12]</td>
<td>Overexpression</td>
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<tr>
<td>RhoC GTPase[48]</td>
<td>Overexpression</td>
</tr>
<tr>
<td>E-cadherin[13]</td>
<td>Overexpression</td>
</tr>
<tr>
<td>p27kip1[19]</td>
<td>Lack of expression</td>
</tr>
<tr>
<td>Estrogenv/ progestrone receptor[10]</td>
<td>Lack of expression</td>
</tr>
<tr>
<td>VEGF[15,16]</td>
<td>Overexpression</td>
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Since the diagnosis of IBC is made on clinical grounds, absence of dermal lymphatic invasion does not exclude the diagnosis. Additional pathologic characteristics (Table 2) include high-grade, negative-hormone-receptor status[10,11] and overexpression of HER2[12]—all factors that predict for a poor outcome.[4] Other molecular features of IBC include mutation of the p53 suppressor gene, overexpression of E-cadherin,[13] and an increased expression of proangiogenic factors. IBC tumors are known to be highly vascular neoplasms with prominent features of angiolympatic invasion manifested pathologically by increased microvessel density, high endothelial cell proliferation, and expression of angiogenic factors (basic fibroblast growth factor [bFGF], vascular endothelial growth factor [VEGF], interleukin [IL]-6 and IL-8).[14-16] The IBC animal xenograft model WIBC-9 has also been shown to overexpress other angiogenic factors such as Ang-1, Tie-1, and Tie-2, compared to noninflammatory breast xenografts (SK-BR3).[17] Lymphangiogenic factors such as VEGF-C, VEGF-D, VEGFR-3, Prox-1, and lymphatic vessel endothelial receptor 1 has also been shown to be strongly expressed in IBC.[18]

The role of p27kip1, a cyclin-dependent kinase inhibitor that is thought to be involved in the induction of apoptosis, cell adhesion, promotion of cell differentiation, and regulation of drug resistance, has recently been evaluated in patients with IBC. M.D. Anderson Cancer Center researchers evaluated the role of p27kip1 in 38 IBC patients who had received primary systemic chemotherapy.[19] In this study, p27kip1 was downregulated in the majority of patients (84.2%) and predicted for poor outcome.

**Diagnostic Imaging**

Diagnostic imaging plays an important role in the staging of breast tumors. In patients with IBC, the characteristic mammographic changes include skin thickening (with associated stromal or trabecular thickening), diffusely increased breast density, and an overall increase in the size of the breast.[20,21] An underlying mass is usually not present or may be obscured by surrounding changes in the breast. Microcalcifications may also be observed but are often masked by the increased breast density. Similarly, ultrasound of the breast in an IBC patient typically shows skin thickening with associated underlying tissue edema and dilated lymphatics. Unlike such changes on mammograms, underlying masses and associated regional lymphadenopathy are more easily visible by ultrasound. Importantly, both imaging modalities cannot distinguish IBC from other breast conditions such as mastitis, locally advanced breast cancer with skin changes, and cutaneous T-cell lymphoma. It is therefore important that clinical history, imaging, and pathologic evidence of invasive carcinoma be used together to make a diagnosis of IBC.

Other imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and positron-emission tomography (PET) scanning have not been studied extensively in IBC patients. MRI is increasingly being used in the diagnosis and staging of patients with breast cancers due to its increased sensitivity for invasive breast cancer,[22] lack of ionizing radiation, and superior characterization of enhancing parenchyma. MRI has also been useful in characterizing tumor physiology and in monitoring the response of breast tumors to primary systemic chemotherapy.[23,24] PET is rapidly emerging as a technique for comprehensive staging; however, its superiority over other imaging modalities has yet to be proven.

**Multidisciplinary Treatment**

FIGURE 2
Algorithm for Inflammatory Breast Cancer Management

IBC is a challenging clinical entity characterized by rapid progression and early dissemination. Historically, treatment with surgery and/or radiation therapy resulted in fewer than 5% of IBC patients surviving beyond 5 years.[25] With the introduction of combination chemotherapy and its integration into a multimodality approach to treatment (Figure 2), the prognosis for IBC patients has undergone a dramatic change: Once a uniformly fatal disease, IBC is now associated with 15-year survival in 20% to 30% of patients.[26,28] Due to the rarity of the disease, its rapid progression, and overall poor prognosis, clinical trials enrolling IBC patients have been few, with the number of evaluable IBC patients small. As a result, most of the data considered instrumental in guiding and improving the management of IBC have been extrapolated from trials showing improvements in the management of non-IBC patients and on retrospective analysis of pooled data from IBC-only cohorts.

Combination Therapy

The integration of chemotherapy, surgery, and radiation therapy has evolved to become a standard approach to treating IBC (Figure 2), with primary systemic chemotherapy being the initial component. The use of anthracycline-based chemotherapy is known to improve both disease-free and overall survival of patients with early-stage breast cancer.[27] Ueno and colleagues[28] published the M.D. Anderson Cancer Center experience of combined-modality treatment in IBC patients over the past 20 years. In this study, a total of 178 patients were treated with doxorubicin-based primary chemotherapy followed by local therapy with irradiation with or without mastectomy, and adjuvant chemotherapy. The results of this study highlighted two important aspects of IBC management. First, using a combined-modality approach, 28% of the patients were alive and without evidence of disease beyond 15 years. Median survival was 37 months, with an overall survival of 40% at 5 years and 33% at 10 years. Second, 71% of all IBC patients had an objective response to the doxorubicin-based primary chemotherapy, with 12% achieving a complete pathologic response. Disease-free survival at 15 years was 44% in patients who attained a complete pathologic response, 31% in those who attained a partial response, and 7% in those who did not respond to primary systemic chemotherapy. These two aspects of the study demonstrate how the integration of combined-modality therapy has essentially changed the natural history of IBC, with the assessment of response to primary chemotherapy also giving us the ability to predict which patients will have a better prognosis.

The addition of taxanes to primary systemic chemotherapy in the treatment of IBC has also shown benefit. A retrospective study that compared FAC (fluorouracil/doxorubicin/cyclophosphamide) alone to FAC followed by paclitaxel in patients with IBC showed higher pathologic response rates (25% vs 10%), median overall survival, and progression-free survival in the group receiving FAC followed by paclitaxel.[29]

Trastuzumab

Trastuzumab (Herceptin), a humanized monoclonal antibody directed against the HER2 receptor, has essentially revolutionized the treatment of HER2-overexpressing breast cancer. The incorporation of
trastuzumab into the treatment of HER2-overexpressing metastatic[30] and early-stage breast cancer has substantially improved overall survival,[31,32] reducing the risk of death by half. A high incidence of HER2 overexpression has been observed in patients with IBC, making it the ideal setting for the use of trastuzumab.

At least two prospective studies that included patients with IBC have addressed the issue of trastuzumab in combination with primary systemic chemotherapy. Using a combination of every-3-week docetaxel and cisplatin with weekly trastuzumab for four cycles in 48 patients with locally advanced disease (including 6 patients with IBC), Hurley and colleagues achieved a complete response (CR) in 22% of patients.[33] Van pelt and colleagues[34] used a combination of docetaxel and trastuzumab in 22 patients (9 of whom had IBC) and achieved a CR in 40%. Although both trials are small, and large randomized trials assessing only IBC cohorts are unlikely, when considered in combination with the survival advantage seen with the addition of adjuvant trastuzumab in early-stage breast cancer,[31,32] these data strongly support the use of trastuzumab-based regimens in the treatment of patients with HER2-overexpressing IBC.

Lapatinib

Lapatinib (Tykerb) is an orally active small molecule that reversibly inhibits the tyrosine kinase component of both HER2 and epidermal growth factor receptor-1 (ErbB-1). A recent study[35] showed that lapatinib in combination with chemotherapy reduces the risk of disease progression by 51% in patients with metastatic breast cancer whose disease had progressed on trastuzumab-containing chemotherapy regimens. Based on previous observations of the activity of this agent in recurrent IBC,[36,37] Cristofanilli and colleagues[38] assessed the role of lapatinib in combination with paclitaxel as part of the primary chemotherapy regimen in patients with IBC. This phase II trial enrolled patients with newly diagnosed IBC who received daily lapatinib at a dose of 1,500 mg initially as monotherapy for 14 days, following which it was given in combination with weekly paclitaxel (80 mg/m$^2$) for 12 weeks. Of the 21 patients who had HER2-overexpressing IBC, 95% had a clinical response. The researchers hope to prospectively validate the observed good tolerance and remarkable clinical activity in a phase III setting.

Other Agents

Other agents that are currently being studied for the treatment of IBC include antiangiogenic agents and Ras pathway inhibitors. IBC tumors are known to be highly vascular tumors that express a number of angiogenic factors such as VEGF.[15] This observation prompted a number of studies looking at the role of anti-VEGF agents (eg, bevacizumab [Avastin],[39] SU5416[40]) combined with chemotherapy in the treatment of IBC, with promising results. Based on encouraging preclinical and phase I studies of farnesyl transferase inhibitors (which block the farnesylation of prenylated proteins, including the Rho subfamily of GTPases that is highly expressed in IBC), these agents are currently being studied in combination with chemotherapy in both the IBC and non-IBC settings.[41,42]

Surgery and Radiotherapy

With advances in primary systemic chemotherapy to control distant metastases, the next component of the multimodality approach (directed at decreasing the risk of locoregional recurrence) is the integration of surgery and radiotherapy—a strategy that has been shown to improve survival.[43] With the introduction of primary systemic chemotherapy into the treatment paradigm of IBC, most patients are able to have adequate surgery, whereby attaining negative margins is the primary goal, with mastectomy and axillary dissection being the preferred choice.[44,45] Flemming and colleagues[45] retrospectively reviewed the effectiveness of mastectomy in patients with IBC treated at the M.D. Anderson Cancer Center. Of the 178 patients treated, those who had a response to primary chemotherapy and underwent a mastectomy had significantly lower rates of local recurrence and exhibited improved disease-specific survival, compared to those who responded to primary chemotherapy but did not undergo mastectomy.

Data concerning the use of sentinel lymphadenectomy (SL) following a mastectomy suggests that it may not be a reliable method of assessing the axillary lymph nodes. Stearns and colleagues[46] reported on the reliability of sentinel lymph node biopsy after primary systemic chemotherapy in a cohort that included eight patients with IBC. Of these eight patients, two had nonidentifiable sentinel lymph nodes, one had negative nodes on both axillary lymph node dissection (ALND) and SL, three had positive nodes on both ALND and SL, and two had positive nodes on ALND that were missed by
SL. These results suggest that SL should not be used routinely in IBC until the approach is prospectively validated in a larger cohort of IBC patients. One explanation for the possible decreased predictive value of SL in IBC is the fact that the presence of tumor cells that block lymphatics results in an inability of these blocked lymphatics to carry either the radiocolloid or blue dye necessary for the evaluation of sentinel lymph nodes.[46]

Apart from the introduction of primary chemotherapy in the management of IBC, another major advance in this setting is our ability to achieve local control rates (70%-80%) using a combination of aggressive surgery and radiation therapy. IBC has long been recognized as having a rapid proliferative potential compared to non-IBC, and one mechanism of developing resistance to standard radiation therapy protocols is the repopulation of tumor cells between radiation treatments. To improve locoregional control rates, research has focused on using accelerated-hyperfractionated radiation therapy in order to circumvent rapid tumor cell growth rate. Current study data generally support the use of postmastectomy accelerated-hyperfractionated radiation to 66 Gy, with target volumes including the chest wall and lymph nodes within the axillary, infraclavicular, supraclavicular, and internal mammary regions.[47]

**Genetic Signature of IBC**

A more thorough understanding of the biology of IBC is required for several reasons:

1. Pending the identification of a molecular signature that can accurately differentiate IBC from other types of breast cancer, IBC remains a clinical diagnosis. This leads to wide variability in clinical reporting, which presents a serious challenge for clinicians when comparing clinical trials involving cohorts of patients with IBC, and also when assessing the accuracy of statistical data regarding the incidence of IBC.[4]

2. Despite a modern multidisciplinary treatment approach to IBC, prognosis is still poor compared to non-IBC.

3. IBC-specific biologic markers need to be identified to develop other therapeutic agents that can affect outcome.

4. It will be important to distinguish locally advanced breast cancer from IBC at the molecular level, so that diagnostic and therapeutic programs can be more individualized.

A number of genes have been identified that might contribute to the aggressive phenotypic feature of IBC. Van Golen and colleagues[48] identified two genes that are uniquely altered in IBC specimens compared to non-IBC samples: (1) Rhoc GTPase, a member of the Ras superfamily of small GTP-binding proteins involved in cytoskeletal reorganization, was found to be overexpressed in > 90% of IBC tumors compared to 38% of non-IBC specimens. Rhoc GTPase is thought to contribute to the metastatic characteristic of IBC by promoting cell motility/invasion, disruption of cell-cell junctions, and upregulation of angiogenic factors (VEGF, bFGF).[49] (2) LIBC (lost in inflammatory breast cancer) gene expression was lost in 80% of inflammatory specimens compared to 21% of non-IBC tumors. Both genes are promising avenues for further investigation.

**Conclusions**

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The management of IBC has evolved over the past few decades. The recognition of the importance of a multidisciplinary approach targeting both local and systemic disease, and the incorporation of anthracyclines and taxanes has resulted in improvements in both disease-free and overall-survival rates. Incorporation of targeted agents such as trastuzumab will likely show further improvements in the future.

Despite the progress made, most women with IBC will relapse and succumb to this aggressive disease. Clearly, further research is required to provide appropriate diagnostics and direct therapeutics that will lead to improved prognoses. The understanding of the genetic components driving the aggressive phenotypic feature of IBC is a critical step in the overall management strategy. Research striving to develop targeted therapies will be driven by our understanding of these genetic components. Future potential targets for therapy include RhoC, angiogenic factors, and overexpressed E-cadherin.

Perhaps the biggest hurdle we must overcome is the need for larger trials to establish efficacy of agents such as lapatinib in patients with IBC. The only way to accomplish this will be through multi-institutional participation in clinical trials geared toward IBC-only cohorts.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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