Inflammatory Breast Cancer

What to Know About This Unique, Aggressive Breast Cancer

Arjun Menta[a], Tamer M. Fouad, MD[b,c], Anthony Lucci, MD[b,d], Huong Le-Petross, MD[b,e], Michael C. Stauder, MD[b,f], Wendy A. Woodward, MD, PhD[b,f], Naoto T. Ueno, MD, PhD[b,g], Bora Lim, MD[b,g,*]

KEYWORDS

• Inflammatory breast cancer • Trimodality care • Clinical trials • Breast changes

KEY POINTS

- Inflammatory breast cancers have unique characteristics that are not typical presentation of breast cancers.
- Inflammatory breast cancer carries features that can be easily confused with other skin diseases, such as infection (mastitis or cellulitis), and often are attempted to be treated with antibiotics.
- Delayed diagnosis of inflammatory breast cancer can result in a dismal clinical outcome; therefore, it is critical to make a timely and accurate diagnosis at the beginning.
- Trimodality care regardless of response is appropriate in all stage III and most stage IV cases: chemotherapy, surgery, and radiation.
- Direct and efficient referral system via networking in community can facilitate this process of accurate and timely diagnosis and treatment of inflammatory breast cancer.

The authors have nothing to disclose.

[a] The University of Texas at Austin, 110 Inner Campus Drive, Austin, TX 78705, USA; [b] Morgan Welch Inflammatory Breast Cancer Research and Clinic Program, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; [c] Department of Medical Oncology, The National Cancer Institute, Cairo University, Cairo 11796, Egypt; [d] Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; [e] Breast Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; [f] Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; [g] Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

* Corresponding author. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030.

E-mail address: blim@mdanderson.org

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INCIDENCE, MORTALITY, AND RISK FACTORS

Incidence of Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare form of breast cancer that accounts for only about 2% to 4% of all breast cancer cases in the United States.[1] Despite its low incidence, IBC contributes to 7% of breast cancer–caused mortality.[2] Based on the data from the Surveillance, Epidemiology, and End Results (SEER) program of National Cancer Institute, the diagnosis of IBC between 1973 and 2002 has increased at an annual rate of between 1.23% and 4.35% per year, which is a much higher rate of increase than the incidence of overall breast cancer diagnosis, which is 0.42%. In Western Africa, or Egypt, this occurrence is as high as 10%, and this justifies a collective international effort to better understand the distinctive biological, clinical aspect of IBC as well as to discover novel targets for this unique and rare disease entity. The first scientific documentation of IBC was noted in the eighteenth century by St. Charles, as a female patient with a red and swollen breast.[3]

Risk Factors of Inflammatory Breast Cancer

High body mass index continues to be recognized as an independent risk factor of IBC.[4] No association with inherited genetic mutations or family history has been clearly demonstrated. Less established and yet possible risk factors that need investigation are the viral infections or chronic inflammation as either causative event for the occurrence of IBC or mediators of the specific pathobiology of IBC, which may explain some racial and regional differences.[5,6] The association between the exposure to certain types of viral infection or chronic inflammation has been suggested and needs to be further studied.

Histopathologic Definition of Inflammatory Breast Cancer

Scattered tumor emboli on biopsy or surgical specimen and dermal lymphatic invasion are key histopathologic findings of IBC.[7,8] About 75% of IBC tumor samples exhibit dermal lymphatic invasion and thereby aid in making the diagnosis, but this is neither required nor suffices for the diagnosis of IBC.[9] The scattered distribution of tumor often as emboli throughout the breast contributes to the difficulty in detecting this disease on mammogram. The relative proportion of breast cancer molecular subtypes is different between IBC and non-IBC. In IBC, the incidence of hormone receptor (HR) -positive subtype is relatively lower, and both HER2-positive and triple-negative breast cancer (TNBC) are higher: 40% of HER2-positive, and 30% in TNBC than non-IBC.[10] A recent retrospective review of 659 patients with IBC showed that about 4.5% IBC showed lobular type lower compared with 10% in all breast cancer. Most tumors are modified nuclear grade 3. All subtypes across showed 62% to 68% 3-year overall survival (OS). This also applies to the HR-positive IBC. Same stage HR positive IBC has significantly worse prognosis compared to HR positive non-IBC.[11] Histologic type of lobular versus ductal did not affect survival.[12]

CURRENT CLINICAL DIAGNOSIS OF INFLAMMATORY BREAST CANCER

Clinical Diagnosis

Rapid changes in the skin overlying the affected breast (erythema, edema, and peau d'orange affecting a large area of breast) and pathologic evidence of invasive carcinoma are basic elements for the diagnosis of IBC. Changes of skin or underlying mass occur within 3 to 6 months, offering an important point to distinguish IBC from noninflammatory locally advanced breast cancer.[13] In some cases, skin can be the only site of disease. The current American Joint Committee on Cancer (AJCC)

guideline defines IBC as a separate "clinico-pathologic entity" with the erythema and edema occupying at least one-third of the breast, that can extend to the whole breast and across to the contralateral breast involving mediastinum, upper extremities, and neck area.[14] A typical case of IBC is depicted in **Fig. 1**.

International expert panel recommended diagnosis guideline of IBC is summarized in **Table 1**.[13] Note the difference in description of onset in the international consensus of erythema, edema, and OR peau d'orange versus the AJCC staging that requires erythema. This diagnosis criteria based on skin changes highlights that at times a patient may not have classically "red" skin but clearly may have skin symptoms consistent with IBC. It is particularly true among women with darker skin tones. Baseline laboratory tests that need to be performed at diagnosis include routine laboratory tests like complete blood count and SMA-12, tumor markers, for example, cancer antigen 15-3 and CEA, which can help assess patients at the initial diagnosis, in support of staging.[15] Local imaging with mammogram and ultrasound (US), complete staging with imaging modality, with more recent emphasis on highly sensitive PET/computed tomography (CT) utilization, is important (covered in later discussion).

Breast Imaging

For locoregional imaging in diagnosis of IBC, mammography and US remain the current standard of care. The baseline mammography imaging can reveal information like microcalcifications, architectural distortion, trabecular thickening, and global skin thickening.[16] Because of the painful inflamed breast-limiting optimal compression required for mammography and the increased mammographic density from global edema obscuring visualization of an underlying breast mass, mammography detects 68% of a primary breast lesion compared 94% with US and 98% with MRI.[17] The actual primary breast lesion may not be detected on imaging in all cases with only diffuse skin thickening seen; however, the lack of an imaging-detected breast mass does not exclude the diagnosis of IBC. Mammography is still recommended to provide screening of the contralateral breast.[16]

US can detect a solid mass, parenchymal changes, or skin thickening in patients with IBC better than mammography, with reported sensitivity of 92% to 96%.[18,19] About one-third of patients had tumor emboli in dermis confirmed by histopathologic

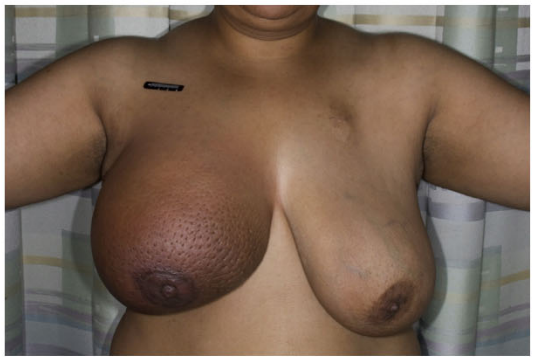

Fig. 1. Swollen, inflamed breast on the right side. The patient first noted a small red patch, which soon spread within a 4-week period of time. Biopsy testing confirmed invasive ductal carcinoma. The patient was treated at Morgan Welch Inflammatory Breast Cancer Clinic at the University of Texas MD Anderson Cancer Center.

Table 1
Diagnosis guideline of inflammatory breast cancer based on expert consensus

Minimum criteria required for the diagnosis of IBC	
Onset	Rapid onset of breast erythema, edema and/or peau d'orange, with or without an underlying breast mass
Duration	History of such findings no more than 6 mo, mostly within 3 mo
Extent	Erythema and/or edema occupying at least 1/3 of whole breast
Pathology	Pathologic confirmation of invasive carcinoma
Pathologic specimen diagnosis	
Parenchyma	Core biopsy-proven invasive carcinoma
Skin	Any suspicious lesions should be biopsied with at least 2 skin punch biopsies
Biomarker	Same procedure for ER/PR and HER2 as in non-IBC

examination.[18] Many have confirmed axillary lymph node involvement better detected by US.[19] Breast MRI and molecular breast imaging (MBI) show higher sensitivity in the detection of invasive breast cancers, including IBC.[20] These modalities provide better visualization of the breast lesions and additional information associated with skin thickening, such as skin enhancement, skin nodules, or tumoral emboli, than conventional modalities like mammography or US (**Fig. 2**).

PET/Computed Tomography Scan

In recent years, accumulating data showed the benefit of PET/CT scan over CT scan and bone scan as a staging modality. For example, a study of 111 patients with IBC who were evaluated with PET/CT scan showed higher detection of lymph node metastasis.[17] This "upstaging" phenomenon was associated with longer progression-free survival,[21] followed by other papers to support similar findings.[22,23] Reviewing the PET/CT in IBC at MD Anderson revealed up to 10% of IBC cases will have contralateral lymph nodes as the only site of M1 disease, potentially a locally controllable dissemination.[24] Another utilization of PET/CT in the IBC is the ability to monitor treatment response. In a study of 53 patients with IBC, the changes in PET/CT during neoadjuvant therapy predicted long-term outcome of patients. This clinical benefit seen in trials is likely due to selection of patients; therefore, prospective study is necessary to

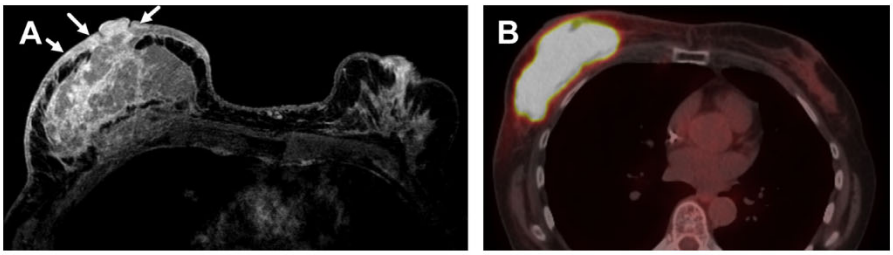

Fig. 2. A 76-year-old woman with a self-palpated left breast mass, and core biopsy revealed triple-negative inflammatory breast carcinoma. (*A*) Contrast-enhanced breast MRI examination showed multicentric breast lesions with diffuse skin thickening and skin enhancement/lesions (*arrows*) secondary to biopsy-proven dermal tumor emboli. (*B*) PET/CT image revealed multicentric hypermetabolism throughout the right breast related to the IBC.

validate such benefit. It is not known whether upstaging from stage III to IV impacts the OS of patients, whereas the initial stage can predict the long-term outcome of patients and need to studied.[23,25]

CURRENT TREATMENT OF INFLAMMATORY BREAST CANCER

General Approach for Stage III Inflammatory Breast Cancer

Both National Comprehensive Cancer Network (NCCN) guidelines and the international IBC expert guidelines recommend intensive therapy for patients with primary IBC to achieve best local control and survival outcome, via trimodality approach: systemic therapy, surgery, and radiation therapy (**Fig. 3**). In the preguideline era, when IBC was treated mainly with surgery and with or without adjuvant radiation therapy, the 5-year survival was only 5%.[26] In a large case series composed of 495 patients that were treated with radical mastectomy from 1935 to 1942, the median survival of patients was 19 months.[27] Anthracycline use was introduced in the treatment of IBC since 1974 at MD Anderson.[28] Then, the presurgical introduction of the systemic therapy (neoadjuvant therapy) approach using anthracycline as a backbone was accepted as a standard of care for IBC.[29] Subsequently, taxane was added to anthracycline-based regimen, showing additional benefit in the neoadjuvant setting.[30] However, without proper locoregional management by surgery and radiation, the response to systemic therapy is not durable in stage III IBC.[31]

There are several critical practice points the authors recommend for appropriate local control in IBC patients: they do not recommend skin-sparing mastectomy, or immediate reconstruction, simultaneous contralateral mastectomy unless the contralateral breast is also involved. All these practices can minimize the immediate recurrence-related treatment delay/complication, and longer-term better cosmetic outcome as well. Local therapy, including both surgery and radiation therapy, is indicated in most cases, and this is recommended in the setting wherein there is no complete resolution of the cancer.

Preoperative Systemic Chemotherapy

Neoadjuvant anthracycline-based chemotherapy for IBC was first introduced in the 1970s. Anthracycline-based combination therapy followed by surgery and adjuvant radiotherapy was proven to be efficacious in several prospective clinical trials.[32] Chemotherapy regimens are similar to the ones used for non-IBC patients. From a

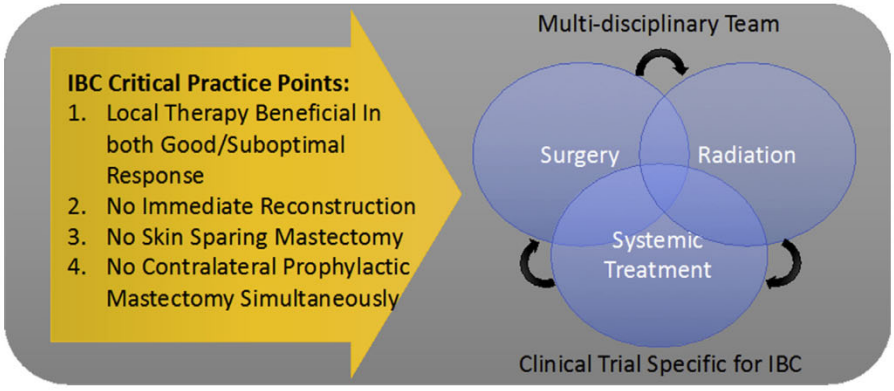

Fig. 3. Critical practice points of IBC.

retrospective MD Anderson data review collected over 20 years, anthracycline-based chemotherapy in IBC patients resulted in 40% OS in 5 years, and 33% in 10 years.[30] Anthracycline containing triplet regimen, including 5-fluorouracil, showed similar efficacy in survival in a retrospective analysis of 68 patients.[33] Furthermore, taxane-based combination chemotherapy was also effective as neoadjuvant treatment of IBC patients, showing median survival of 46 months.[34] The same investigators also showed the addition of paclitaxel to FAC regimen (5-fluorouracil, Adriamycin, and cyclophosphamide) in IBC improved benefit. However, this benefit was more prominent in the subset of HR-negative IBC patients.[35] At MD Anderson, taxane treatment followed by anthracycline-containing regimen is the standard regimen for IBC neoadjuvant therapy. Historical rates of pathological complete response are summarized in **Table 2**. Although both HR-positive and TNBC IBC undergo the same anthracycline- and taxane-based chemotherapy, if IBC overexpresses HER-2/*neu*, double-HER2 targeting therapy is combined similar to treatment of non-IBC. If the patient does not achieve meaningful clinical response after routine neoadjuvant chemotherapy treatment, additional neoadjuvant chemotherapy might be recommended before surgery. If there are available neoadjuvant therapy clinical trials, patients with IBC are strongly recommended to enroll into clinical trials to optimize clinical outcomes. Clinical evaluation of response to chemotherapy is performed based on the RECIST response criteria by medical examination and radiological assessment every 6 to 12 weeks. In addition, baseline and repeated medical photography are extremely useful in monitoring skin changes, such as erythema and edema.[36] Current and upcoming available clinical trials for neoadjuvant therapy in IBC at the MD Anderson, Dana Farber, and other major IBC treatment centers are summarized in **Table 3**, along with other trials available in different settings.

The success of systemic therapy in stage III IBC is measured by the pathologic response to the therapy. Patients who achieved pathologic complete response (pCR) have significantly improved outcomes compared with patients who did not.[37] A historical collection of patient IBC data showed that the pCR rate in stage III IBC was about 15.2%; it is slightly different among molecular subtype groups. The pCR rate of HR-positive/HER2-negative subtype and HR-negative/HER2-positive subtype was 7.3% and 30.6%, respectively. Triple-negative IBC showed about 18.6% pCR rate. Although there are small differences, pCR in patients with IBC is lower compared with stage and molecular subtype-matched non-IBC breast cancers. More importantly, pCR has been shown to be a predictive marker of survival in IBC. Contrastingly, from non-IBC HR-positive breast cancer, the pCR in HR-positive IBC also was able to predict the long-term survival.[11]

Based on most recent survival analysis of stage IV patients, with median follow-up of 4.7 years of IBC patients between 1987 to 2012, the median survival of patients with

Table 2
Summary of pathologic complete response rate in inflammatory breast cancer patients, data collected from 1989 to 2011, at the MD Anderson Cancer Center in comparison with noninflammatory breast cancer historical data

	TNBC, %	$ER^+/HER2^-$	$ER^+/HER2^+$, %	ER^-HER2^+, %
Historic pCR rate of IBC	12	7.4%	30	15
Historic pCR rate of non-IBC	30–40	7%–16%, but not clearly related to worse clinical outcome	35	40–60

Table 3
Clinical trials portfolio for inflammatory breast cancer that are currently open for accrual as of February 2018

Neoadjuvant	Adjuvant	Metastatic	Metastatic Maintenance
Bevacizumab + FEC followed by adjuvant therapy by docetaxel ± trastuzumab phase 2 (NCT01880385)	A study of anti-PD-1 (pembrolizumab) + hormonal therapy in HR-positive localized IBC patients with non-pCR to neoadjuvant chemotherapy phase 2 (NCT02971748)	Nintedanib for HER2-negative IBC phase 2 (NCT02389764)	Pembrolizumab single-agent maintenance phase 2 (NCT02411656)
Eribulin followed by AC phase 2 (NCT02623972)		T-VEC phase 2 (NCT02658812)	
Carboplatin + nab-paclitaxel phase 2 (NCT01525966)		Olaparib and radiotherapy in inoperable breast cancer (NCT02227082)	
Paclitaxel + trastuzumab + pertuzumab phase 2 (NCT01796197)		Romidepsin + abraxane phase 1/2 (NCT01938833)	
Ruxolitinib + chemo phase 1/2 (NCT02041429)		Study of triple combination of atezolizumab + cobimetinib + eribulin (ACE) in patients with chemotherapy resistant recurrent/metastatic IBC phase 2 (NCT03202316)	
3HT with Taxol for HER2-positive IBC, and neratinib + taxol for HR–positive IBC in neoadjuvant setting phase 1/2 (NCT03101748)			

IBC versus that of non-IBC was 2.27 versus 3.40 years ($P = .0128$).[38] This significantly lower survival of patients with IBC remains to be significant regardless of molecular subtype and tumor stage.[39] In previous analysis of 68 stage III IBC patients with median follow-up greater than 10 years, 4-year median survival ranged from 5 months to 14.7 months. The OS rate at 5 years and 10 years were 44% and 32%, respectively.[33] Collectively, the survival of patients with IBC is lower than same stage, same molecular subtype of patients with non-IBC.

Surgery

Surgical treatment, in the form of a modified radical mastectomy, needs to be offered to those patients who have at least a partial response to neoadjuvant systemic therapy.[40] Patients with developing disease progression during primary systemic therapy are generally not candidates for surgery at this point; they are offered additional local and systemic therapeutic options, with the exception of some limited cases whereby salvage therapy is indicated (discussed later). Surgery to prevent morbid local spread in patients switching systemic therapies should be watched closely to not lose the window of operability when this control is desired.

The surgical goal for treatment of patients with IBC is the complete removal to pathologically negative margins. Removal of all involved areas in the skin is strongly recommended, because the remnant cells within the skin can further manifest as a recurrence of disease.

Patients with IBC commonly present with detectable lymph node involvement, including the infraclavicular lymph nodes. Sentinel node mapping is not recommended for IBC patients, because it has not proved to be accurate in this population,[41] and axillary node dissection is recommended.

Although advances in the treatment of non-IBC have gradually focused more on breast-conserving operation with sentinel node biopsy, more extensive surgery in the form of mastectomy with axillary node dissection is still the optimal method of surgery in patients with IBC.[42] Skin-sparing approaches, including placement of a tissue expander, are discouraged to avoid leaving disease behind. Immediate reconstruction further compromises radiation planning. Contralateral mastectomy should be delayed until reconstruction if desired so as not to incur side effects from an elective surgery that reduces the timeliness of the oncologic care for the IBC.

Radiation Therapy

Consistent with current NCCN guidelines for breast cancer,[26] the authors' institutional approach to the management of IBC includes radiation therapy, after chemotherapy, and surgery as a major and necessary treatment modalities. Preoperative radiation therapy for IBC has previously been shown to have high complication rates, and the benefit to the patient who is not a surgical candidate is debatable. However, radiation techniques have progressed substantially since these reports, and this may be considered when surgery is not feasible or for local control without surgery.

Postmastectomy radiation, including the chest wall, undissected high axilla (level III), supraclavicular, and internal mammary lymph nodes, is the standard of care.[43] Medical photography at diagnosis can ensure all affected skin areas are covered with radiation. It is important to treat the field with large radiation coverage in patients with IBC, given involvement of skin and dermal lymphatic system at presentation. Radiation therapy for IBC often involves crossing midline to provide adequate margin on the medial scar.

Contralateral nodal basins should always be imaged before beginning systemic therapy, and consideration should be given to bilateral therapy in selected cases whereby metastases are limited to the contralateral regional nodes or breast. In addition, postoperative changes to blood flow and lymphatic drainage can allow progression to the contralateral breast, lymph node areas, or the skin of the upper abdomen. Anecdotally, many treatment failures are seen at the most medial aspect of the surgical scar or within the contralateral skin and lymph nodes. Inadequate coverage of this area can promote progression and recurrence in these areas.[44,45]

Dose escalation in IBC is critical to prevent local recurrence, more so than non-IBC patients.[45] Twice-daily treatment, as well as radiosensitizer combination with radiation, may help to lower the local failure rate in young patients and women with inadequate response to therapy.[46] Boost targets are dependent on sites of initially involved gross disease. If there is no N3 nodal disease at presentation, only the chest wall flaps are included in the boost field to cover the entire mastectomy surgical bed. If any N3 nodes were involved at presentation, that nodal bed is included in the boost field.

Importance of a Multidisciplinary Team Approach

Although trimodality therapy is critical in the treatment of IBC, the adaptation of multimodality therapy ranged from 58.4% to 73.4% annually in IBC patients who were diagnosed between 1998 and 2010 who had local resection. For this study, patients without all 3 modality treatments were associated with a lower 5- and 10-year OS.[47] Based on the analysis of 107 patients with stage III IBC, only 25.8% received treatment concordant with NCCN guidelines.[48]

From the same analysis, IBC patients receiving guideline-based treatment survived longer with a statistically significant difference. The same trends were observed between 2003 guidelines and 2013 guidelines.

Among 10,197 patients with nonmetastatic IBC from 1998 to 2010 analyzed by SEER data, the rate of utilization of full trimodality fluctuated between 58.4% and 73.4%. Patients who had trimodality showed the best overall survival (including reported 5 and 10 years survivals), compared to patients who had only one or two modalities of therapy.[47] Therefore, the authors at the MD Anderson IBC Clinic make every effort for a newly diagnosed patient with IBC to be evaluated by the multidisciplinary team consisting of a medical oncologist, surgeon, and radiation oncologist.

The multidisciplinary team approach is critical in the care of patients with IBC (**Fig. 3**). Timely referral of patients to an expert can also be a critical matter in urgent treatment initiation of this rare disease, improved understanding of disease biology, and collaboration with IBC-specific education program and advocacy.

Management of Stage IV

Approximately one-third of patients with IBC present with metastatic disease at diagnosis (stage IV), whereas most patients ultimately develop distant relapse.[49–51] Several clinical trials tried to address the question of benefit in local therapy in patients with stage IV IBC and non-IBC, including the ECOG E2108 study, hoping to address currently available conflicting results, although this is not directly targeted to the IBC population only.[52,53] Akay and colleagues compared the OS of patients presenting with stage IV IBC (n = 218) with those presenting with stage IV non-IBC (n = 1454). Patients with IBC were associated with significantly shorter OS compared with non-IBC (2.3 vs 3.4 years; $P = .004$) (hazard ratio = 1.33; 95% confidence interval: 1.05-1.69).[54] Importantly, local therapy in stage IV IBC also has shown benefit. When local therapy was combined, the outcome was the best: based on review of a total of 172 cases of metastatic IBC, with all patients undergoing chemotherapy, but with or

without local therapy, with stratification of response to chemotherapy. Both 5-year OS and distant progression-free survival (DPFS) and local control evaluation showed that among 172 patients total, 79 patients (46%) were able to undergo surgery. Both OS (47% vs 30% with $P<.0001$) and DPFS were better (10% vs 3% with $P<.0001$) with patients who underwent surgery. Addition of radiation therapy to the surgery improved this OS and DPFS (OS rate: 50% vs 25% vs 14%, respectively; DPFS rate: 32% vs 18% vs 15%, both $P<.0001$). Interestingly, this survival advantage remained even after stratification with response to chemotherapy, and the benefit of surgery plus radiation therapy remained after multivariate analysis. Intact local control at the last follow-up in patients who underwent surgery and radiation was 4-fold higher compared with patients who only had chemotherapy (81% vs 18%; $P<.0001$), independent of chemotherapy itself. Given significant morbidity related to the skin involvement of IBC, this higher rate of local control also offered clinical benefit.[38] Based on this significant difference, patients with stage IV IBC are strongly encouraged to consult for whether undergoing aggressive local therapy is appropriate. However, one should note that although this large case analysis study showed benefit of local therapy in patients who had poor response to chemotherapy, the possibility of a "window of opportunity" to have salvage local control surgery is not always possible. When cancer is refractory to chemotherapy, patients quickly recur (median recurrence within 5 months) with all patients further developing metastasis or death.[55] Moreover, a tailored trial to validate this in prospective manner is warranted, to facilitate the compliance of this approach in a broader community setting practice.

CLINICAL TRIALS FOR PATIENTS WITH INFLAMMATORY BREAST CANCER

Since 2009, more than 50 publications specifically aimed to determine the biology of IBC have been published with active studies ongoing. The major knowledge gap is that the following have yet to be found: (1) IBC-specific treatment or (2) IBC-specific diagnosis tool. Clinical trials that are specific to IBC are critical to improving patient treatment and outcome. Clinical trials for localized IBC need to use innovative strategies to develop a novel combination to induce higher pCR. Identifying new molecular targets and investigating the impact of novel agents and treatment approaches in IBC are critical. At the national level, patients with IBC are encouraged to enroll in clinical trials, including phase 1 trials when possible. More effort needs to be channeled toward adherence to diagnosis and treatment guidelines at the community level by reaching out and engaging with community oncologists and researchers (see **Table 1**).

SUMMARY AND FUTURE DIRECTION

IBC is a rare but deadly disease. Timely and accurate diagnosis based on a high index of suspicion, followed by guideline-based trimodality treatment, including chemotherapy-based neoadjuvant approach to induce best response and aggressive local therapy, is a basic requirement. A team approach, using team science to understand both the tumor and the microenvironment that are distinct in IBC, a team of clinicians to improve rapid initial management necessary referral of patients, a team of advocates, and an educational team are crucial to enhance community-based understanding of IBC. Last, a team approach is required to improve the standard of care for diagnosis and treatment based on the most updated understanding of IBC. These strategies are keys to a better understanding of the biological mechanisms that promote the aggressiveness of this disease and subsequently reduce the mortality of patients with IBC.

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