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International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment

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Background: Inflammatory breast cancer (IBC) represents the most aggressive presentation of breast cancer. Women diagnosed with IBC typically have a poorer prognosis compared with those diagnosed with non-IBC tumors. Recommendations and guidelines published to date on the diagnosis, management, and follow-up of women with breast cancer have focused primarily on non-IBC tumors. Establishing a minimum standard for clinical diagnosis and treatment of IBC is needed.

Methods: Recognizing IBC to be a distinct entity, a group of international experts met in December 2008 at the First International Conference on Inflammatory Breast Cancer to develop guidelines for the management of IBC.

Results: The panel of leading IBC experts formed a consensus on the minimum requirements to accurately diagnose IBC, supported by pathological confirmation. In addition, the panel emphasized a multimodality approach of systemic chemotherapy, surgery, and radiation therapy.

Conclusions: The goal of these guidelines, based on an expert consensus after careful review of published data, is to help the clinical diagnosis of this rare disease and to standardize management of IBC among treating physicians in both the academic and community settings.

Key words: guidelines, inflammatory breast cancer, management

introduction

Inflammatory breast cancer (IBC), a term first introduced by Lee and Tannenbaum [1], represents the most aggressive presentation of breast cancer. The incidence in the United States ranges from 1% to 5% [2]. The epidemiological study of this disease has been greatly hampered by use of inconsistent diagnostic criteria. Women diagnosed with IBC are also known to have poorer survival outcomes compared with those with non-IBC tumors. Published guidelines have focused on non-IBC tumors primarily due to the scarcity of data and experience in the field of IBC. This paper summarizes guideline recommendations based on the consensus of a panel of recognized international experts that met during the First International Conference on Inflammatory Breast Cancer. The panel focused primarily on minimum requirements for appropriate diagnostic work-up and therapeutic management of the disease. Additionally, critical areas of research to be supported and developed in the following years were identified.

methods

In December 2008, an international panel of experts in the field of IBC convened for the first IBC conference held in Houston, TX, under the leadership of MC and TAB. The panel comprised members who are experts in the fields of breast medical oncology, radiation oncology, surgery, breast diagnostics, and pathology, with the participation of representative patient advocates organizations. The panel identified a number of deficiencies in the diagnosis and management of IBC together with a lack of adequate prospective trials being conducted for this aggressive disease. Bringing together their extensive experience and expertise, the panel members summarized a series of critical data and developed the first consensus

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statement of its kind for this disease. The goal of these guidelines, based on an expert consensus after careful review of published data, is to help the clinical diagnosis of this rare disease and to standardize management of IBC among treating physicians in both the academic and community settings. Furthermore, in the first consensus statement, the panel also makes recommendations on the building of tumor registries, tissue banks, and clinical trials specific to IBC to aid in better understanding this disease and to gain enough information to develop therapeutic regimens and agents that specifically target IBC. The ultimate goal is to improve the survival of a disease that is historically known to be associated with a poor prognosis (Table 1).

The sections below describe some of the important questions that were addressed and the panel's recommendations. The panel recommendations are summarized in Table 2.

the diagnostic criteria for IBC

Because IBC is known to be an aggressive disease, the timing of diagnosis may be critical to direct appropriate therapy and as such has the potential to impact long-term survival outcomes. The first diagnostic criteria for IBC were published in 1956 by Haagensen [3] and are still widely used. These criteria are the basis of the definition of IBC set forth by the American Joint Committee on Cancer (AJCC) as ' a clinicopathological entity characterized by diffuse erythema and edema of the breast, often without an underlying palpable mass' [4]. The nonspecificity of the current diagnostic criteria coupled with the recognition that many women with IBC are misdiagnosed with mastitis are the primary causes of delayed diagnosis and management of this aggressive disease. Also a number of women with neglected locally advanced breast cancer are often diagnosed with IBC. Kim et al. [5] conducted a systematic review of published literature on IBC with the goal to identify causes of differences in treatment outcomes across the different studies. The authors concluded that a main cause was the variable criteria used to identify IBC.

Recognizing the difficulties encountered in identifying IBC, a set of diagnostic criteria were defined by the panel members. In general, the panel members agreed that the diagnosis of IBC should remain a clinical one with essential pathological confirmation of invasive carcinoma, while dermal lymphovascular tumor emboli, when a skin punch biopsy is carried out, is pathogneumonic but not required for a diagnosis. Although routine breast radiological investigations are recommended as part of staging work-up, the panel is in agreement that the data are currently not sufficient to define any radiological signs specific for IBC and is therefore not part of the diagnostic criteria. These are discussed in detail in a later section. The panel agrees that the minimum criteria required for the diagnosis of IBC include the following:

- History of rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass.

Table 1. Goals of IBC panel

Overall objective
To develop standardized guidelines for the diagnosis and management of IBC and encourage IBC-specific research with the ultimate goal of improving long-term survival.
Specific goals
Define diagnostic criteria for IBC.
Develop an algorithm for the diagnosis and management of IBC allowing for standard management of this disease in both the academic and community setting.
Promote patient and physician education on IBC.
Encourage the establishment of tumor registries and tumor banks specific for IBC.
Encourage the development of prospective clinical trials specific for IBC.
Encourage international multicenter collaboration for IBC-specific research.

IBC, inflammatory breast cancer

Table 2. Summary of minimum recommendations

Diagnostic criteria
Minimum criteria required for the diagnosis of IBC include the following:
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 of no more than 6 months.
Erythema occupying at least one-third of the breast.
Pathological confirmation of invasive carcinoma.
Pathological specimen and marker evaluation
Core biopsy to confirm invasive carcinoma.
Strongly recommend that every patient who meets the diagnostic criteria for IBC undergo a skin punch biopsy (at least two).
All IBC tumors be tested for hormone receptors and HER2.
Imaging and staging work-up
All women with a suspected IBC undergo a diagnostic mammogram with accompanying ultrasound the breast and regional lymph nodes.
Routine use of diagnostic MRI breast is not recommended. Panel recommends use of MRI breast in instances where breast parenchymal lesions are not detected by mammography or breast ultrasound.
All women with IBC have systemic staging studies with CT and bone scan.
The data on the use of PET or PET/CT are not sufficient to recommend its routine use in staging of women with IBC.
Management
A multidisciplinary approach is recommended.
Women with IBC should be offered primary systemic chemotherapy consisting of an anthracycline and taxane. Anti-HER2 therapy should be used among women with HER2-positive disease. Monitoring of response to primary systemic chemotherapy should including a combination of physical examination and radiological assessment.
The only method of definitive surgery to be offered to women with IBC following preoperative systemic treatment is a modified radical mastectomy.
Breast reconstruction is an option that can be recommended to women with IBC who have undergone a modified radical mastectomy. However, immediate reconstruction is not recommended.
Postmastectomy radiation is recommended with the cumulative radiation dose recommended to be escalated to 66Gy in the subset of women who are >45 years of age, who have close or positive surgical margins, have four or more positive lymph nodes following preoperative systemic treatment, or who have demonstrated a poor response preoperative systemic treatment.

CT, computed tomography; IBC, inflammatory breast cancer; MRI, magnetic resonance imaging; PET, positron emission tomography

- History of flattening, crusting, or retraction of the nipple may be present.
- Patients may have a history of being diagnosed with mastitis not responding to at least 1 week of antibiotics.
- Duration of history of no more than 6 months.
- Clinical examination revealing erythema occupying at least one-third of the breast.
- Clinical examination may reveal underlying palpable mass with or without palpable locoregional lymph nodes with or without nipple abnormalities.
- Pathological confirmation of invasive carcinoma from a core biopsy of the breast.
- Recommendation to obtain adequate skin punch biopsy to possibly document dermal lymphovascular tumor emboli (see below).

pathological specimen and marker evaluation

Primary systemic chemotherapy is recommended as a standard treatment option for all patients diagnosed with IBC. As such, obtaining a good tissue sample before administration of primary systemic chemotherapy serves several important goals:

- It is required for the confirmation of the presence of invasive carcinoma.
- It is required for determination of histological subtype, histologic tumor grade (Nottingham combined histologic grade according to Elston and Ellis) estrogen receptor (ER), progesterone receptor (PR), and HER2 status.
- In patients who attain a pathological complete response (pCR), preoperative biopsy specimens of the breast and lymph nodes will be the only source of available tissue that can be stored in tumor banks for future research purposes.

The panel recommends that all patients suspected of having IBC undergo a series of imaging studies (see below). If an underlying intraparenchymal tumor and regional lymph node metastases (axillary or supraclavicular) are present, an image guided core biopsy is then recommended for pathological tumor classification, staging, as well as determination of prognostic and predictive markers.

dermal lymphovascular invasion

The growth pattern of IBC is characterized by minimal *in situ* component or lack of *in situ* component. There is often an extensive component of intraparenchymal lymphovascular tumor emboli. IBC growth pattern is less compact than non-IBC (leaving more available space for migration of cancer cells) with large tumor-free skip areas and small areas of invasive carcinoma, sometimes still surrounding vascular emboli.

The inflammatory skin changes of a breast afflicted with IBC represents the presence of dermal lymphatic invasion (DLI), a state in which dilated dermal lymphovascular spaces are filled with tumor emboli that are often retracted away from the surrounding endothelial lining [6]. Considered to be a histological hallmark of IBC, DLI subsequently leads to lymphatic obstruction and is ultimately responsible for the highly metastatic potential of IBC [7]. A number of investigators have proposed that since DLI is specifically associated with IBC, skin punch biopsies should be a standard requirement for diagnosis of all clinically suspected cases of IBC [8, 9]. However, a number of studies have shown that despite adequate sampling of skin, including assessment of multiple sections of the tissue block, DLI is identified in <75% of patients with IBC indicating that it is not an absolute requirement for the diagnosis of IBC [6, 10].

Although proof of DLI is not a requirement for the diagnosis of DLI, the panel members strongly recommend that every patient who meets the diagnostic criteria for IBC undergo a skin punch biopsy (at least two). This helps not only determining the presence of DLI but will also help in confirming the diagnosis of an invasive carcinoma in the absence of the presence of an underlying intraparenchymal lesion or regional metastases. The best area to sample is the most prominent area of skin discoloration of the breast with punches of 2–8 mm in diameter considered to be sufficient for the determination of the presence or absence of DLI.

hormone receptors and HER2

Unlike non-IBC tumors, several studies have documented a higher frequency of negative ER and PR status in IBC tumors with some studies reporting up to 83% of tumors being ER negative [11, 12]. Lack of expression of hormone receptors has been shown to be associated with a more aggressive clinical course and is associated with a decreased overall and breast cancer-specific survival among women with IBC tumors [13]. Analysis of population-based data derived from the Surveillance, Epidemiology and End Results database has shown a statistically significant improvement in median survival among women with ER-positive IBC compared with those with ER-negative IBC (4 versus 2 years, $P < 0.0001$) [14].

A higher incidence of HER2 overexpression has been reported among IBC tumors [13, 15]. However, unlike the non-IBC tumors, where HER2 overexpression is typically associated with poor prognostic outcome, the true prognostic significance of HER2 overexpression among women with IBC tumors is currently unknown [13, 16]. In a case-only analysis of >2000 women with IBC registered in the California Cancer Registry, there was only a borderline significant association for breast cancer-specific survival favoring women with HER2-positive IBC tumors as compared with those with HER2-negative tumors [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.68–0.99] [13]. In a smaller retrospective study of 179 women with stage III IBC, no significant difference in recurrence-free survival was observed between women with HER2-positive and -negative IBC tumors [16].

At this time, the panel members agreed that there is sufficient evidence indicating that hormone receptors have both a prognostic and therapeutic predictive role in the management of IBC. Although the prognostic role of HER2 has yet to be accurately defined in IBC, as will be explained later on, there is evidence to indicate that HER2 has a predictive role in indicating which patients with IBC will benefit from therapeutic agents targeted against HER2 [16, 17]. Thus, the panel members recommend that all IBC tumors be tested for hormone receptors and HER2. The members recommend that

standard guidelines be used for the testing and reporting procedures of these markers.

other markers

A number of other markers have been studied in IBC. p53 mutations have been shown to occur in IBC and is associated with decreased response to chemotherapy and poor survival outcomes [18, 19]. Chemokine receptors CXCR4 and CCR7 expression in IBC tumors have been shown to be associated with poor prognostic outcome [20]. Expression of Notch-1, E-cadherin, and lympho angiogenic factors [(e.g. vascular endothelial growth factor (VEGF)-C, VEGF-D, VEGFR-3, Prox-1, lymphatic vessel endothelial receptor1] have been shown to be increased in IBC tumors compared with non-IBC tumors [21–24]. RhoC guanosine triphosphatase (GTPase), a breast-specific oncogene, has been shown to be overexpressed in ~90% of IBC tumors compared with 38% of non-IBC tumors and is associated with high histologic grade, advanced stage, and poor prognostic outcome [25–27]. Of note, studies have also shown Rhoc GTPase to be overexpressed in a number of other tumors including those of the colon, lung, pancreas, head and neck, as well as in testicular germ cell tumors [28]. Loss of Wisp 3, a breast tumor suppressor gene located at 6q22–q23, expression has also been shown to occur with high frequency in IBC tumors [25].

At present time, there is insufficient evidence to define the prognostic or predictive role of these markers in IBC and the panel members currently do not recommend routine testing of these makers outside the context of a clinical trial.

imaging and staging work-up

The use of imaging modalities is important in IBC for several reasons. These include the following.

- Defining the presence of an intraparenchymal breast lesion that can be biopsied.
- Defining the presence or absence of ipsilateral and contralateral disease in the nodal regional.
- Defining the presence or absence of distant metastatic disease.

The panel members recommend use of the AJCC tumor–node–metastasis (TNM) system for the staging of IBC. This system designates IBC as follows:

- IBC is defined as T4d
- N staging will depend on the presence of involvement of nodes
- Patients with nonmetastatic disease are designated as stage IIIB and those with metastatic disease are designated as stage IV
- As preoperative systemic chemotherapy is the standard of care (irrespective of the ER and PR status), it is recommended that baseline TNM staging recorded be based on clinical parameters.

mammogram and breast ultrasound

The panel recommends that all women with a suspected IBC undergo a diagnostic mammogram with accompanying ultrasound the breast and regional lymph nodes. Key features seen on a mammogram of a patient with IBC include skin thickening and trabecular distortion [29]. Ultrasound imaging is important as a localizing tool for biopsy of underlying masses, parenchymal architectural distortions, or involved regional lymph nodes [30, 31]. In a retrospective study from the MD Anderson Cancer Center, breast ultrasound imaging was useful in determining a breast parenchymal lesion in ~95% of breasts affected with IBC [31].

magnetic resonance imaging of the breast

Magnetic resonance imaging (MRI) of the breast is currently becoming popular as a diagnostic imaging modality with an advantage of lack of ionizing radiation and superior sensitivity in diagnosing invasive breast cancer over conventional imaging techniques. However, the data of its use in IBC are scarce. A study from the M. D. Anderson Cancer Center revealed that in women with IBC breast parenchymal lesions were detected in all cases by breast MRI compared with 80% of cases with mammography and 95% of cases with ultrasound imaging [31]. MRI of the breast, however, has several limitations, including high cost, increased time commitment, and available breast coils are only available in one size. The panel members agreed that until more data are available, routine use of diagnostic MRI breast is not recommended. However, the panel strongly recommended:

- Use of MRI breast in instances where breast parenchymal lesions are not detected by mammography or breast ultrasound.
- Enrollment of women with IBC in clinical trials investigating MRI of the breast.

distant metastases

The majority of women with IBC have locoregional disease at diagnosis and ~30% have stage IV *de novo* disease. Determining stage and extent of disease at diagnosis is important to help with treatment planning, such as surgery and radiation therapy [32]. The panel recommends all women with IBC have systemic staging studies with computed tomography (CT) and bone scan. 2-[Fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) is increasingly being used as a staging imaging modality in women with locally advanced breast cancer [33–35]. FDG–PET has been shown to be particularly useful in detection of involvement of internal mammary lymph nodes that are predictive of recurrence [36, 37]. A recent retrospective review on the role of PET/CT in the initial staging of IBC patients ascribes value in the diagnosis of locoregional and distant disease [38]. The use of cross-sectional imaging that includes the neck is particularly important for radiation treatment planning where pretherapy imaging of gross disease allows targeted radiation therapy to the high-risk disease typically unresected disease in the infraclavicular and supraclavicular fossa. These sites are typically not well easily localized for treatment planning on non-cross-sectional imaging modalities and a CT of the chest typically will not include the entire supraclavicular fossa. Important limitations in the use of PET or PET/CT include accessibility and cost. At this time, the panel members agreed that the data on the use of PET or PET/

CT are not sufficient to recommend its routine use in staging of women with IBC but they recognize that additional prospective data be collected to determine the role of this imaging modality.

recommendations for the management of IBC

The panel recommends a multidisciplinary approach for women with IBC. Primary systemic chemotherapy, surgery, and radiation therapy should all be included in the treatment plan. The panel's recommendations on the individual components are given in the following sections.

primary systemic treatment

Due to the fact that most women with IBC will have locoregional disease at presentation and the presence of extensive skin involvement, breasts afflicted with IBC are considered ineligible. If surgery is attempted upfront, the probability of residual disease being left behind is high and therefore, it is strongly recommended that patients with clinical diagnosed IBC be referred to a medical oncologist. As such, the panel recommends that all women with IBC be offered primary systemic chemotherapy as the first line of treatment with the goal of downstaging the tumor to allow for definitive surgery.

There are no data from large randomized clinical trials looking at the optimal chemotherapeutic regimen specifically for women with IBC. Thus, recommendations made are based primarily on retrospective studies, small prospective studies, and extrapolation of data available from prospective trials evaluating women with non-IBC tumors (Table 3) [39–43]. The largest study looking at ~178 women with IBC who all received an anthracycline-based regimen followed by local therapy reported 5- and 10-year survival rates of 40% and 33%, respectively [39]. The incorporation of taxanes has also been shown to be associated with higher pCR rates and better survival outcomes. The panel members agreed that the data are sufficient to recommend that all women with IBC receive a primary systemic regimen consisting of an anthracycline and taxane. No recommendations were made regarding use of additional adjuvant chemotherapies in patients with residual disease. Furthermore, although results of studies looking at the use of high-dose chemotherapy among women with IBC have been encouraging, this modality of treatment is still considered investigational and not recommended outside the confines of a clinical trial [44–47]. This represents an area for further investigation.

The panel strongly recommends the administration of trastuzumab among women with HER2-positive disease with studies indicating that its addition to primary systemic chemotherapy being associated with higher pCR rates (Table 3) [17, 48–52]. A recent prospective study that randomized women with locally advanced breast cancers, including those with IBC, to an anthracycline-based chemotherapy with or without 1 year of trastuzumab (preoperative followed by adjuvant) demonstrated that the addition of trastuzumab significantly improved the pCR rates (38% versus 19%, $P = 0.001$) and event-free survival (3-year event-free survival 71% versus 56%, HR 0.59, $P = 0.013$) [52]. The members agreed that there is insufficient safety data to recommend the routine combination of trastuzumab with an anthracycline outside the context of a clinical trial. One small study has also evaluated the use of lapatinib (a reversible inhibitor of HER1 and HER2) in the preoperative setting among women with IBC with good clinical response observed [53]. However, at this time outside the context of a clinical trial, its routine use is not recommended without large studies demonstrating safety and comparable efficacy.

The panel recommends that a minimum of six cycles of preoperative treatment be administered over a course of 4–6 months before proceeding for definitive surgery. However, this may be modified in cases where disease progression is observed.

monitoring response to treatment

The panel members recommend that monitoring of response to primary systemic chemotherapy be a combination of physical examination and radiological assessment. Physical examination of the breast for response may be conducted every 6–9 weeks [54]. Radiological assessment should be carried out at the end of treatment and compared with baseline results. Where warranted, radiological assessment may also be carried out mid-treatment to confirm or refute results of clinical assessment. Use of mammogram or ultrasound imaging techniques is recommended. Although the data are scarce, the panel agreed that where available and affordable MRI of the breast maybe better option for monitoring response to treatment.

definitive surgery

Studies have shown that physical examination and imaging techniques can underestimate the extent of residual disease in ~60% of patients [55, 56]. Furthermore, despite a clinical response to treatment, residual disease may still be present in the affected skin of the involved breast. Current data also indicate that sentinel lymph node biopsy is not a reliable method of assessing axillary lymph nodes among women with IBC [57]. The panel members agreed that the only method of definitive surgery to be offered to women with IBC following preoperative systemic treatment is a modified radical mastectomy. A skin sparing mastectomy approach is contraindicated and breast-conserving approaches may only be attempted within the context of a clinical trial.

reconstruction

Breast reconstruction is an option that can be recommended to women with IBC who have undergone a modified radical mastectomy. However, the timing of the reconstruction in this cohort is controversial. Several small studies have reported reasonable success with no outcome differences when immediate reconstruction was compared with delayed reconstruction [58, 59]. Studies have also shown that the presence of a reconstructed breast limits radiation coverage and may also compromise coverage of the internal mammary lymph nodes [60]. The panel members agreed that until larger studies are conducted immediate reconstruction is not recommended.

pathology evaluation of postmastectomy specimen

Postmastectomy specimen should be examined using a standard approach. The panel members recommend that the approach set forth by the 'international expert panel on the use

Table 3. Preoperative regimens in IBC

Author	Type of study	No. of patients with IBC	Regimen	% Overall response	% pCR	Survival
Anthracycline-based regimens						
Ueno et al. [39]	Pooled analysis of four prospective clinical trials	178	Anthracycline based	71	N/A	5-year OS 40%
Harris et al. [40]	Retrospective	54	CMF or CAF		30	5-year OS 56%
Baldini et al. [41]	Pooled analysis of two prospective clinical trials	68	CEF or CAF	73.6		5-year OS44%
Low et al. [42]	Prospective	46	CAFM	57		10-year OS 26.7%
Anthracycline and taxane-based regimens						
Cristofanilli et al. [43]	Retrospective	240	FAC versus FAC + P	74 versus 82		N/A
Trastuzumab-based regimens						
Hurley et al. [48]	Prospective	48	D + CDDP + T	N/A	17	4-year OS 86%
Van Pelt et al. [53]	Prospective	22 LABC (9 IBC)	D + T	N/A	40	N/A
Limentani et al. [50]	Prospective	31 LABC (9 IIIB including IBC)	D + V + T	N/A	39	N/A
Burstein et al. [51]	Prospective	40 (6 with IBC)	P + T	N/A	18	2-year DDFR 83.3%
Gianni et al. [52]	Prospective	235 (63 with stage III IBC)	AP + T followed by P + T followed by CMF + T versus same chemotherapy without T	N/A	38 (T) versus 19 (no T)	3-year EFS 71% (T) versus 56% (no T)
Lapatinib-based regimen						
Cristofanilli et al. [49]	Prospective	21	Lapatinib + P	95	N/A	N/A
High-dose regimens						
Veyret et al. [44]	Prospective	120	FEC-HD	91.1	N/A	10-year OS 41.2%
Cheng et al. [45]	Prospective	177 (10% with IBC)	CBT followed by autologous hematopoietic stem cell transplantation	N/A	N/A	5-year OS 36%
Conti et al. [46]	Prospective	62 (15 with IBC)	CEF	N/A	N/A	10-year OS 36%
Viens et al. [47]	Prospective	90	CA	90	32	3-year OS 70%

CAF, combination chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil; CDDP, cisplatin; CMF, combination chemotherapy with cyclophosphamide, methotrexate, and fluorouracil; EFS, event-free survival; IBC, inflammatory breast cancer; OS, overall survival; pCR, pathological complete response; AP, doxorubicin, paclitaxel; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; CAF-M, cylophosphamide, doxorubicin, 5-fluorouracil, methotrexate; CDDP, cisplatin; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; D, docetaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HD, high dose; IBC, inflammatory breast cancer; LABC, locally advanced breast cancer; NA: Not available; OR, overall response; OS, overall survival; P, paclitaxel; pCR, pathological complete response; T, trastuzumab; V, vinorelbine; DDFR, distant disease-free survival.

of neoadjuvant (primary) systemic treatment of operable breast cancer' [54]. In brief, the information reported on the specimen should include the size of residual disease, regression core, margins (for the presence or absence of disease involvement), and number of nodes removed and whether any are involved with disease with the greatest dimension of the metastatic foci. In the presence of residual disease, it is also recommended that ER and PR as well as HER2 status be repeated on the postmastectomy specimen.

adjuvant radiation therapy

All women with IBC who undergo a modified radical mastectomy are recommended to receive postmastectomy radiation therapy. Since a high probability exists of involvement of locoregional lymph nodes, which would predict for a high likelihood of locoregional recurrence, the panel members recommend that radiation therapy also encompass these regions including the supraclavicular regions and internal mammary lymph nodes. It is also recommended that the cumulative radiation dose be escalated to 66Gy in the subset of women who are <45 years of age, who have close or positive surgical margins, have four or more positive lymph nodes following preoperative systemic treatment, or who have demonstrated a poor response preoperative systemic treatment [61]. Skin dose should be modulated to ensure moderate acute erythema in response to radiation. Among women with

HER2-positive disease, trastuzumab may be administered concomitantly with radiation therapy.

trastuzumab and hormone therapy

All women with hormone receptor-positive IBC are recommended to receive a minimum of 5 years of hormone therapy with either tamoxifen or an aromatase inhibitor depending on their menopausal status. There are no current data to indicate the optimal duration of trastuzumab specifically among women with IBC. However, a recent randomized clinical trial evaluated women with locally advanced breast cancer that included 63 women with IBC evaluated the addition of 1 year of trastuzumab among women with HER2-positive disease with the results favoring the group receiving trastuzumab [52]. As such, the panel members agreed that in the absence of data derived from a large prospective randomized trial, it is reasonable to administer a total of 1 year of trastuzumab among women with HER2-positive IBC tumors.

follow-up

Following trimodality treatment, standard follow-up as per guidelines set forth by the American Society of Clinical Oncology in 2006 is recommended [62]. In brief, physical examinations should be conducted every 3–6 months in combination with yearly mammogram of the contralateral unaffected breast. In addition, the panel members agreed that yearly ultrasound of the locoregional lymph nodes may also be considered, but there are currently limited data on the value of these additional imaging modalities and prospective studies are encouraged. Additional radiological imaging and laboratory work-up with tumor markers for early detection of systemic recurrence are not recommended; however, prospective studies in this population at high risk of recurrence are encouraged. Genetic screening should be recommended for women with a strong family history of breast and or ovarian cancer as per published guidelines [62]. At present time, the panel members do not recommend routine prophylactic mastectomy of the contralateral breast unless specifically requested by the patient.

specialized centers and enrollment into clinical trials

Due to the rarity of IBC, the panel members recommend that patients consult with a center or a physician who specializes or has extensive experience in IBC. The panel members wish to promote communication between community oncologists and experts with the goal of promoting proper management of women with IBC. IBC specialists will be actively participating in a number of clinical trials specific for IBC and enrollment into these trials is highly encouraged. An international IBC-specific registry is currently under construction. The goal will be to monitor women with IBC being treated at these centers and procure tumor samples for research. The registries will adhere to the diagnostic criteria set forth by the panel. It is expected that this registry will provide a wealth of important epidemiological information and an opportunity to conduct innovative research across nations that will serve to better understand this aggressive disease. Furthermore, a future goal will be to set up IBC-specific tissue banks at these centers that will allow for future study of IBC at the molecular level.

education

The panel strongly encourages education of physicians and awareness of the public on the diagnosis and management of IBC. The panel in collaboration with a number of patient advocates has developed educational materials that are available for distribution to women with IBC. Grants are being set up to specifically encourage both translational and clinical research in the field of IBC and will be available in the near future.

summary

The panel of experts reached a consensus on minimum requirements for the diagnosis and management of IBC. Based on the current knowledge, it is felt that there is sufficient evidence to suggest that IBC differs from non-IBC locally advanced disease. Translational research efforts based on established preclinical models should be directed to clarify the etiology and biology of this aggressive entity.

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