

Update on the Management of Inflammatory Breast Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Recognize the differences in biology and clinical outcome of IBC compared with non-IBC.
2. Summarize the standard of care for IBC.
3. Identify molecular targets and novel agents for future treatments of IBC.

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ABSTRACT

Inflammatory breast cancer (IBC) is the most aggressive manifestation of primary breast carcinoma, with the clinical and biological characteristics of a rapidly proliferating disease. The multidisciplinary management of IBC has changed in the past 3 decades and is presently clearly outlined in sequence, with preoperative or neoadjuvant chemotherapy representing the mainstay of treatment. Anthracyclines and taxanes are the most effective cytotoxic agents in the management of primary breast cancer and should be the standard of treatment for women with IBC. Locoregional treatment includes radiotherapy with

or without surgery and continues to play a major role after appropriate medical treatment. The many investigations into the particular molecular determinants of IBC development have provided several interesting new therapeutic targets. Combination regimens that include angiogenic modulators, farnesyl transferase inhibitors, and p53 modulators hold great promise in the medical management of IBC. Future therapeutic approaches should focus on these discoveries so that we can improve the overall prognosis for women with IBC. *The Oncologist* 2003;8:141-148

INTRODUCTION

Inflammatory breast carcinoma (IBC) is the most aggressive manifestation of primary breast carcinoma. It is relatively rare, with an incidence of only 1%-6% in the U.S. [1]. African Americans have a higher incidence of IBC than do Caucasians and other ethnic groups (10.1%, 6.2%, and 5.1%, respectively). Furthermore, a review of

the Surveillance, Epidemiology, and End Results (SEER) program data comparing trends and patterns for breast cancer between 1975-1977 and 1990-1992 revealed that the incidence of IBC increased from 0.3 to 0.7 cases per 100,000 person-years, a much larger increase than that observed for noninflammatory forms of breast cancer during the same period. [2].

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The clinical presentation of IBC is quite characteristic and has been extensively described [3-7]. Patients usually present with a rapid onset of swelling of the involved breast. The classic criteria for clinical diagnosis established by *Haagensen* [8] include diffuse erythema, edema involving more than two-thirds of the breast, peau d'orange, tenderness, induration, warmth, enlargement, and diffuseness of the tumor on palpation. These symptoms usually progress rapidly, and patients frequently have axillary node involvement by the time they seek medical attention. Pathologically, there is extensive lymphovascular invasion by tumor emboli that involves the superficial dermal plexus of vessels in the papillary and high reticular dermis [9].

Primary IBC is the simultaneous development of inflammatory skin changes and carcinoma in a previously healthy breast, whereas secondary IBC is the development of inflammatory changes in a breast that has had a previous malignancy or has a mastectomy scar or changes caused by irradiation. However, the distinction between the two has been highly controversial [10, 11]. Interestingly, *Piera et al.* [12] reported that locally advanced disease associated with a clinically detectable inflammatory component had a worse prognosis than stage III cancer without associated skin changes.

A review of the SEER data that compared IBC with non-IBC clearly showed that IBC had a statistically significantly ($p = 0.0001$) lower overall survival (OS) rate [2]. Additional support for this observation comes from a more recent analysis by *Low et al.* [13] who reported a long-term follow-up study of 106 patients with locally advanced disease. Those authors retrospectively analyzed the outcome of combination chemotherapy in patients with IBC compared with patients with stage III non-IBC. The 10-year OS rates for patients with non-IBC and those with IBC were 44.8% and 26.7%, respectively ($p = 0.031$). Because of the relative infrequency of IBC, no phase III trials have been reported or performed, so all available knowledge is derived from single-arm clinical trials and retrospective chart reviews.

We recently reviewed The University of Texas M.D. Anderson Cancer Center's experience treating 635 patients with locally advanced breast cancer, including IBC with a median follow-up of 90 months (unpublished data). The median progression-free survival (PFS) and OS rates were lower in the group with IBC (214 patients) than in the group with stage III non-IBC (421 patients). Median PFS times were 24 months for IBC (95% confidence interval [CI], 19-29) and 35 months for non-IBC patients (95% CI, 25-45). Likewise, the median OS times were 42 months for IBC (95% CI, 35-49) and 60 months (95% CI, 47-73) for non-IBC patients. The data from these studies show that IBC is a clinically aggressive disease with an overall worse prognosis than non-IBC. These findings suggest that the underlying molecular determinants of the IBC phenotype will require more investigation so that we can design more effective targeted treatments. This review provides a summary of the traditional approaches used for IBC and specifically addresses the new directions in the management of this entity.

MULTIDISCIPLINARY TREATMENT OF IBC

The management of IBC has substantially evolved in the past 3 decades [14]. Surgery was the first therapeutic modality used, but it had disappointing results [9]. The mean survival of patients treated with mastectomy alone ranged from 12 to 32 months. The addition of radiotherapy improved the locoregional control rate, but it had no significant effect on survival [14-18]. Because IBC is a rare disease, patients with IBC were usually treated with the same modalities as, and included in clinical trials designed for, patients with noninflammatory locally advanced breast cancer. The M.D. Anderson Cancer Center has had the most experience of any cancer center in the U.S. with the management of IBC, having treated a total of 242 consecutive patients in IBC-directed clinical trials between 1974 and 2001. Two hundred twenty-two patients were treated in five studies (Table 1); the other 20 were enrolled in a recent pilot study, which is described later.

Table 1. Summary of clinical responses in five consecutive clinical trials for patients with IBC [20-23]

Clinical response	Protocol A, n (%)	Protocol B, n (%)	Protocol C, n (%)	Protocol D, n (%)	Protocol E, n (%)
CR	6 (15)	3 (13)	3 (7)	9 (13)	3 (7)
PR	26 (65)	10 (44)	25 (58)	45 (63)	31 (70)
MR	6 (15)	8 (35)	11 (26)	13 (18)	0 (0)
SD	1 (3)	0 (0)	0 (0)	2 (3)	1 (2)
PD	1 (3)	2 (9)	0 (0)	1 (1)	6 (14)
N/A	0 (0)	0 (0)	4 (9)	2 (3)	3 (7)
Total	40 (100)	23 (100)	43 (100)	72 (100)	44 (100)

Abbreviations: PD = progressive disease; N/A = not applicable.

One hundred seventy-eight patients were treated as part of four consecutive multimodality protocols between April 1974 and September 1993 [19-22]. Protocol A evaluated the use of 5-fluorouracil/doxorubicin/cyclophosphamide (FAC) as induction chemotherapy, followed by radiotherapy and then further chemotherapy (FAC and/or cyclophosphamide/methotrexate/5-fluorouracil [CMF]). Protocol B used the same induction regimen followed by mastectomy, adjuvant FAC, and radiotherapy. In protocol C, vincristine and prednisone were added to the FAC combination (FACVP). Patients in the last group, protocol D, underwent induction FACVP and surgery followed by FACVP in those who experienced a complete response ([CR] defined as complete disappearance of any clinical evidence of disease) during induction chemotherapy and FACVP plus methotrexate and vinblastine (MV) or MV alone in those who experienced a partial response ([PR] clinical reduction of tumor size by more than 50%) or minimal response ([MR] clinical reduction of tumor size from 25%-50%) using bidimensional criteria, respectively. This strategy was used to investigate the role of alternate therapy with potentially non-cross-resistant drugs. The overall response rate for all four groups combined was 72%, including a 12% clinical CR rate [18, 22]. No significant differences were found in the disease-free survival (DFS) or OS rates among the four protocols. The addition of surgical treatment in protocols B and C did not alter the risk of local recurrence in patients with poorly responsive disease. The results of protocols C and D indicate that the addition of vincristine and prednisone and the introduction of non-cross-resistant MV had no favorable effect on either DFS or OS [21, 22]. However, the modest sample size of all four clinical trials suggests that moderate differences in outcome might have gone undetected. The median survival was 37 months for patients on all four protocols combined (38, 38, 64, and 34+ months, respectively). The estimated DFS rates for all 178 patients at 5, 10, and 15 years were 32%, 28%, and 28%, respectively. Patients who experienced a CR or PR after induction chemotherapy had an estimated 15-year DFS rate of 44% and 31%, respectively, and a 15-year OS rate of 51% and 31%, respectively. Those patients who experienced an MR or stable disease (SD) had estimated 15-year DFS and OS rates of 7%, confirming the prognostic significance of response to induction chemotherapy.

Protocol E was initiated in 1994 (Table 1) and incorporated, for the first time, paclitaxel in the management of IBC [23]. Forty-four patients were enrolled and treated with FAC as induction and adjuvant chemotherapy. Paclitaxel was used preoperatively to treat patients who achieved only an MR or SD after undergoing FAC treatment and as adjuvant therapy in all patients. Local treatment consisted of mastectomy after

induction chemotherapy and then radiotherapy at the completion of adjuvant chemotherapy. The overall response rate was 77%, which was not significantly different from the rates documented in previous studies. The 2-year OS rates of the historical control group of 178 patients treated with anthracycline-based regimens (protocols A-D) and the patients on protocol E were 71% and 74%, respectively, showing a marginal, but not statistically significant, difference in favor of the paclitaxel-containing regimen.

A subsequent pilot study was initiated to test the feasibility of using the sequence of FAC plus weekly high-dose paclitaxel as induction chemotherapy (protocol F) [24]. This sequence was followed by chemotherapy with cyclophosphamide, etoposide, and cisplatin (CVP) for bone marrow mobilization followed by high-dose chemotherapy with cyclophosphamide, carmustine (BCNU), and thiotepa (CBT) and peripheral blood stem cell support (in patients who did not experience a clinical CR). In the original design of the study, the locoregional treatment consisted of radiotherapy combined with paclitaxel. After the first three patients had been treated, mastectomy was reintroduced as the primary locoregional treatment. The protocol was completed after 20 patients had been enrolled. A preliminary analysis of the data revealed that, of the 18 evaluable patients, seven (31%) experienced a clinical CR and 11 (61%) experienced less than a CR (defined as clinical and radiological persistence of disease). Thirteen patients underwent mastectomy; six (46%) of those experienced pathological CR. These data are encouraging, but they are from a small pilot study, which limits their use when developing standard-of-care recommendations for patients with IBC.

To better clarify the role of paclitaxel in treating this disease, we retrospectively compared the records of patients with IBC who had been treated at our institution on the basis of whether paclitaxel had been included in their induction or adjuvant chemotherapy regimen [25]. Two hundred forty patients, all of whom had been included in the earlier protocols, were included in this analysis; 178 had been treated with anthracycline-based regimens (group A), and 62 had been treated with paclitaxel (group B). The analysis demonstrated that objective response rates (CR + PR) were similar (A = 72% versus B = 79%). The 3-year OS and PFS rates were higher in group B, but these differences did not reach statistical significance (OS: A = 53% versus B = 71%, $p = 0.12$; PFS: A = 39% versus B = 46%, $p = 0.19$). Moreover, the 3-year OS and PFS rates were significantly higher in the subgroups of patients with estrogen receptor (ER)-negative tumors (OS: A = 43% versus B = 71%, $p = 0.035$; PFS: A = 31% versus B = 39%, $p = 0.042$). This analysis provides further evidence that paclitaxel is an important agent in the management of IBC.

MOLECULAR DETERMINANTS OF IBC DEVELOPMENT: FUTURE OF TARGETED THERAPIES

IBC is often characterized by invasive carcinoma of high histological grade and the presence of molecular markers of aggressive disease, including high S phase, aneuploidy, absent ER expression, and high expression of p53 and epidermal growth factor (EGF) [26].

Aziz *et al.* compared the expression levels of several prognostic markers, including p53 and erbB-2, in 40 IBC patients with those from 40 matched patients with non-IBC [27]. p53 was expressed in 70% of tumors in the IBC group and 48% in the control group ($p = 0.0238$). No statistically significant difference in expression was detected for erbB-2 (38% in the IBC group versus 35% in the control group). Other authors have investigated the incidence of erbB-2 overexpression in IBC, and, while some controversies persist, most have found that the incidence in IBC does not differ significantly from the incidence in non-IBCs [26, 28]. The subset of patients with erbB-2 overexpression might benefit from trastuzumab-based therapies [29, 30]. Patients with IBC are commonly included in clinical trials that enroll patients with erbB-2-overexpressing locally advanced disease [31].

Regarding the role of p53 in IBC, some authors have found a process of nuclear exclusion and cytoplasmic sequestration as the predominant mechanism of protein function inactivation, which clearly differs from the most common explanation that the inactivation is caused by missense gene mutations [32, 33]. The process of p53 inactivation by nuclear exclusion is a phenomenon that has been found in 37% of IBCs and in approximately 95% of undifferentiated neuroblastomas [32]. Further studies have clarified that the formation of cytoplasmic aggregates is mediated by the C-terminal domain of p53 and results in high molecular weight complexes with half-lives of about 6 hours.

The functions of *Mdm2* and *PTEN* are thought to be critical to the regulation of p53 function [34]. In fact, the level of p53 activity is regulated in part by the Mdm2 oncoprotein. *Mdm2* shuttling from the cytoplasm to the nucleus promotes p53 protein degradation through the ubiquitin-dependent proteasome pathway [34, 35]. *PTEN* has been shown to inhibit the phosphatidylinositol 3-kinase/Akt signal that regulates translocation of Mdm2 into the nucleus, resulting in persistent p53 activation [35]. *PTEN* is a tumor-suppressor gene localized to chromosome 10q23 that regulates cell migration, growth, and survival by dephosphorylating phosphatidylinositol 3-kinase second messengers and signaling phosphoproteins [36]. Through this mechanism, *PTEN* also inhibits the nuclear entry of Mdm2, causing its degradation by the proteasome and increasing the cellular content of p53 [35, 37]. Loss of *PTEN* has been found in invasive breast

cancer and has been associated with a poor prognosis [38, 39]. These findings suggest the possibility that mechanisms that inhibit Mdm2 function or control cytoplasmic degradation of the p53 protein may be an alternative and indirect approach to overcoming the effects of p53 inactivation. These data also support the use of more direct therapeutic approaches aimed at restoring p53 function with agents that act directly on the p53 protein [40, 41].

Recent studies with human xenograft models have provided some insight into the pathogenesis of IBC and suggest that angiogenesis may be a novel therapeutic target. Two groups of investigators recently reported the establishment of a human xenograft model of IBC [42, 43]. *Alpaugh et al.* established the first transplantable human IBC xenograft, MARY-X, in severe combined immunodeficient (SCID) mice [42]. Unlike other human xenografts that grow as isolated subcutaneous nodules, MARY-X grows exclusively within murine lymphatics and blood vessels and exhibits striking erythema of the overlying skin, and its molecular markers mirror those of human IBC—ER and progesterone receptor negative, HER-2/neu negative, and p53 and EGF receptor positive. *Shirakawa et al.* [43, 44] also established an IBC xenograft, WIBC-9, that is transplantable into SCID mice. WIBC-9 exhibits erythema of the overlying skin, and histological studies showed that WIBC-9 has a hypervascular structure of solid tumor cell nests and marked lymphatic permeation in the overlying skin. A comparative analysis of WIBC-9, three established non-IBC xenografts, and a human breast cancer cell line showed that certain human and murine genes (interleukin-8 [IL-8], vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF], angiopoietin 13, Flt-1, Tie-2, Tie-1, integrin- $\alpha_v\beta_3$, and CD31) are overexpressed in IBC. Many of these factors mediate angiogenesis. In another study, *Shirakawa et al.* [44] found that murine VEGF exhibits a more than 30-fold amplification of expression in WIBC-9. Furthermore, WIBC-9 tumors have a higher population of tumor-infiltrating endothelial cells and endothelial precursor cells than non-IBC tumors. Moreover, *Shirakawa et al.* also have described a particular pattern of neovascular growth in IBC [45, 46]. The phenomenon of “vascular mimicry” indicates a condition in which blood vessels within cancer tissue do not have a lining of endothelial cells. In subsequent experiments, the therapeutic use of agents that target VEGF receptors proved, as predicted, to be more effective in the human IBC xenograft model [46].

Cadherins are transmembrane components that play crucial roles in epithelial morphogenesis and mediate intercellular adhesion [47]. These receptors bind catenins and are involved in signal transduction pathways that regulate cell growth and apoptosis. Epithelial cadherin (E-cadherin) is a potent tumor suppressor in breast cancer, and loss of

E-cadherin expression has been found to correlate with poor prognosis [48, 49]. The E-cadherin gene (CDH1) is located on human chromosome 16q22.1, a region frequently affected by loss of heterozygosity in sporadic breast cancer [48]. Overexpression of E-cadherin has been described as characteristic of IBC [50]. Subsequent investigations demonstrated that IBC is associated with intact and overexpressed E-cadherin/ $\alpha\beta$ catenin and the lack of sialyl-Lewis (x/a) carbohydrate ligand-binding epitope [51, 52]. These two biological characteristics explain the presence of diffuse lymphovascular tumor emboli and the lack of endothelial adherence of the cells constituting it. Together, these unique molecular features suggest that angiogenesis has an important role in IBC and indicate that angiogenesis modulation may be an important therapy.

van Golen et al. [53] recently identified two additional molecular targets for IBC therapy. These investigators used differential display and Northern blot analysis to screen a cell line from a primary IBC and cells lines from non-IBCs. They identified two transcripts with distinct expressions in IBC: a novel low-affinity insulin-like growth factor binding protein, LIBC (lost in inflammatory breast cancer), and RhoC guanosine triphosphatase (GTPase). In situ hybridization of archival material showed that LIBC was absent in 80% of IBCs but only 21% of non-IBCs ($p = 0.0013$). RhoC GTPase was overexpressed in 90% of IBCs compared with only 38% of non-IBCs ($p = 0.0095$).

LIBC has subsequently been demonstrated to have tumor suppressor activity in *in vivo* studies in which mice injected with an IBC-derived cell line (SUM149) transfected with LIBC survived longer than did mice injected with the same cell line transfected with a vector control [54].

Because further studies were necessary to determine the oncogenic potential of RhoC in IBC, the same investigators [55, 56] transfected RhoC GTPase in nontransformed, immortalized HME cells. The transfection was associated with malignant transformation, growth under anchorage-independent conditions, and the ability to produce tumors in nude mice. RhoC GTPase overexpression was also associated with increased levels of VEGF, bFGF, IL-6, and IL-8 in conditioned media, suggesting modulation of angiogenic factors.

We find it interesting that the use of farnesyl transferase inhibitors (FTIs), which inhibit RhoC proteins, decreased angiogenesis in some animal studies [57]. FTIs inhibit Rho protein function by inhibiting its posttranslational modification [57, 58]. Although FTIs were designed to inhibit Ras, subsequent studies have shown that Ras may not be the only target of FTIs, and other studies suggest that inhibition of Rho proteins may mediate their therapeutic effects. These data suggest that RhoC may be an excellent target in the treatment of IBC.

SUMMARY AND CONCLUSIONS

IBC is the most aggressive manifestation of primary breast carcinoma, with the clinical and biological characteristics of a rapidly proliferating disease. The management of IBC has changed in the past 3 decades and, presently, the standard of care requires having a team of dedicated and experienced specialists (e.g., pathologist, surgeon, radiotherapist, diagnostic imager, and medical oncologist) involved in the complex management of this entity. The multidisciplinary treatment of IBC is clearly outlined in sequence, with preoperative or neoadjuvant chemotherapy representing the mainstay of treatment (Fig. 1). Locoregional treatment includes radiotherapy with or without surgery and continues to play a major role after appropriate systemic treatment. Its sequence is greatly dependent on the quality of objective response achieved with induction chemotherapy. In the majority of cases, after optimal remission, defined as partial objective clinical disease remission with resolution of the characteristic skin changes, patients are considered surgical candidates and a modified radical mastectomy is recommended followed by radiotherapy [59].

Anthracyclines and taxanes are the most effective cytotoxic agents in the management of primary breast cancer and have demonstrated their importance in the management of early breast cancer and IBC as well [23-25]. The use of a sequence including an anthracycline-containing regimen (e.g., AC, FAC) followed by a taxane (either docetaxel or paclitaxel) is associated with a higher probability of objective remission and should be used routinely as standard of care [25]. The

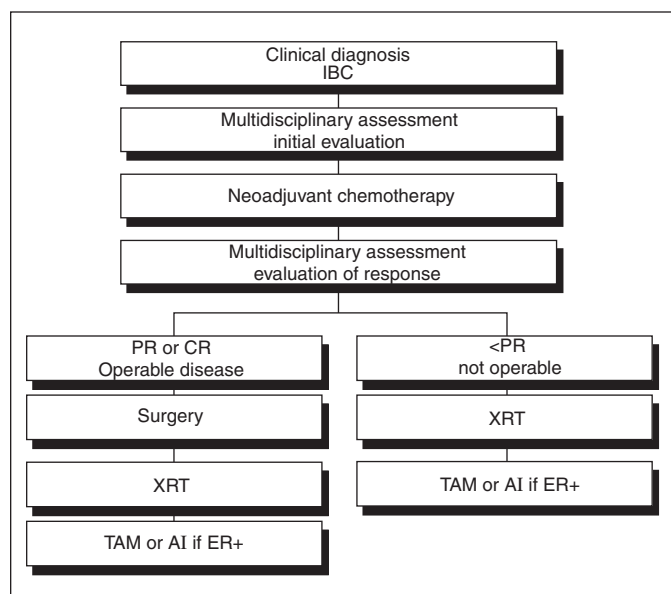


Figure 1. Schematic representation of the proposed optimal sequence of treatment for newly diagnosed IBC. Abbreviations: XRT = radiotherapy; TAM = tamoxifen; AI = aromatase inhibitor.

Table 2. Summary of biological targets in IBC

Category	Molecular marker	Agents
Oncogenes [26, 28, 53]	Her-2/neu	mAbs, RTKs
	RhoC GTPase	FTIs
Tumor suppressor genes [27, 32, 34, 37]	p53	Gene therapy, p53-stabilizing agents
	<i>PTEN</i>	Proteasome inhibitors, PI3K-inhibitors
Angiogenesis modulators [42, 43, 50-53]	Tie-2	Tie-2 kinase inhibitor
	Flt-1/Flk-1	RTKs, mAbs
	E-cadherin, VE-cadherin	VE-cadherin inhibitors
	RhoC GTPase	FTIs

Abbreviations: mAbs = monoclonal antibodies; RTKs = receptor tyrosine kinases; PI3K = phosphatidylinositol-3-kinase; VE = vascular endothelial.

optimal schedule of administration of paclitaxel remains to be established, but several trials suggest that a weekly schedule is associated with a higher pathological CR rate [24, 60]. Patients who undergo modified radical mastectomy and who are found to have extensive residual disease after optimal preoperative chemotherapy have a grim prognosis, and the role of alternate further adjuvant chemotherapy remains to be established. For patients who do not achieve an optimal debulking response, radiotherapy (alone or followed by surgical resection) represents an adequate locoregional treatment [61].

The many investigations into the particular molecular determinants of IBC development have provided several interesting new therapeutic targets (Table 2). Combination regimens that include angiogenic modulators and FTIs hold great promise in the medical management of IBC. The use of

agents or modalities that are able to restore p53 function could also lead to dramatic improvements in objective response. Researchers in that field should direct future therapeutic approaches so that we can improve the overall prognosis of women with IBC.

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