Update on systemic treatment for newly diagnosed inflammatory breast cancer

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Abstract

Background: Inflammatory breast cancer (IBC) is a rare and aggressive disease, accounting for 2–4% of new cases of breast cancer. Owing to its aggressive nature, IBC represent approximately 8–10% of breast cancer deaths. Management of IBC requires a multidisciplinary team for decision-making involving a composite of systemic treatment, surgery, and radiation, or “Trimodality Treatment.” Because of the rarity of the disease, systemic therapy of IBC traditionally has been extrapolated from non-IBC clinical trials.

Aim of Review: The purpose of this review is to provide an overview of the development of systemic treatment of IBC from the past to the present by focusing on IBC clinical trials, including chemotherapy and targeted therapies.

Key Scientific Concepts of Review: We discuss their effects on pathologic complete response (pCR) and survival outcomes, the predictive markers, and the adverse events of these therapies. Further, we summarized the current standard treatment stratified by molecular subtypes based on clinical data. Finally, we discuss the future trend of systemic therapy, including immunotherapy and ongoing IBC clinical trials.

Introduction

Over the past two decades, treatment for breast cancer overall has improved, leading to excellent outcomes. Inflammatory breast...
cancer (IBC) is a unique, rare entity with more aggressive behavior and worse prognosis than non-IBC or locally advanced breast cancer (LABC) [1]. In the United States, the incidence of IBC is 1.6–3.1 per 100,000 women with a higher incidence among black women and younger women, but owing to its aggressive nature, IBC represents approximately 8–10% of breast cancer deaths. [1,2]. Black women with IBC have worse survival than white women regardless of hormone receptor (HR) status and age [3,4]. Asian women with IBC tend to have longer survival than white women [3]. The survival is significantly shorter in IBC compared with non-IBC [5]. The 5-year overall survival (OS) rate for stage IV IBC is only 25–33% [6]. For de novo stage IV disease, the median OS time is 2.27 years for IBC but 3.40 years for non-IBC [7]. For stage III disease, the median OS is 4.75 years for IBC in contrast to 13.40 years for non-IBC [8]. Therefore, we classify IBC as a high-risk disease because of its high rate of distant metastasis (approximately 30–40%) at first diagnosis, and approximately 80% of stage III IBC has clinical lymph node involvement [9,10].

Definition of IBC

According to the American Joint Committee on Cancer (8th edition) [11], diagnostic criteria for IBC (T4d) are based on clinical diagnosis by a rapid onset of diffuse erythema and edema (or peau d’orange) involving approximately at least one-third of breast skin, with or without an underlying palpable mass. The skin changes may be due to lymphedema caused by tumor emboli within dermal lymphatics, which may be present or absent in biopsy specimens. Although tumor emboli are a hallmark of IBC, only around 75% of diagnosed IBC cases show tumor emboli on pathologic analysis [12]. Interestingly, we classify the presence of tumor emboli in dermal lymphatics without any skin changes as non-IBC breast cancer [11]. The onset of symptoms in IBC should be rapid, with no more than 6 months [11,13].

Subtypes and characteristics of IBC

Like non-IBC, IBC can be categorized into four subtypes; hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−), HR+/HER2-positive (HER2+), HR-negative (HR−)/HER2+, and HR−/HER2− (or triple-negative receptor status) [6,14,15]. Bone is the most common metastasis site in all the subtypes; liver metastasis has frequently occurred in the HER2+ subtype; and lung metastasis has frequently occurred in the triple-negative subtype. IBC has lung/pleural effusion metastasis around 21–29% [16]. As in non-IBC, triple-negative IBC has the worst survival outcomes, with a 5-year survival rate of less than 30% [6,17]. Approximately 15% of IBC develop brain metastasis [18]. Data from Surveillance, Epidemiology, and End Results (SEERs) database and our institute also showed the same results that triple-negative IBC has a higher rate of brain metastasis than non-IBC [18,19]. Our institute also reported that survival after brain metastasis in IBC was shortest in the triple-negative subtype, with a median OS of 3.8 months [18]. In contrast, after brain metastasis, HER2+ subtype IBC showed the longest median OS of 16.6 months, and the improvement of survival in HER2+ subtype relates to the anti-HER2 therapy era [18].

Pathological complete response

Pathologic complete response (pCR) is a well-known prognostic marker of neoadjuvant therapy for breast cancer, including IBC. Its definition is the absence of residual invasive cancer in the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ypT0/Tis ypN0 in American Joint Committee on Cancer staging system [11]). pCR predicts long-term survival outcomes, including event-free survival and OS [15,20–22]. Similar to non-IBC patients, IBC patients who experience pCR status have better survival than non-pCR, and those with HR−/HER2+ IBC have the highest pCR rate among all the subtypes. However, triple-negative IBC remains to have a poor outcome despite achieving pCR [15,23].

Treatment of IBC

Historically, local treatment of IBC by surgery or radiation alone has shown poor results, with a 5-year OS rate of less than 5% [24]. Systemic neoadjuvant regimens are a critical part of IBC treatment. Currently, the management of IBC requires a multidisciplinary team comprising a medical oncologist, surgeon, pathologist, diagnostic radiologist, and radiation oncologist. The principal goal of this team is to improve the survival of IBC by determining the optimal combination of systemic treatment, surgery, and radiation, or “trimodality treatment” [25]. However, at present, even though all standard guidelines [26,27] have defined IBC separately from non-IBC disease, the systemic treatment used in the clinic is still the same as that used for non-IBC. Current IBC systemic treatment has been extrapolated from non-IBC clinical trials and stratified by breast cancer molecular subtypes the same way as in non-IBC. In recent years, clinical research, including clinical trials, has investigated the potential role of several new systemic regimens in patients with IBC, but quite limited the number of patients. In this review article, we summarize the clinical data, including clinical trial results, regarding systemic treatment specifically for IBC, and we discuss the efficacy and toxicity of these treatments.

Developments of systemic treatment for IBC

Various systemic treatments have been used for breast cancer worldwide. The optimal selection of systemic treatment strategy depends on both tumor and patient characteristics. We discuss the systemic therapy of IBC from the past to the present (chemotherapy and targeted therapy eras). Further, we summarize the current standard treatment in real practice stratified by subtypes based on clinical trials. Finally, we provide the future direction of systemic therapy (immunotherapy era).

Chemotherapy

A large retrospective study from MD Anderson reported that 178 IBC patients treated with upfront anthracycline-based chemotherapy, combined with radiation therapy with or without mastectomy, had an objective response rate of 74%, a median OS of 37 months, and a 10-year OS rate of 33% [22]. These results are consistent with those of other anthracycline-based studies in IBC, which have reported a 10-year OS rate of 27–35% [28–30]. As in non-IBC, paclitaxel is well known as an active agent against breast cancer. Cristofanilli et al. [31] showed that adding taxane to a fluorouracil, doxorubicin, and cyclophosphamide (FAC)–based regimen in 240 IBC patients improved the pCR rate from 10% to 25% (p = 0.012). Paclitaxel addition regimen also had a numerically longer median OS in the study than did the FAC-based regimen alone (52 vs. 41 months, p = 0.11) and a statistically significantly longer OS among estrogen receptor (ER)–negative (ER−) patients than other subtypes [31]. Furthermore, paclitaxel showed benefit in anthracycline-refractory IBC, in which 44% of IBC non-responders who treated with FAC regimen four cycles became resectable after treatment with paclitaxel [32].

Many studies have demonstrated that increased dose intensity improves the efficacy of chemotherapy in breast cancer [33]. For
IBC, studies of chemotherapy dose intensity were undertaken based on data from prospective studies of non-IBC and reported results specific to an IBC cohort. Ditsch et al. [34] reported 101 IBC patients treated preoperatively with either epirubicin followed by paclitaxel every 2 weeks (dose-dense sequential group) with granulocyte colony-stimulating factor (G-CSF) support or standard combination chemotherapy every 3 weeks. After surgery, all patients received adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil), radiation therapy, and anti-hormonal therapy if clinically indicated. The dose-dense sequential group and the standard group did not significantly differ in pCR rate (12% vs. 10%, respectively; odds ratio = 1.27; p = 0.33) or in OS (hazard ratio = 1.4, 95% CI 0.71–2.75, p = 0.327). Similarly, Ellis et al. [35] enrolled patients with high-risk breast cancer in a phase 3 randomized clinical trial, including 115 patients with IBC and 249 patients with LABC. All patients were randomized into two groups, treated with a neoadjuvant standard-dose (21-day) doxorubicin and cyclophosphamide (AC) regimen or a weekly AC regimen with G-CSF support (dose-dense), and both groups were subsequently treated with weekly paclitaxel. The pCR rate in IBC patients was numerically higher in the dose-dense group compared with the standard, 21-day group, but the difference was not statistically significant (27% vs. 13%, p = 0.60).

The efficacy of neoadjuvant chemotherapy (NAC) depends on the breast cancer subtypes, ER- IBC has a higher pCR rate than ER-positive IBC, as same as in non-IBC [36]. Response evaluation by imaging in the middle of NAC also predicts final pathologic response in IBC; breast MRI, in particular, showed a better correlation than did mammography or sonography [37]. For predictive gene expression signatures, hyperactivation of IFN-α and hypoactivation of EGFR, p53, and TGF-β were associated with pCR in IBC after treatment with NAC [38]. This study also found that the predictive gene signatures were significantly enriched for immunity-related genes involved in CD8-positive T-cell lymphocyte activation processes, suggesting that adaptive immunity determined response to chemotherapy in IBC [38].

Today, there are no data from large randomized controlled trials for IBC; therefore, anthracycline- and taxane-based chemotherapy are still recommended as the backbone of primary chemotherapy regimens by international expert consensus. However, the chemotherapy schedule and dose density can differ between centers where have their own IBC specialized clinics [39].

**High-dose chemotherapy with autologous hematopoietic stem cell transplant**

Before 2000, high-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (AH SCT) was extensively investigated for IBC with the same rationale as that of studying dose-intensity relationships. In 1997, the International Blood and Marrow Transplant Registry reported a 3-year OS rate of 52% in 253 IBC patients treated with HDCT with AH SCT [40]. A larger and updated registry of HDCT with AH SCT, comprising 527 IBC patients and 2,860 non-IBC patients from the Center for International Blood and Marrow Transplant Research, reported a 10-year OS rate of approximately 30% with no difference between IBC and non-IBC [41]. However, among non-metastatic patients with no evidence of disease at transplant, the 10-year OS was worse for IBC patients than for non-IBC patients (37% vs. 45%, respectively; p = 0.03). Multivariate analysis in this study showed worse outcomes for stage III IBC than for stage III non-IBC. Multiple single-arm phase 2 trials of AH SCT specifically for IBC patients have reported varying pCR rates of 17–39%, 3-year OS rates of 68–72%, and favorable prognostic factors including HR positivity, the involvement of less than four axillary lymph nodes, and receipt of adjuvant radiation [42–44].

Owing to the diversity of these pilot studies [42–44] of HDCT with AH SCT for IBC, the French PEGASE experience perform larger, randomized comparative studies to demonstrate the survival benefit of HDCT with AH SCT for non-metastatic IBC: two phase 2 clinical trials (PEGASE 02 and PEGASE 05) and one phase 3 clinical trial (PEGASE 07). PEGASE 02 [45] treated 100 IBC patients with four cycles of high-dose FAC plus G-CSF and with the administration of AH SCT after cycles 3 and 4. The pCR rate was 32%, and the 3-year OS rate was 70%. Febrile neutropenia was the most frequent adverse event, resulting in 85% of rehospitalizations. One case had treatment-related death by septic shock. The phase 2 trial PEGASE 05 sought to determine the efficacy of adding dose-dense docetaxel to the high-dose AC regimen with AH SCT. After 54 patients were enrolled, the study was prematurely stopped owing to toxicity (eight cases had a severe infection, and two cases died of febrile neutropenia). In the 48 patients analyzed, the pCR rate was 30%, similar to that of PEGASE 02. The investigators concluded that adding dose-dense docetaxel did not improve the pCR rate and was too toxic [46,47].

In the randomized clinical trial PEGASE 07 [48], 174 IBC patients were treated with HDCT, comprising epirubicin (150 mg/m²) and cyclophosphamide (4 g/m²), with G-CSF support for four cycles followed by AH SCT. After surgery and radiation, patients were randomized to either observation or adjuvant therapy with four cycles of docetaxel (85 mg/m²) and 5-fluorouracil (3000 mg/m²), with continuous infusion for 4 days. There were no differences in 5-year disease-free survival (DFS) (55.0% vs. 55.5%, respectively; hazard ratio = 0.947, 95% CI 0.61–1.48, p = 0.810) or in 5-year OS rate (70.2% vs. 70.0%, respectively; hazard ratio = 0.938, 95% CI 0.55–1.60, p = 0.814). The pCR of both arms was 20%.

Although many publications have shown the efficacy of HDCT with AH SCT in IBC, the standard of care did not change because randomized trials of this approach showed a lack of positive benefits and the presence of toxic risks, including fatal infection, is a major problem. Also, the chemotherapy agents used in high-dose trials are currently not commonly used to treat IBC in the clinic. Furthermore, predictive biomarkers to guide the use of HDCT with AH SCT in IBC have not been discovered. Finally, HDCT was associated with worse quality of life [49]. Therefore, there is no currently recommended role for this strategy for newly diagnosed IBC.

**Targeted therapy**

At present, there are limited targeted therapy studies specific to IBC. Because IBC classified as a high-risk disease, systemic targeted therapy of IBC has mainly based on extrapolation of data available from the high-risk group of non-IBC studies.

**a Trastuzumab**

IBC has higher rates of HER2 overexpression than does non-IBC, with an estimated prevalence of 25–35% in IBC [50–53], and trastuzumab has been approved for HER2+ disease in both early and metastatic stages. Many randomized controlled trials have confirmed the survival benefits of NAC combined with trastuzumab for patients with LABC, including IBC [54,55]. However, the number of IBC patients was limited in those trials. The NOAH study [54], a randomized phase 3 clinical trial, enrolled 235 patients with HER2+ LABC (including 47 IBC patients) and evaluated the efficacy of neoadjuvant trastuzumab plus chemotherapy compared with NAC alone. The NAC regimen was doxorubicin and paclitaxel for three cycles, followed by paclitaxel for four cycles, and then cyclophosphamide, methotrexate, and fluorouracil for three cycles. Subgroup analysis in IBC showed that the addition of trastuzumab increased the 5-year event-free survival rate (64% vs. 24%, hazard ratio = 0.34, 95% CI 0.15–0.80) and 5-year OS rate (74% vs. 44%, haz-
ard ratio = 0.38, 95% CI 0.15–0.95) without any serious cardiac events. The efficacy of trastuzumab was confirmed in single-arm studies specifically for IBC [56,57], which reported a high pCR rate of 54–66% for patients with HER2+ IBC treated with an anthracycline-containing regimen plus trastuzumab without relevant cardiac toxicity. The NOAH study also reported that the HER2+/HR− subtype was a predictive marker for the efficacy of trastuzumab addition, with a hazard ratio of 0.51 (95% CI 0.29–0.91) for OS and a hazard ratio of 0.58 (95% CI 0.35–0.94) for event-free survival. Now, trastuzumab is a part of the anti-HER2 backbone for the HER2+ IBC.

b Pertuzumab

Pertuzumab is a humanized anti-HER2 monoclonal antibody that binds the HER2 receptor at a different epitope from that bound by trastuzumab, instead of binding to the subdomain II of the HER2 extracellular domain and preventing HER2 from dimerization with other ligands HER receptors, most notably HER3 receptor [58]. Like trastuzumab binding, pertuzumab binding induces antibody-dependent cell-mediated cytotoxicity [59]. Because of these similar but distinct mechanisms of binding to HER2 epitopes, the concept of the synergistic combination of pertuzumab with trastuzumab was tested in clinical trials [55,58,60].

In the NeoSphere trial [55,61], a phase 2 randomized neoadjuvant trial enrolled 417 patients with breast cancer, including 29 IBC patients. All patients were randomized into four neoadjuvant arms: docetaxel plus trastuzumab, docetaxel plus trastuzumab, and pertuzumab (THP), trastuzumab and pertuzumab without docetaxel, and docetaxel and pertuzumab. After surgery, all patients were treated with adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) and adjuvant trastuzumab for 1 year. NeoSphere reported promising pCR rates: 45.8%, the highest, in the THP arm; 29.0% for docetaxel plus trastuzumab; 16.8% for trastuzumab and pertuzumab without docetaxel; and 24.0% for pertuzumab plus docetaxel. Rates of cardiac adverse events were similar between all arms (4–5%). At the 5-year follow-up, NeoSphere [61] reported progression-free survival rates of 81% for docetaxel plus trastuzumab, 86% for THP, 73% for trastuzumab and pertuzumab without docetaxel, and 73% for pertuzumab plus docetaxel.

TRYPHAENA [62], a randomized phase 2 study, evaluated the safety and tolerability of dual anti-HER2 antibodies combined with NAC in 225 patients, including 13 IBC patients. All patients were randomized into three groups: FEC regimen plus pertuzumab and trastuzumab followed by THP; FEC followed by THP; and docetaxel and carboplatin plus pertuzumab and trastuzumab (TCHP). The incidence of left ventricular ejection fraction (LVEF) declines was low, around 4–5% in each group. Interestingly, this study reported pCR rates of 50.7%, 45.3%, and 51.9%, respectively. At the 3-year follow-up for TRYPHAENA, DFS and OS did not significantly differ between groups [63].

Overmoyer et al. reported the efficacy of neoadjuvant weekly paclitaxel combined with pertuzumab and trastuzumab, followed by surgery in only IBC patients. All patients received postmastectomy radiation, maintenance pertuzumab and trastuzumab for 36 weeks, and an adjuvant AC regimen for the non-pCR case. This study was closed owing to slow accrual, with 20 IBC patients. The pCR rate was 56%, and toxicity was minimal [64].

Now, a regimen containing pertuzumab plus trastuzumab is a standard neoadjuvant treatment for HER2+ IBC. In contrast to non-IBC, IBC is classified as a high-risk disease, and escalation strategies are preferred over de-escalation strategies. Therefore, short-duration or lower amounts of anti-HER2 therapy should be avoided.

c Lapatinib

Lapatinib is a small-molecule tyrosine kinase inhibitor that blocks intracellular HER2 and EGFR (epidermal growth factor receptor) signaling pathways [65]. The GeparQuinto study [66], a randomized neoadjuvant phase 3 trial, enrolled 620 HER2+ breast cancer patients (including 83 IBC patients). They were then treated with four cycles of epirubicin and cyclophosphamide followed by four cycles of docetaxel combined throughout all cycles with either trastuzumab or lapatinib. The pCR rate was higher in the trastuzumab arm than in the lapatinib arm (30.3% vs. 22.7%, odds ratio = 0.68, 95% CI 0.47–0.97, p = 0.04). However, the trastuzumab and lapatinib arms did not differ in 3-year OS rate (91.7% vs. 93.6%, respectively; p = 0.297) [67]. Interestingly, the combination of NAC with lapatinib had a lower pCR rate than expected in HER2+ patients. Similarly, a phase 2 IBC trial reported a low pCR rate of 17.6% in 32 patients with HER2+ IBC treated with neoadjuvant paclitaxel and lapatinib [68]. Concerning adverse events seen with lapatinib included diarrhea and rash, found around 50% of cases and sometimes leading to dose reduction or discontinuation of treatment [66,68]. One IBC study of NAC plus lapatinib was prematurely stopped owing to severe toxicity (>15% of patients) [69]. Combination chemotherapy plus lapatinib is currently not recommended to treat newly diagnosed IBC due to a low response rate and concerning toxicity.

Like trastuzumab, the HER2+ subtype is a strong predictive marker for lapatinib efficacy [68]. One study also reported that co-expression of phosphorylated (p) HER2 and pHER3 in IBC patients was associated with response to lapatinib [70]. Furthermore, a proof of concept for the synergistic combination of lapatinib and trastuzumab has been demonstrated in the clinical trial. The NeoALTO trial [71] reported promising results of dual antibody treatment with trastuzumab plus lapatinib combined with paclitaxel in HER2+ early breast cancer; the pCR rate for dual anti-HER2 combination was 51.3%, higher than that of paclitaxel combined with single-antibody treatment with trastuzumab (29.5%) or lapatinib (24.7%). However, most combination trastuzumab and lapatinib studies have excluded IBC patients or did not report their inclusion.

d Trastuzumab emtansine

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that has efficacy against breast cancer and acceptable toxicity. The conjugate comprises trastuzumab linked with the cytotoxic anti-microtubule agent DM1 (emtansine) and acts by directly binding on HER2 receptors of tumor cells. T-DM1 gains intracellular entry via endocytosis, and DM1 is released by lysosomal degradation [72]. Notably, T-DM1 is cytotoxic by itself, without coupling with chemotherapy. The KRISTINE trial [73], a randomized phase 3 trial, evaluated neoadjuvant treatment with a T-DM1 plus pertuzumab regimen or a TCHP regimen in 444 patients with HER2+ breast cancer, including IBC. Unfortunately, the pCR rate was significantly higher for the TCHP regimen than for T-DM1 plus pertuzumab (56% vs. 44%, respectively; p = 0.016). However, the TCHP regimen had a higher rate of serious adverse events (31% vs. 29%), including febrile neutropenia, diarrhea, and vomiting. Therefore, T-DM1 plus pertuzumab in the neoadjuvant setting is not superior to trastuzumab plus pertuzumab-containing regimen in terms of response; however, T-DM1 is more favorable in terms of toxicity. Therefore, the T-DM1 plus pertuzumab regimen is another option for patients in whom the TCHP regimen is not well tolerated.

Recently, the KATERINE trial [74] evaluated adjuvant therapy in patients with HER2+ breast cancer who did not experience a pCR after treatment with a taxane-based regimen plus trastuzumab. A total of 1,486 patients, including 22 IBC patients, were randomized...
to treatment with either adjuvant T-DM1 or trastuzumab for 14 cycles. The primary endpoint, invasive DFS, defined as freedom from invasive breast cancer recurrence or death, was 88.3% in the T-DM1 group and 77% in the trastuzumab group with a hazard ratio of 0.50 (95%CI 0.39–0.64, p < 0.001). However, adjuvant anti-HER2 therapy should be considered, as shown by a previously published study. An APHINTITY trial [75] showed greater benefit from adjuvant pertuzumab plus trastuzumab than adjuvant trastuzumab alone in lymph node-positive disease or high-risk node-negative disease: 3-year invasive DFS rates were 94.1% and 93.2%, respectively, with a hazard ratio of 0.81 (95% CI 0.66–1.00, P = 0.045). In summary, adjuvant pertuzumab plus trastuzumab are recommended in HER2+ IBC who achieve a pCR, and adjuvant T-DM1 is recommended in IBC cases with a non-pCR.

e Neratinib

Neratinib is a tyrosine kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4. The ExteNET study showed benefit from adjuvant neratinib for 1 year after completion of adjuvant trastuzumab, with an invasive DFS rate of 90.2% compared with 87.7% from placebo (hazard ratio = 0.73, 95% CI 0.57–0.92, p = 0.008) [76]. After amendments, the eligibility of the ExteNET study was restricted to patients with high-risk recurrent disease (e.g., node-positive disease). Therefore, the role of adjuvant neratinib should be considered with high-risk recurrent disease like IBC. However, the toxicity risk of neratinib should also be considered, particularly diarrhea, which is the most common adverse event (grade 3, 40%; grade 4, 0.1%).

f Bevacizumab

Bevacizumab is a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), a known angiogenesis activator in tumors. In preclinical data, the combination of bevacizumab with taxane-based chemotherapy inhibited tumor growth and metastasis of IBC cells (SUM149) [77]. In clinical data, three studies evaluated the addition of bevacizumab to neoadjuvant therapy, specifically in IBC patients.

The BEVERLY-1 and BEVERLY-2 studies, with similar study designs, evaluated the pCR rate in non-metastatic IBC patients with both HER2- (BEVERLY-1) and HER2+ (BEVERLY-2) disease. BEVERLY-1 [78], a single-arm phase 2 study, treated HER2- IBC patients (n = 100) with an FEC regimen plus bevacizumab for four cycles followed by docetaxel plus bevacizumab for four cycles. After surgery, patients received adjuvant radiation, adjuvant bevacizumab for ten cycles, and adjuvant hormonal therapy as clinically indicated. Results were disappointing, with a low pCR rate of 19%, similar to the pCR rates in the studies of chemotherapy without the targeted therapy mentioned above. Around one-third of all patients had serious adverse events, including febrile neutropenia, anal abscess, and LVEF decrease. BEVERLY-2 also reported that among patients with no detection of circulating tumor cells at baseline (<1 cell/7.5 ml) and achieved a pCR were a good prognosis with a high 3-year DFS rate of 98% [79].

The third study, by Palazzo et al., assessed the pCR rate in 34 IBC patients treated with paclitaxel, carboplatin, and oral cyclophosphamide combined with bevacizumab for 24 weeks before surgery. If tumors were HER2+ or HR+, trastuzumab and endocrine therapy were added as indicated. The pCR rate was 29% overall, 57% in HER2+ cases, 20% in triple-negative cases, and 0% in the HR+ subtype. The treatment was well tolerated; only one patient developed a serious adverse event of grade 4 neutropenia [80].

Concerning predictive biomarkers, a pooled analysis of BEVERLY-1 and BEVERLY-2 [81] again reported that patients with no detection of circulating tumor cells at baseline (<1 cell/7.5 ml) and a pCR showed good prognosis, with a high 3-year OS rate of 94%. The AVEREL study [82], a randomized phase 3 trial, aimed to evaluate first-line therapy with docetaxel and trastuzumab with or without bevacizumab in HER2+ metastatic breast cancer. The study reported that VEGF-A showed potential as a biomarker for bevacizumab efficacy; a high plasma concentration of VEGF-A was associated with greater benefit from therapy than a low concentration. This result was consistent with the BEATRICE study [83], which also found that high plasma VEGF-A concentration was associated with greater benefit from adding bevacizumab to neoadjuvant therapy. However, the absolute differences in the benefits associated with VEGF-A were not statistically significant. Bevacizumab was approved by the U.S. Food and Drug Administration for metastatic breast cancer; however, the approval was withdrawn after safety and efficacy concerns arose. At present, the role of bevacizumab is used in certain circumstances with paclitaxel for metastatic breast cancer [26].

g Panitumumab

Around one-third of IBC cases typically express EGFR, and higher EGFR expression correlates with worse prognosis [84,85]. The humanized anti-EGFR antibody, panitumumab, besides being approved for the treatment of colorectal cancer, also has clinical efficacy in breast cancer. In a single-arm phase 2 study, panitumumab was combined with preoperative carboplatin and nab-paclitaxel for four cycles, followed by an FEC regimen for four cycles in 47 patients with newly diagnosed HER2- IBC regardless EGFR expression status, leading to a pCR rate of 28% [86]. The triple-negative IBC subtype had the highest pCR at 42%. Among the expressed proteins of baseline tissues, only pEGFR expression was associated with pCR (p = 0.05), but EGFR was not (p = 0.14). Hematologic toxicity was moderate, 30% of patients had grade 4 neutropenia, and 15% had grade 3 or 4 thrombocytopenia. The most frequent non-hematologic toxicity related to panitumumab affected the skin; six patients (15%) had grade 3 skin rash. To our knowledge, this targeted therapy study is the first to show a high pCR for the poor-prognosis disease triple-negative IBC [86]. Now, an ongoing clinical trial is evaluating combination NAC plus panitumumab for IBC (NCT01036087) in Table 1.

h Pazopanib

Pazopanib is a small-molecule multi-tyrosine kinase inhibitor of VEGFR1-3, FGFR1 and -3, PDGFRα and -β, and c-Kit. A randomized phase 2 study, VEG20007 [87], evaluated first-line lapatinib plus pazopanib therapy or lapatinib monotherapy in patients with HER2+ locally advanced and metastatic breast cancer (n = 190), including IBC. HER2+ status was defined as 3+ by immunohistochemistry or HER2 gene amplification by fluorescence in situ hybridization. The primary endpoint was the rate of progressive
Afatinib is an irreversible ErbB family blocker that has shown preclinical activity in trastuzumab-resistant cell lines [89]. A phase 2 clinical trial evaluated afatinib with or without vinorelbine in metastatic HER2+ IBC. However, the trial was stopped early after another study showed that afatinib was associated with shorter survival, 26 IBC patients who remained showed a clinical benefit rate of 35% from afatinib monotherapy [90]. An oral multi-tyrosine kinase inhibitor, sunitinib, was evaluated in a phase 2 trial in combination with NAC in patients with HER2- LABC or IBC (n = 70). The neoadjuvant treatment was sunitinib combined with weekly paclitaxel followed by AC regimens with G-CSF. Disappointingly, overall results showed a low pCR rate of 24% [91].

Over two decades, there have been many changes in systemic treatment leading to improved survival outcomes for breast cancer, specifically IBC (Fig. 1). We had chemotherapy as a tool against breast cancer in the past, and today we have a combination of targeted therapy and chemotherapy, which has a higher pCR rate. Not all strategies or agents are effective in IBC (e.g., the HDCT strategy has a higher pCR rate than conventional chemotherapy but has too great a toxicity risk). Now, we know that the identification of breast cancer subtypes dictates the prognosis and specific treatment. Therefore, practical treatment guidelines in the era of personalized medicine are classified by subtypes.

### The current standard of care for newly diagnosed IBC

Based on the above information and international consensus on IBC [39], based on collaboration with experts from high-volume centers, there is broad agreement that upfront systemic treatment should be administered before surgery. This systemic treatment comprises sequential treatment with anthracycline-based and taxane-based chemotherapy, with or without carboplatin. Although different centers with IBC clinics may administer slightly different systemic regimens, the backbone chemotherapy regimen is the same. We present the current neoadjuvant and adjuvant treatments leading to improved survival outcomes for breast cancer.

| Table 1                                                                 |
|-------------------------------------------------------------------------|
| Ongoing clinical trials for IBC.                                         |
| Identifier (Status) | Population | Phase | Regimen | Endpoint |
| NCT03151798 (Recruiting) | HER2-, IBC | Randomized phase 2 | Arm 1: (FEC + weekly paclitaxel) + pemetrexed | pCR rate |
| NCT02971748 (Recruiting) | HR+, IBC | Single-arm phase 2 | Non-pCR case treated with adjuvant pemetrexed + hormone therapy | 2-year DFS |
| NCT02876302 (Recruiting) | Triple-negative IBC | Phase 2 | Weekly paclitaxel + ruxolitinib then AC regimen | Change of JAK expression |
| NCT01036807 (Active, not recruiting) | Triple-negative IBC | Randomized phase 2 | Arm 1: panitumumab + carboplatin + nab-paclitaxel then FEC | pCR rate |
| NCT02623972 (Recruiting) | HER2-, IBC | Phase 2 | AC then eribulin | pCR rate |
| NCT03598257 (Recruiting) | Non-metastatic IBC | Phase 2 | Concurrent radiation + olaparib vs radiation alone | Invasive DFS |
| NCT03101748 (Recruiting) | LABC or metastatic IBC | Phase 1b/2 | Neratinib + paclitaxel + pertuzumab + trastuzumab | pCR rate |
| NCT03202316 (Recruiting) | Recurrent or metastatic IBC | Single-arm phase 2 | Atezolizumab + cobimetinib + eribulin | Response rate |
| NCT02411656 (Recruiting) | Stage IV, IBC or triple-negative | Single-arm phase 2 | Maintenance pemetrexed in non-PD cases after chemotherapy | Disease control rate |
| NCT03101748 (Recruiting) | HER2+ or -, IBC | Single-arm phase 2 | Cohort 1: paclitaxel + pertuzumab + trastuzumab + neratinib then AC regimen | pCR rate |
| NCT03742986 (Recruiting) | Newly diagnosed IBC | Non-randomized phase 2 | Cohort 2: paclitaxel + neratinib then AC regimen | pCR rate |
| NCT02658812 (Active, not recruiting) | Local recurrence IBC or inoperable non-IBC | Single-arm phase 2 | Cohort HER2+: weekly paclitaxel + nivolumab then AC regimen | pCR rate |
| NCT03742986 (Recruiting) | Local recurrence IBC or inoperable non-IBC | Single-arm phase 2 | Talimogene laherparepvec | Response rate |

Abbreviations: IBC, inflammatory breast cancer; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; AC, doxorubicin and cyclophosphamide; LABC, locally advanced breast cancer; DFS, disease-free survival; PD, progressive disease (accessed clinical-trial.gov on April 23, 2020).
platin to a neoadjuvant regimen increases the pCR rate in TNBC [92,93], but these data do not include IBC patients. Hence, there are no data to support carboplatin for IBC [39]. A randomized phase 3 study, CREATE-X [94], showed that patients with HER2- non-pCR breast cancer treated with adjuvant capecitabine had longer OS than those given an adjuvant placebo (hazard ratio = 0.59, 95% CI 0.39–0.90), suggesting that adjuvant capecitabine for six to eight cycles can be considered in cases without a pCR. Interestingly, a more pronounced OS benefit was observed in triple-negative disease (hazard ratio = 0.52, 95% CI 0.30–0.90).

**b HR-positive**

The response rate to NAC is low in HR+ breast cancer compared with TNBC. Nevertheless, NAC, similar to that used in TNBC, is recommended for HR+ breast cancer. As for adjuvant therapy, a key consideration is that IBC carries a high risk for recurrence. Furthermore, ER+ breast cancer has a risk of recurrence after 5 years. Therefore, extended adjuvant endocrine therapy can help reduce recurrence risk. The use of either tamoxifen or aromatase inhibitors for extended adjuvant therapy for up to 10 years has been associated with improved survival outcomes in breast cancer [95–98]. Among premenopausal breast cancer patients, based on the TEXT and SOFT trials, the addition of ovarian suppression to adjuvant endocrine therapy showed higher rates of DFS and OS in high-risk patients than endocrine therapy alone [99].

Despite the potential survival benefit of extended adjuvant endocrine therapy and ovarian suppression, these approaches also may incur their own adverse events and long-term toxicity. For example, the addition of ovarian suppression increased the rate of osteoporosis, diabetes, cardiovascular disease, and depression [99]. Some of these adverse effects may be treatable; for example, the use of bisphosphonate can increase bone density and may also improve survival in breast cancer patients [100]. Now, an ongoing trial of adjuvant endocrine therapy plus immune checkpoint inhibitors in patients with non-pCR, HR+/HER2- breast cancer after neoadjuvant therapy is enrolling (NCT02971748).

**c HER2-positive**

For HER2+ IBC, based on the NeoSphere and TRYPHAENA trials, the recommended neoadjuvant therapy is a regimen containing

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**Fig. 1.** Timeline of systemic treatment for inflammatory breast cancer.
pertuzumab plus trastuzumab (dual anti-HER2 antibodies) in combination with an anthracycline-containing regimen (specifically, THP for four cycles followed by an anthracycline-containing regimen for four cycles). No data are demonstrating the superiority of dual anti-HER2 antibodies with a non-anthracycline regimen (TCHP regimen for six cycles) over the dual anti-HER2 antibodies with the anthracycline-containing regimen, because the primary endpoint of TRYPHAENA trial [62] was safety and tolerability, which cannot be used to determine conclusions about the efficacy of each regimen. Therefore, we still have recommended the dual anti-HER2 antibodies in combination with an anthracycline-containing regimen for HER2+ IBC.

Even for patients who experience a pCR after neoadjuvant therapy, those with HER2+ IBC are still at a high risk of recurrence [15]. Adjuvant pertuzumab plus trastuzumab for 1 year are recommended in HER2+ breast cancer based on the APHINITY trial [75], which showed benefit from adjuvant dual anti-HER2 antibodies in high-risk patients. In HER2+ IBC cases without a pCR, adjuvant T-DM1 is recommended (KATERINE trial [74]). After the completion of adjuvant anti-HER2 therapy, neratinib is recommended in the high-risk situation, especially non-pCR patients, and should discuss to risk-benefit assessment for pCR patients [76]. However, grade 3-4 diarrhea was commonly found (40%) with neratinib compared with placebo (2%), leading to discontinuation of neratinib in up to 28% of patients treated with neratinib [76]; anti-diarrheal prophylaxis should be offered.

### Future directions

**De novo stage IV IBC**

For patients with de novo stage IV IBC, we recommend similar systemic treatment to that of non-metastatic IBC, intending to achieve optimal response. Patients should then be evaluated for surgery and radiation therapy by a multidisciplinary team. In cases that show a response or stable disease after neoadjuvant therapy, local therapy at the primary breast tumor (e.g., modified radical mastectomy followed by radiation) should be discussed working with a multidisciplinary team. Although the survival impact of local therapy of the primary tumor in the metastatic setting is controversial, loco-regional progression in IBC can lead to serious morbidity [39].

### Immunotherapy and future directions

**Role of immunotherapy in clinical data**

Recently, the U.S. Food and Drug Administration accelerated approval of the anti–PD-L1 immune checkpoint inhibitor atezolizumab in combination with nab-paclitaxel in patients with unresectable or metastatic triple-negative breast cancer (TNBC) whose tumor expresses PD-L1 (≥1%), based on phase 3 randomized trial (IMpassion130) [101]. In the neoadjuvant setting, immunotherapy for breast cancer has been investigated in two randomized trials, KEYNOTE-522 [102] and I-SPY2 [103]. KEYNOTE-522 studied the combination of anti–PD-1 (pembrolizumab) with preoperative chemotherapy, carboplatin plus paclitaxel followed by the AC regimen, in patients with TNBC (including IBC patients), followed by adjuvant pembrolizumab, met one of the dual-primary endpoints (pCR rate). The combination of pembrolizumab and chemotherapy showed significant improvement in pCR rate compared with placebo plus chemotherapy (64.8% vs. 51.2%, P < 0.001). The improved benefit was consistent with respect to the pCR rate across subgroups, including both PD-L1 expressions positive or negative. Besides, an ongoing phase 2 trial, the adaptively randomized I-SPY2 trial [103], is evaluating the effect of pembrolizumab on pCR rate in high-risk stage II-III breast cancer. This study is using multiple investigational arms in parallel and using the standard neoadjuvant arm as the common control arm; weekly paclitaxel for 12 cycles followed by AC regimen for 4 cycles. They reported the pCR rate of HER2- patient treated with weekly paclitaxel plus every 3 weeks of pembrolizumab for 12 weeks, then AC regimen for 4 cycles was 44% compared with pCR rate of control arm 17%. For the triple-negative subtype and the HR+/HER2- subtype, pCR rates were 60% and 30%, respectively, in the pembrolizumab arm but 22% and 13%, respectively, in the control arm.

**Future directions**

Previously mentioned studies suggest that the combination of an immune checkpoint inhibitor and chemotherapy increases response rate and efficacy in breast cancer; however, the number of IBC patients in those trials was limited. A study from our institute showed that PD-L1 was expressed in 36.8% of IBC tumor cells on immunohistochemical staining (monoclonal rabbit anti–PD-L1 antibody, clone 28-8). PD-L1 expression in the tumor was not associated with clinicopathologic characters, including histologic type, tumor grade, or ER, progesterone receptor, or HER2 status; however, PD-L1–positive tumors (>1% of tumor cells) were associated with worse OS [104]. The incidence of PD-L1 expression in this study was similar to that of a study by Bertucci et al., which reported PD-L1 overexpression in 38% of IBC tumor cells and 28% in non-IBC tumors, according to mRNA expression using DNA microarray [105]. On the other hand, PD-L1 mRNA overexpression was associated with ER- status, basal and HER2+ subtypes, and higher pCR rate after NAC, but not OS [105]. PD-L1 expression is found not only in tumor cells but also in tumor-infiltrating lymphocytes (TILs), which are considered to be the main effector of immunotherapy. Arias-Pulido et al. reported 221 IBC samples had PD-L1 positivity of 66% in the TILs and more than 8% in the tumor cells and also showed that PD-L1 expression (≥5%) in the TILs was associated with the better DFS [106]; Berckelaer et al. reported 105
IBC samples had PD-L1 positivity (≥1%) in the TILs, more than in the TILs of non-IBC samples, 42.9% vs. 23.7%, respectively [107].

Taken together, these findings indicate that PD-L1 is an immune checkpoint molecule that is found in both the tumor cells and the TILs of IBC more frequently than in non-IBC, and thus is a potential predictive biomarker for immunotherapy. Beyond the combination of chemotherapy and an immune checkpoint inhibitor, as used in the KEYNOTE-522 and I-SPY2 trials, our institute also demonstrates IBC preclinical data supporting a combination of targeted therapy and an immune checkpoint inhibitor [108]. Further, an anti–EGFR agent combined with an anti–PD-L1 antibody inhibited the growth of IBC tumors more than either single-agent treatment (unpublished data). Even if immunotherapy studies conducted specifically in IBC patients have not been established, these findings provide a rationale for future studies of the use of immune checkpoint inhibitors as a part of IBC treatment. To fill this gap in knowledge, ongoing immunotherapy studies are enrolling patients with IBC in many trials, as shown in Table 1. Another issue is a slow accrual problem of IBC clinical trials; multicenter clinical trials are an important key to resolve this problem. Hopefully, clinicians and researchers will be motivated to cooperate.

Conclusion

Frequent distant metastases and poor prognosis indicate that IBC is a unique entity rather than a subtype of LABC. IBC has high potential for fatality, urgently necessitating the development of novel systemic treatments. This review shows that anthracycline and taxane are the backbone of chemotherapy and remain a current treatment. We do not have scientific evidence to deescalate the treatment as in non-IBC settings. We have learned from the past that high-dose chemotherapy with AHSCST is too toxic a strategy, with no apparent benefit. In the targeted therapy era, only anti–HER2 therapies have been incorporated into the current standard IBC treatment. Recently, a high PCR rate has been produced by immune checkpoint inhibitors for non-IBC; the preclinical findings suggest a possible role for immunotherapy in IBC in the future. We hope this review provides a foundation of knowledge for the development of new treatment approaches, especially for IBC-specific clinical trials. Utilizing a multicenter approach in a global level is a key to improved success of IBC clinical trials.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

Naoto T. Ueno has a research agreement with Amgen, Celgene and PUMA Oncology. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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