What is the best systemic treatment for newly diagnosed inflammatory breast cancer?—a narrative review

Sudpreeda Chainitikun[1], Siyamol Mingmalairak[1], Napa Parinyanitikul[2]

[1]Department of Medical Oncology, MedPark Hospital, Bangkok, Thailand; [2]Department of Medical Oncology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

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Correspondence to: Sudpreeda Chainitikun, MD. Department of Medical Oncology, Light of Day Center, MedPark Hospital, 3333 Rama IV Rd., Khwaeng Khlong Toei, Khet Khlong Toei, Bangkok 10110, Thailand. Email: Sudpreedac@Medparkhospital.com.

Objective: The propose of this review to discuss of the systemic treatment options for newly diagnosed inflammatory breast cancer (IBC) including the recent data of immune checkpoint inhibitor, CDK4/6 inhibitor and anti-HER2 therapy. Aim to provide a pragmatic treatment in a gray area or concerning issues of real-world practice.

Background: IBC is a rare and aggressive disease. Upfront systemic treatment followed by surgery and radiation therapy or "Tri-modality" treatment is a standard of care for newly diagnosed IBC. Due to its rarity, the data of systemic treatment for IBC has been extrapolated mostly from non-IBC clinical trials.

Methods: We summarized the recent data of systemic treatment stratified by concerning topics and breast cancer subtypes. Some topics are less likely to have strong data from IBC clinical trial to supports. Therefore, we interpolate the non-IBC data to support our review.

Conclusions: IBC is challenging in the clinical management. The development of novel systemic treatment is urgently needed, especially for IBC-specific clinical trials.

Keywords: Inflammatory breast cancer (IBC); immunotherapy; anti-HER2 therapy; CDK4/6 inhibitor

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Introduction

Term "Inflammatory breast cancer (IBC)" is an entity of aggressive form of breast cancer. Its aggressiveness shows poor survival outcome compared with those women diagnosed with non-IBC (1-4). Interestingly, diagnostic criteria for IBC are based on clinical diagnosis, including the involvement at least one-third of the breast skin, a rapid onset of architectural changes such as erythema and edema (or peau d'orange) (5). These clinical characters may be due to the presence of tumor emboli within dermal lymphatics. Despite, tumor emboli are pathognomonic of IBC, but these are not required to make the diagnosis (6). Only around 75% of diagnosed IBC present tumor emboli on pathological report (7). Pathological analysis of IBC also shows the hypervascularity, around four times higher than non-IBC vascularity (8). This is consisted with that IBC has higher levels of vascular endothelial growth factor D (VEGF-D), which is an angiogenesis marker (9,10). Several studies reported the different higher mutations in gene expression between IBC and non-IBC, e.g., MYC, PIK3CA, ERBB2 and p53 mutation (11-13). However, all of them have not been able to identified as a specific mutation for IBC (10). Recently, the tumor microenvironment (TME) of IBC has been investigated and may play a crucial role in aggressiveness of IBC.

Tumor-associated macrophages (TAMs) isolated from TME of IBC patients (especially M2 TAMs) produce several cytokines that promote progression and invasion of IBC cells (9,10). Tumor-infiltrating lymphocytes also play an essential role in predictive chemotherapy response (9,10). Finally, there are no the distinct genomic signatures that specifically distinguish IBC from non-IBC (9). Implication, there are many specific intrinsic factors contribute to aggressive behavior, potential metastasis, and chemotherapy resistance of IBC.

Due to the aggressiveness of IBC as aforementioned, there are no de-escalation strategies for systemic treatment. It is not feasible to omit or short-course of IBC systemic treatment without affect to survival outcomes. Differently to non-IBC, de-escalation treatment is preferred in some situations. Recommended approach in newly diagnosed patient with IBC is upfront systemic treatment followed by surgery and radiation therapy (tri-modality) using a multidisciplinary team (14,15). Due to the rarity, current standard guideline of IBC has been extrapolated mostly from the non-IBC clinical trials. Similarly to non-IBC, anthracycline- and taxane-based chemotherapy are still recommended as the backbone of chemotherapy regimens. For example, doxorubicin and cyclophosphamide (AC) regimen followed by taxane or instead of AC with fluorouracil, epirubicin and cyclophosphamide (EFC) regimen (14,15). Targeted therapy or immune checkpoint inhibitor adding is considered depends on the IBC subtypes. Dual anti-human epidermal growth factor receptor 2 (HER2) blockade; trastuzumab and pertuzumab (HP), combined with chemotherapy has been recommended in HER2+ IBC. The propose of this review is to discuss the concerning topics that we are facing in the real-world practice of IBC. We discussed the treatment based on subtypes, mostly extrapolated form the non-IBC data. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/cco-21-81).

Role of CDK4/6 inhibitor in adjuvant systemic treatment of HR+/HER2– IBC

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has been approved in metastasis hormone receptor-positive (HR+) and HER2– breast cancer. Currently, the CDK4/6 inhibitor may shift role to adjuvant setting. The recent published study, Monarch-E (16), showed the efficacy of adjuvant abemaciclib combined with endocrine therapy (ET). Adjuvant abemaciclib 150 mg twice daily (for 2 years) combined with ET (for 5 to 10 years, as clinical indicated) in high-risk early breast cancer (n=5,637) significantly improved invasive disease-free survival (IDFS) with hazard ratio 0.75, 95% CI: 0.6–0.93; P=0.01 compared with adjuvant ET alone, and the 2-year IDFS rates were 92.2% *vs.* 88.7%, respectively. The safety profile of abemaciclib in this study was manageable and consistent with the known adverse events form previously reported in the metastasis studies. In contrast, PALLAS study (17) enrolled patients with stage II–III HR+, HER2– breast cancer (n=5,760), adjuvant palbociclib 125 mg once daily 3 weeks of 4 weeks cycle (for 2 years) combined with ET did not improve IDFS compared with standard ET alone (hazard ratio 0.93, 95% CI: 0.76–1.15; P=0.51), and the 3-year IDFS rates were 88.2% *vs.* 88.5%, respectively. Palbociclib also demonstrated the negative results in the other adjuvant clinical trial, Penelope-B trial (18). That trial included the patients with residual disease and high-risk feature considered by clinical pathological staging-estrogen receptor grading score (CPS-EG score) after neoadjuvant chemotherapy (NACT) with taxane based regimen. The result showed that the standard dose of palbociclib (for 1 year) combined with ET (at least 5 years) after surgery did not improve IDFS compared with the standard ET alone (hazard ratio 0.93, 95% CI: 0.74–1.17, P=0.52). The 3- year IDFS rates were 81.2% *vs.* 77.7%, respectively.

Because HR+/HER2– early breast cancer has a very good prognosis when treated with adjuvant ET. The clinical studies of HR+/HER2– breast cancer need to identify and select the patients who might have the greatest benefits from the adjuvant combination of CDK4/6 inhibitor and ET. In this rationale, those studies trend to enroll the patients with high-risk feature of recurrence. All studies had their individual criteria for high-risk definition, based on tumor characteristic. Not only baseline tumor factor, abemaciclib showed the positive outcome while palbociclib did not. Abemaciclib also has the clinical efficacy as monotherapy in metastasis setting. Imply, that abemaciclib has more strong data than palbociclib to support the adjuvant strategy in early breast cancer with high-risk feature. IBC is also classified as a high-risk disease that might has the potential benefits along with this strategy. However, all mentioned studies did not have the IBC data (IBC was excluded in Monarch-E). The other concerning issues are treatment

duration and adherence. Monarch-E study, adjuvant abemaciclib combined with ET treated for 2 years with 16.6% of early discontinuation because of adverse events (16). While, early stopped palbociclib due to adverse events in PALLAS study was 27.1% (17). Neutropenia was the most common adverse event of palbociclib, while of abemaciclib was diarrhea (16,17). NATALEE study (19) is currently ongoing clinical trial (NCT03701334) and enrolling patients with stage II (high-risk) and III HR+/HER2– early breast cancer. NATALEE study evaluates the efficacy and safety of adjuvant ribociclib (for 3 years) combined with ET compared with ET alone (19).

Role of immunotherapy for triple negative IBC in neoadjuvant setting

In neoadjuvant setting, immunotherapy for triple negative breast cancer (TNBC) has been investigated, KEYNOTE-522 (20), I-SPY2 (21), IMpassion031 (22) and GeparNuevo (23) studies. KEYNOTE-522 study investigated pembrolizumab with NACT, carboplatin plus paclitaxel followed by the AC regimen then adjuvant pembrolizumab. The combination of pembrolizumab and NACT showed significant improvement in pCR rate compared with placebo plus chemotherapy (64.8% *vs.* 51.2%; P<0.001) (20). An ongoing phase 2 trial, the adaptively randomized I-SPY2 trial, is evaluating the effect of pembrolizumab on pCR rate in high-risk stage II–III, HER2– breast cancer (21). This study is using multiple investigational arms in parallel and using the standard NACT as the common control arm; weekly paclitaxel for 12 cycles followed by AC regimen for 4 cycles. This study added pembrolizumab concurrently with weekly paclitaxel and reported the pCR rates for HR+/HER2– and TNBC were 30% and 60%, compared with control arm were 13% and 22%, respectively (21). Randomized phase 3 trial, Impassion031, investigated the pCR rate of atezolizumab combined with nab-paclitaxel followed by AC in TNBC. The pCR rate was significantly higher in the atezolizumab combination than NACT alone (58% *vs.* 41%; P=0.0044) (22). Recently, GeparNuevo study (ASCO 2021) presented the adding durvalumab (anti-PD-L1) to standard NACT; weekly nab-paclitaxel for 12 cycles followed by dose-dense epirubicin and cyclophosphamide regimen for 4 cycles. The pCR rate of durvalumab combination was 53.4% *vs.* 44.2% with standard NACT (95% CI: 0.80–2.63, P=0.224). The 3-year IDFS rates were 84.9% *vs.* 76.9% (hazard ratio 0.54, 95% CI: 0.27–1.09; P=0.0559) and the 3-year overall survival rates were 95.1% *vs.* 83.1% (hazard ratio 0.26, 95% CI: 0.09–0.79; P=0.0076), respectively (23).

Immune checkpoint inhibitor improves the efficacy of chemotherapy for TNBC in metastasis setting (24,25). Similarly to neoadjuvant studies as mentioned, either anti-PD-1 or anti-PD-L1 is recommended to combine with the NACT for TNBC; anthracycline and/or taxane containing regimen, regardless to the PD-L1 status. IBC patients were enrolled in all previously mentioned studies, however the sample size of IBC patients were limited. Considering on the PD-L1 status which is a potential biomarker for immunotherapy, IBC is more overexpression PD-L1 than non-IBC and also found both in tumor cells and in tumor-infiltrating lymphocytes of IBC (26-28). All mentioned findings provide a rationale of the use of immune checkpoint inhibitor as a part of NACT. All immune checkpoint inhibitor combination studies showed not only the pCR rates is higher, but trends to improve the survival outcome as recently presented by GeparNuevo study.

Systemic treatment for neoadjuvant HER2+ IBC

NACT with dual anti-HER2 antibodies (HP) is a standard regimen for HER2+ IBC based on multiple clinical data (14,29). In the TRYPHAENA study (30,31) reported the non-anthracycline regimen for 6 cycles [docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) regimen] had the promising highest pCR rate of 66.2% compared with 57.3–61.6% of anthracycline containing regimens for 6 cycles (FEC followed by docetaxel regimen). Similarly to 8 cycles of the anthracycline containing regimen in the BERENICE trial (32), 4 cycles of dose-dense AC, followed by 12 doses of standard paclitaxel plus HP compared with 4 cycles of FEC followed by 4 cycles of docetaxel plus trastuzumab and pertuzumab (THP) reported the pCR rates were 61.8% *vs.* 60.7%, respectively. However, TRAIN-2 study (33) evaluated the efficacy of anthracycline containing regimen compared with non-anthracycline. Nine cycles of HP combined with anthracycline containing regimen; FEC for 3 cycles followed by carboplatin plus paclitaxel for 6 cycles, had a pCR rate of 67%, did not significantly different to the pCR rate of 68% (P=0.95) with non-anthracycline regimen; carboplatin/paclitaxel for nine cycles. Neoadjuvant clinical trial for HER2+ specifically for IBC (n=20) was reported by Overmoyer *et al.* (34), showed

safety and efficacy of paclitaxel combined with HP, pCR rate was 56% with manageable toxicity. However, this study was stopped due to slow accrual. The KRISTINE trial (35) compared the efficacy of neoadjuvant trastuzumab emtansine (T-DM1) plus pertuzumab regimen with TCHP regimen in HER2+ patients including IBC patients. This study showed the negative results, the pCR rates of T-DM1 plus trastuzumab and TCHP regimes were 44% *vs.* 56% (P=0.016) (35). The TCHP regimen is remain in recommend by the current standard guideline (36).

In the TRYPHENA study (30), the HR–/HER2+ subtype had the pCR rates of 50.7% (FEC+HP– > THP), 45.3% (FEC– > THP) and 51.9% (TCHP). Interestingly, both regimens (FEC+HP– > THP regimen and TCHP regimen) consisted with 6 cycles of HP achieved the higher pCR rate than 3 cycles of HP containing regimen (FEC– > THP). These results imply the high pCR rate of HR–/HER2+ subtype was produced by number of dual anti-HER2 therapy cycles, neither by anthracycline nor non-anthracycline regimens. In contrast to the subgroup analysis of the TRAIN-2 study, showed the dual HER2 blockage (for nine cycles) combined with anthracycline containing regimen favored in HR–/HER2+ subtype more than combined with non-anthracycline regimen (33). However, cross clinical trial comparison needs careful interpretation.

Adjuvant systemic treatment for HER2+ IBC

It has well known that adjuvant anti-HER2 therapy is a standard treatment for HER2+ breast cancer (36). Two published phase 3 clinical trials, the KATERINE (37) and APHINITY (38) trials, need to be discussed. The KATERINE trial evaluated the adjuvant treatment either T-DM1 or trastuzumab in patients with HER2+ (n=1,486, including 22 IBC patens) who did not achieve a pCR after NACT. Adjuvant T-DM1 for 14 cycles showed the significantly improved IDFS than adjuvant trastuzumab with hazard ratio 0.50, 95% CI: 0.39–0.64; P<0.001 (37). The 3-year IDFS rates were 88.3% *vs.* 77.0%, respectively (37). The APHINITY trial randomized HER2+ patients (n=4,805) treated with either adjuvant HP or adjuvant trastuzumab and placebo. Adjuvant HP showed significantly higher IDFS than adjuvant trastuzumab and placebo in preplanned cohort node-positive disease with hazard ratio 0.77, 95% CI: 0.62–0.96; P=0.02 (38). The 3-year IDFS rates were 92.0% *vs.* 90.2%, respectively (38). Subgroup analysis for HR+ or HR– subtype population did not significantly improve from both studies (37,38).

Owing to different study design, the KANTERINE evaluated in residual disease of HER2+ patients after neoadjuvant treatment while HER2+ patients in APHINITY trial did not treat with neoadjuvant treatment. However, both clinical trials provided the positive results in high-risk recurrence patients (residual disease or node-positive disease), we recommend to applying this strategy for high-risk disease like IBC. But cross clinical trial comparison is not feasible. To apply in real-practice, needs to consider to individual case-scenario. In HER2+ IBC with a pCR, adjuvant HP for 1 year is recommended (APHINITY trial). Even though patients who achieved pCR after neoadjuvant treatment have a very good prognosis, but the de-escalation strategy is not recommended for IBC because of its aggressiveness. For whom has a residual disease after neoadjuvant treatment, adjuvant TDM-1 is recommended (KATERINE trial).

Conclusions

IBC is an aggressive disease with high-risk of recurrence. Clinical trials specifically for IBC population are limited, therefore the systemic treatment for IBC has been based on non-IBC data. Novel treatments e.g., immune check point inhibitor and targeted therapy, will play a role for IBC treatment. Ongoing immunotherapy and targeted therapy studies are enrolling IBC patients in many trials as shown in *Table 1*. We hope to encourage the IBC clinical trial participation aims to reduce mortality rate of IBC.

Table 1 Ongoing clinical trials for IBC

Identifier (status)	Population	Phase	Regimen	Endpoint
NCT05041101 (not yet, recruiting)	Metastatic IBC	Phase 1b/2	Grapiprant + eribulin	Dose-limiting toxicity
NCT03515798 (recruiting)	HER2–, IBC	Randomized phase 2	Arm 1: (FEC + weekly paclitaxel) + pembrolizumab	pCR rate
			Arm 2: FEC + weekly paclitaxel	
NCT02971748 (recruiting)	HR+, IBC	Phase 2	Non-pCR case treated with adjuvant pembrolizumab + hormone therapy	2-year DFS
NCT02411656 (recruiting)	Stage IV, IBC or triple-negative	Phase 2	Maintenance pembrolizumab in non-PD cases after chemotherapy	Disease control rate
NCT03598257 (recruiting)	Non-metastatic IBC	Phase 2	Concurrent radiation + olaparib *vs.* radiation alone	Invasive DFS
NCT03101748 (recruiting)	LABC or metastatic IBC	Phase 1/2	Neratinib + paclitaxel + pertuzumab + trastuzumab	pCR rate
NCT03202316 (recruiting)	Recurrent or metastatic IBC	Phase 2	Atezolizumab + cobimetinib + eribulin	Response rate
NCT02876302 (active, not recruiting)	Triple-negative IBC	Phase 2	Weekly paclitaxel + ruxolitinib then AC regimen	Change of JAK expression
NCT01036087 (active, not recruiting)	Triple-negative IBC	Randomized phase 2	Arm 1: panitumumab + carboplatin+ nab-paclitaxel then FEC	pCR rate
			Arm 2: carboplatin+ nab-paclitaxel then FEC	
NCT02623972 (active, not recruiting)	HER2–, IBC	Phase 2	AC then eribulin	pCR rate
NCT02658812 (active, not recruiting)	Local recurrence IBC or inoperable non-IBC	Phase 2	Talimogene laherparepvec	Response rate
NCT01796197 (active, not recruiting)	HER2+, IBC	Phase 2	Paclitaxel + pertuzumab + trastuzumab	pCR rate

Accessed clinicaltrial.gov on September 20, 2021. IBC, inflammatory breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; 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.

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