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EDITORIAL

Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) Guidelines in 2024: International Contributions from China

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The Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guidelines have been widely implemented in China since the first release in 2017. The Guideline Working Committee has also published multiple versions in English, Arabic, and other languages to facilitate communications with international experts. The 2024 CSCO BC guidelines continue the tradition to formulate recommendations based on medical evidence, while taking into account the accessibility of products and expert consensus[1]. The latest edition of the guidelines not only highlights international progress but also emphasizes the contributions from Chinese scholars by conducting high-quality evidence-based clinical and real-world studies so that recommended regimens are suitable for the actual situation in China. These contributions have not only brought more credible evidence to the CSCO BC guidelines but have also greatly benefited international guideline updating.

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer: target drugs from meager-to-abundant

The emergence of trastuzumab improved the prognosis for patients with HER2-positive breast cancer. However, it was not until 2017, when trastuzumab was included in the national insurance reimbursement, that accessibility to targeted drugs in China was achieved and the usage proportion of trastuzumab finally surpassed that of the United States[2]. The listing approval for pertuzumab and concurrent inclusion in the medical insurance catalog in China in 2020 rapidly elevated patients with breast cancer in China into the era of dual-target therapy.

The international consensus opines that anthracycline-containing regimens should be replaced by taxane, carboplatin, trastuzumab and pertuzumab (TCHP) in the neoadjuvant setting to reduce cardiotoxicity[3]. A platinum-free regimen (THP) can be considered for patients who do not tolerate TCHP. Some pivotal studies, such as Neosphere and PEONY[4], chose four cycles of THP as the neoadjuvant regimen to promote the launch of pertuzumab, hoping to rapidly achieve pathologic complete remission (pCR) (**Table 1**). However, insufficient cycles of dual-target neoadjuvant therapy was unacceptable by Chinese clinicians. Although there is a lack of solid evidence, six cycles of THP have become an alternative regimen for patients who cannot tolerate carboplatin compared to four cycles of THP. We also showed that a six-cycle THP regimen has a similar pCR rate compared to a six-cycle TCHP regimen and a lower proportion of adverse reactions in a multi-center real-world study[5]. Therefore, six cycles TCHP and THP have become the level I recommendation according to CSCO BC guidelines.

In addition, the domestic PHEDRA study[6] showed that the pyrotinib and trastuzumab combination further improves the pCR from 22% to 41%. However, how to choose adjuvant target drugs if pyrotinib is used in neoadjuvant treatment is controversial. Pyrotinib as first choice in neoadjuvant treatment is limited by non-reimbursement policy. Therefore, pyrotinib combined with trastuzumab is a special regimen in the level II

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Table 1 Some pivotal randomized clinical trials with breast cancer led by China

Trials	Stage	Phenotypes	Experimental groups	Control groups	Primary endpoint	Result of primary endpoint
PEONY	Neoadjuvant	HER2-positive	TH+pertuzumab	TH	pCR	39.3% *vs.* 21.8%
PHEDRA	Neoadjuvant	HER2-positive	TH+pyrotinib	TH	pCR	41% *vs.* 22%
PHILA	First-line	HER2-positive	TH+pyrotinib	TH	PFS	24.3 *vs.* 10.4 months
PHENIX	Second-line	HER2-positive	Pyrotinib+capecitabine	Capecitabine	PFS	11.1 *vs.* 4.1 months
PHOEBE	Second-line	HER2-positive	Pyrotinib+capecitabine	Lapatinib+capecitabine	PFS	12.5 *vs.* 6.8 months
cTRIO	Neoadjuvant	TNBC	TP+tislelizumab	–	pCR	56.5%
NeoTennis	Neoadjuvant	TNBC	AC-T+toripalimab	–	pCR	55.7%
SYSUCC-01	Adjuvant	TNBC	Capecitabine	Placebo	5y-DFS	82.8% *vs.* 73.0%
TORCHLIGHT	First-line	TNBC	T+toripalimab	T	PFS	8.4 *vs.* 5.6 months
Monarch plus	First-line	HR-positive	Cohort A: AI+abemaciclib Cohort B: F+abemaciclib	Cohort A: AI Cohort B: F	PFS	Cohort A: 14.7 *vs.* not reached Cohort B: 11.5 *vs.* 5.6 months
DAWNA-1	Second-line	HR-positive	F+dalpiciclib	F	PFS	15.7 *vs.* 7.2 months
DAWNA-2	First-line	HR-positive	AI+dalpicclib	AI	PFS	30.6 *vs.* 18.2 months
ACE	First-line	HR-positive	AI+chidamide	AI	PFS	7.4 *vs.* 3.8 months

T: taxane; H: trastuzumab; P: carboplatin; AC: by anthracycline with cyclophosphamide; AI: aromatase inhibitor; F: fulvestrant; pCR: pathologic complete remission; PFS: progression-free survival; DFS: disease-free survival; HER2: human epidermal growth factor receptor 2; TNBC: triple-negative breast cancer; HR: hormone receptor.

recommendation of the guidelines compared to other international guidelines.

A stratified treatment strategy is increasingly adopted in the salvage stage due to the emergence of targeted drugs. Trastuzumab with pertuzumab is undeniably the first choice combination in patient sensitive to trastuzumab. However, due to the special medical insurance policy in China, pertuzumab is not included in medical insurance for first-line treatment, which contributes to poor cost-effectiveness of this regimen. The PHILA study[7] was the first phase III clinical study conducted in China that compared docetaxel and trastuzumab (TH) and pyrotinib with TH alone. The results of the study confirmed that TH+pyrotinib achieved a median progression-free survival of 24.3 months with a hazard ratio of 0.41. The study included more early-stage patients treated with trastuzumab and pertuzumab (HP), which is more consistent with clinical practice. Although pyrotinib and pertuzumab combined with TH are level I recommendations for first-line treatment, it seems that the combination of pyrotinib and TH have a higher level of expert consensus in China given the advantages of insurance reimbursement.

Based on the PHENIX[8] and PHOEBE studies[9], the pyrotinib with capecitabine combination has been the first choice for domestic patients resistant to trastuzumab. According to other international guidelines, trastuzumab-deruxtecan (T-Dxd) has surpassed trastuzumab-emtansine (T-DM1) as the new standard treatment for patients who failed trastuzumab treatment based on the Destiny-Breast 03 study[10]. However, head-to-head studies comparing the efficacy of pyrotinib to T-Dxd are lacking. Although both regimens are listed as level I recommendations, the pyrotinib and capecitabine combination has a higher consensus among experts than T-Dxd according to CSCO BC guidelines.

The latest CSCO BC guidelines have also added a stratification for patients who have failed tyrosine kinase inhibitor (TKI) therapy ascribed to the large domestic population taking pyrotinib. For such patients, T-Dxd should undeniably be the first choice. Some real-world studies[11] have explored optimization of the regimen after TKI and reported that T-DM1 or

the combination of dual-targeted drugs as options. However, due to the lack of clinical studies, these regimens are all listed as level II recommendations. Solid evidence for patients who have failed TKIs are desperately needed.

Triple negative breast cancer (TNBC): the torchlight brought by immunotherapy

Chemotherapy has long been the only choice for TNBC. The emerging of immune checkpoint inhibitors has created more options for these patients. With the approval of pembrolizumab for TNBC, the role of immunotherapy has become increasingly important. In 2024 the CSCO BC guidelines listed chemotherapy and immunotherapy separately to address the growing demand for immunotherapy.

Based on the KEYNOTE-522 study, the taxane+carboplatin followed by anthracycline+cyclophosphamide (TP-AC) and pembrolizumab combination has been adopted as the standard neoadjuvant treatment option. Considering poor tolerance, several domestic studies are exploring the feasibility of combining different chemotherapy regimens with immunotherapy. The cTRIO study[12] suggested that 6-cycles of nab-paclitaxel and carboplatin (TP) combined with tislelizumab achieves a pCR rate of 56.5%. The NeoTennis study[13] also showed that intensive anthracycline and cyclophosphamide followed by taxane combined with toripalimab achieves a pCR rate of 55.7%. Therefore, a variety of chemotherapy combination strategies with immunotherapy are recommended according to those studies.

The Torchlight study[14], conducted by Chinese scholars, confirmed that the nab-paclitaxel and toripalimab combination further improves progression-free and overall survival in patients with advanced-stage breast cancer. The Torchlight study also promoted the approval of toripalimab as a second immune checkpoint inhibitor for patients with TNBC in China. Furthermore, the survival benefit boundary from immunotherapy was reduced from a combined positive score (CPS) ≥10% to a CPS ≥1%, setting a new standard for the first-line treatment of TNBC with the chemotherapy and immunotherapy combination. On this basis, Chinese scholars have also explored the efficacy of metronomic chemotherapy, conventional chemotherapy, and anti-angiogenic therapy combined with toripalimab[15], providing more options for immunotherapy combinations among patients with TNBC.

Considering the significance of immunotherapy, the CSCO BC Committee has also synchronously published a consensus on the clinical application of immunotherapy in breast cancer[16], providing a comprehensive overview of immunotherapy in treatment, management of immune-related adverse events (irAEs), biomarkers, and future directions. The consensus consolidated these deliberations into 15 evidence-based recommendations, serving as a complementary guide for clinicians to systematically manage the clinical application of immunotherapy.

Hormone receptor (HR)-positive breast cancer: comprehensive era of cyclin D kinase 4/6 (CDK4/6) inhibitors

CDK4/6 inhibitors have become a breakthrough for HR-positive breast cancer, achieving significant success in both early and advanced stages. In the adjuvant setting, based on the results of the MonarchE study[17], the CSCO BC guidelines have added abemaciclib combined with endocrine drugs as level I recommendations for adjuvant endocrine therapy. The NATALEE[18] study also showed the survival significance when adding ribociclib to endocrine therapy, yet no worldwide indication has been approved at the time of publication of guidelines. The latest CSCO BC guidelines has added annotations about the NATALEE study[18] and emphasized that patients who cannot tolerate adverse reactions when taking abemaciclib, a switch to ribociclib should be considered as an alternative.

In the advanced stage, CDK4/6 inhibitors combined with endocrine therapy, such as an aromatase inhibitor or fulvestrant, are recommended as the only strategy in level I recommendations. The Monarch plus study[19] and the DAWNA 01 and 02 studies[20,21], which were conducted by Chinese scholars, have made available more choices for CDK4/6 inhibitors. Due to the differences in medical insurance, indications, and clinical enrollment data for different CDK4/6 inhibitors, the guidelines suggest that patients should make reasonable choices based on their actual needs and abilities.

When patients progress while on a CDK4/6 inhibitor, it is necessary to make reasonable choices based on different mutations. For example, patients with PIK3CA mutations could consider endocrine therapy combined with alpelisib.

The CAPItello-291 study[22] showed that the combination of an Akt inhibitor (capivasertib) and fulvestrant significantly improves the progression-free survival, especially for those who have been treated with CDK4/6 inhibitors. In addition, a real-world study showed that switching to another CDK4/6 inhibitor is an option for those who have previously benefited from long-term CDK4/6 inhibitor therapy[23]. However, like the stratification after TKI treatment in HER2-positive breast cancer, more high-quality clinical studies are needed to explore the strategies of treatment after CDK4/6 inhibitors.

HER2 low-expression breast cancer: new field, new journey

Patients with HER2 low-expression breast cancer is a unique and clinically relevant population. The emergence of T-Dxd has opened a new field for HER2 low-expression breast cancer. The DAISY study[24] explored the benefit of T-Dxd in breast cancer with different HER2 expressions and the results suggested that the level of HER2 expression directly affects the survival benefit. With the new definition of HER2 ultra-low expression according to the Destiny Breast 06 study[25], it is essential to use new sensitive methods to express the minimum threshold of HER2 expression in the clinic setting.

The CSCO BC guidelines in 2024 have added a new chapter on HER2 low-expression and have made reasonable recommendations according to HR status. For patients with HR-positive and HER2 low-expression breast cancer, endocrine therapy with CDK4/6 inhibitors or taxane-based chemotherapy are recommended first, then antibody-drug conjugates (ADCs), such as T-Dxd or sacituzumab govitecan (SG), should be considered. After ADC failure, subsequent treatment should be chosen based on previous treatment, including some new targeted therapies, such as AKT inhibitors and PIK3CA inhibitors.

For patients with HR-negative/HER2 low-expression breast cancer, taxanes combined with immunotherapy is recommended first. After failure of first-line treatment, SG or T-Dxd can be chosen. Based on monotherapy, multiple clinical studies have explored the feasibility of combining ADC with other treatments, such as immunotherapy or anti-angiogenic drugs. This combination strategy may become a new direction for ADC therapy[26].

Conclusions

In addition to the updates mentioned above, the CSCO BC guidelines in 2024 have made several significant updates, including subcutaneous formulations of trastuzumab, denosumab biosimilars[27] to recommend optimal treatment for patients with different subtypes and stages of breast cancer.

Furthermore, to promote the application of CSCO BC guidelines, we also established and updated the decision-making system (CSCO AI) based on the guidelines. We have subsequently conducted clinical studies to verify the consistency of the CSCO AI system with the guidelines[28]. The CSCO AI decision-making system is also continuously updated and improved during its national promotion process, establishing a medical ecosystem that includes intelligent decision-making, toxicity early warning, disease management, and resource sharing, to assist in improving the survival rates and quality of life for breast cancer patients in China. We believe this system can assist healthcare providers in swiftly determining the best treatment plans, thereby enhancing decision-making efficiency in the future.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Zefei Jiang.
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Contributed data or analysis tools: Jianbin Li.
Performed the analysis: Jianbin Li.
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