Editorial

Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) guideline update: adjuvant therapy for triple negative breast cancer in 2022

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Introduction

Breast cancer (BC) is the most common malignancy among women worldwide, with approximately 1.6 million new cases and 1.2 million BC-related deaths in China every year (1). Triple negative breast cancer (TNBC), an aggressive subtype of BC, accounts for about 15% of BC cases and carries a poor prognosis (2). The Chinese Society of Clinical Oncology (CSCO) BC guidelines have long been considered the gold standard reference for BC treatment in China. Chinese scholars have updated the guidelines annually since 2017, based on reliable clinical evidence and national conditions. Most significantly, risk stratification was introduced to provide precision medicine for BC and maximize the therapeutic benefits. This article aimed to summarize the most recent clinical studies and provide an in-depth insight into adjuvant therapy for TNBC after risk stratification.

Adjuvant treatment for TNBC patients

Surgery and chemotherapy are the mainstay for the treatment of TNBC, given that TNBC patients do not benefit from human epidermal growth factor receptor 2 (HER2)-targeted therapy or endocrine therapy (3). Randomized clinical trials have revealed that the sequential addition of taxane to anthracycline plus cyclophosphamide (AC) confers a prolonged disease-free survival (DFS) (4). According to the CSCO Guidelines for the Diagnosis and Treatment of Breast Cancer (2021 version), TNBC patients are recommended surgery followed by chemotherapy. The chemotherapy regimen differs based on risk stratification.

In the CALGB9344 study (5), the sequential addition of paclitaxel to AC chemotherapy was shown to prolong the DFS of patients with node-positive BC. Therefore, AC-T (anthracycline plus cyclophosphamide followed by taxane) is an effective and efficient scheme which is currently recommended for some patients with a higher risk of recurrence. However, no difference was observed in overall survival (OS) and DFS of node-positive BC between patients receiving TAC (docetaxel, anthracycline, and cyclophosphamide) and those treated with AC-T. Based on the CALGB 9741 study, which further revealed the effects of dose-dense (dd) chemotherapy in improving the DFS in BC, ddAC-ddT has been considered as an alternative treatment strategy for high-risk BC patients who are partially tolerable. As for those with a lower risk for recurrence, the US Oncology Research Trial 9735 showed that docetaxel and cyclophosphamide (TC) is superior to AC in improving the DFS of both younger and older patients (6).

The application of platinum agents has provided a new impetus due to DNA repair defects in TNBC, but the inclusion of platinum agents in adjuvant chemotherapy of TNBC is still controversial. The PATTERN study (7) showed that the paclitaxel-plus-carboplatin (PCb) regimen conferred significant improvements in DFS compared to cyclophosphamide, epirubicin, and fluorouracil followed by paclitaxel (CEF-T) regimen that was recommended in previous guidelines. Meanwhile, PCb was found to prolong the relapse-free survival (RFS) of patients with high homologous recombination defect (HRD) scores,

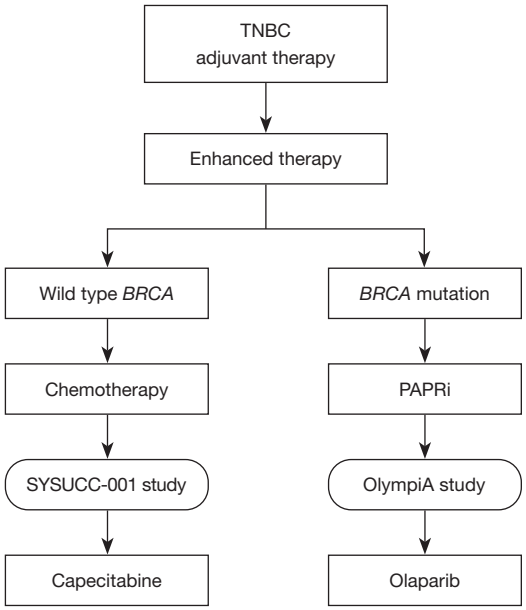

Figure 1 Enhanced therapy after adjuvant therapy of TNBC. TNBC, triple negative breast cancer; *BRCA*, breast cancer susceptibility gene; PARPi, poly-ADP-ribose polymerase inhibitor.

highlighting the key role of carboplatin in adjuvant therapy. Recently published clinical research showed no difference in the DFS and OS between the subjects treated with taxanes combined with platinum (TP) and the counterparts with epirubicin, cyclophosphamide and taxanes (ECT) (8). Taken together, PCb could serve as an effective alternative adjuvant chemotherapy option for patients with operable TNBC, especially those with high HRD scores.

Capecitabine (X), an oral prodrug of fluorouracil (5FU), was approved in 1998 for the treatment of metastatic HER2-negative BC. A recent randomized clinical trial in China (CBCSG-010 study) (9) demonstrated that capecitabine concomitant with docetaxel, epirubicin, and cyclophosphamide conferred a more favorable DFS compared to a non-capecitabine regime, especially for patients with T2/T3, positive lymph nodes, histological grade III, and high expression of Ki-67. These findings demonstrated that capecitabine can be combined with anthracycline and taxol in early adjuvant therapy. Hence, three cycles of docetaxel and capecitabine followed by three cycles of capecitabine, epirubicin, and cyclophosphamide (TX-XEC) after surgery are strongly recommended for high-risk early TNBC patients.

In general, the addition of platinum or capecitabine to anthracycline + taxane regimen for TNBC patients may be applied.

Enhanced therapy after adjuvant therapy

Breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations are well documented and potent drivers for BC, as they are key molecules involved in DNA repair (10-12). Poly-ADP-ribose polymerase (PARP) is a nuclear enzyme that plays a pivotal role in DNA single-strand break repair (13). *In vivo* data demonstrates that functional deficiencies in *BRCA1/2* enhance the sensitivity of cells to PARP inhibitor (PARPi) (14). In the OlympiA clinical trial (15), patients receiving olaparib, an oral PARPi, after completing local treatment and neoadjuvant or adjuvant chemotherapy, showed markedly longer survival free of invasiveness and distant disease compared to those in the placebo group. Therefore, we recommend olaparib for enhanced treatment after standard adjuvant chemotherapy in high-risk TNBC patients (i.e., those with positive axillary lymph nodes or tumor sizes <2 cm) with *BRCA* mutations (*Figure 1*). PARPis, unlike conventional chemotherapy, are an effective targeted therapy with a lower likelihood of acquired resistance. The TBCRC 048 study (16) uncovered that the patients with germline partner and localizer of *BRCA2* (gPALB2) mutation or somatic *BRCA1/2* mutation could achieve objective response rates (ORRs) of 80% and 50%, respectively, which is encouraging. With advances in high-throughput sequencing, genetic testing has shown promise for the maximal efficacy of targeted therapy.

As for wild-type *BRCA* patients, capecitabine appears to be an effective strategy, which has been well illustrated in the SYSUCC-001 randomized clinical trial (17). This study, for the first time, introduced metronomic chemotherapy into the adjuvant treatment of TNBC. The dose for capecitabine metronomic chemotherapy, which has fewer safety concerns, was much lower than maximum tolerated dose. Furthermore, capecitabine effectively improved the prognosis of BC patients. Consequently, capecitabine is recommended to serve as maintenance therapy for low- and high-risk patients without *BRCA* mutations (*Figure 1*).

Immunotherapy for TNBC

Despite the high mutational load, programmed death ligand 1 (PD-L1) expression, and tumor-infiltrating lymphocytes, immunotherapy remains controversial in the treatment of TNBC. Keynote-522 (18), a prospective phase III study,

was designed to explore the efficacy of pembrolizumab in neoadjuvant and adjuvant therapy of early TNBC. The promising results obtained in this trail lead to the National Comprehensive Cancer Network (NCCN) recommending the use of pembrolizumab combined with chemotherapy as neoadjuvant therapy. However, there was no direct evidence for the use of pembrolizumab in adjuvant treatment. Chinese scholars have voiced reservations about immunotherapy in TNBC, which is consistent with 2021 Chinese Anti-Cancer Association, Committee of Breast Cancer Society (CACA-CBCS) guidelines. As a result, immunotherapy in the adjuvant treatment of BC is not recommended. More research with larger sample sizes is required to identify effective immunotherapies in the future.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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