Editorial

Differences between Japan and China in perioperative pharmacotherapy of early-stage breast cancer in breast cancer guidelines (2022 edition)

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In recent years, many drug therapies for cancer have been developed in large-scale global trials, and a worldwide consensus has been reached by the St. Gallen Consensus Conference and the Advanced Breast Cancer Conference. Therefore, the concept of standard treatment tends to be standardized. However, there are differences in the guidelines developed in each country due to the status of health insurance approval, delays or discontinuation of drug development, and historical background of breast cancer treatment. Here, we review the differences between the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guideline 2022 (1) and the Japanese Breast Cancer Society (JBCS) Clinical Practice Guidelines for systemic treatment of breast cancer, 2022 edition, mainly with regard to early-stage breast cancer treatment.

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer

Recently, there has been a trend toward omitting anthracycline as perioperative chemotherapy for HER2-positive breast cancer. In the 2022 edition of the National Comprehensive Cancer Network (NCCN) guidelines, anthracycline-containing regimens were excluded from the list of preferred regimens, such as neoadjuvant and adjuvant chemotherapy. Avoidance of cardiotoxicity would be one reason for this change, although there are no trials designed to directly compare the effectiveness of anthracycline and non-anthracycline regimens. However, the BCIRG005 trial showed that docetaxel (T) + carboplatin (Cb) + trastuzumab (H) performed similarly to doxorubicin and cyclophosphamide followed by docetaxel (AC-TH) (2). More recently, the Aphinity trial reported that the docetaxel + carboplatin + trastuzumab + pertuzumab (P) (TCbHP) arm had a similar incidence of invasive disease-free events to the anthracycline regimen arm (3), although this is a point where statistical interpreting is not possible. Many neoadjuvant trials have reported favorable pathologic complete response (pCR) rates with non-anthracycline regimens, and these circumstances have gradually led to a shift toward non-anthracycline regimens. The CSCO breast cancer guidelines recommend non-anthracycline regimens, such as taxane + CbHP or taxane + HP regimens, as the first recommendation in preoperative chemotherapy, and both anthracycline and non-anthracycline regimens are listed as the first recommendation in the postoperative setting. In Japan, one arm of the Neo-Peaks trial (JBCRG20) included six cycles of TCbHP for HER2-positive early breast cancer and reported a 56.9% pCR rate (4). The pCR rate was 76.2% in the estrogen receptor (ER)-negative group and 43.3% in the ER-positive group, with favorable results, especially in the ER-negative group. No prognosis is reported from this study at this time. However, the 2022 edition of the Japanese guidelines only lists omission of anthracycline as a "future research question" because there are no studies directly examining the prognostic impact of it in HER2-positive patients. The Japanese guidelines only mention previous clinical trials which contain TCbH (2),

weekly paclitaxel + H (5), or docetaxel + cyclophosphamide (TC) + H (6). TCbHP was not mentioned either preoperatively or postoperatively. In Japanese clinical practice, TCbHP has been slow to spread due to concerns about the tolerability of carboplatin used in doses with the area under the curve (AUC) 6. Prognostic results from trials such as the PEONY (7) and CompassHER2 trials, in which taxane + HP regimens were tried, are awaited.

According to the CSCO guidelines, adjuvant pertuzumab for HER2-positive early-stage breast cancer is recommended for patients with positive lymph nodes or other risk factors. The Japanese guidelines follow a similar policy. This finding was based on the results of the APHINITY trial. In this trial, subgroup analysis showed an improvement of HR =0.77 (95% CI: 0.62–0.96, P=0.02) in patients with positive lymph nodes, whereas HR =1.13 (95% CI: 0.68–1.86, P=0.64) in patients with negative lymph nodes (3).

For non-pCR cases after neoadjuvant therapy, the primary recommendation in both China and Japan is the adjuvant use of trastuzumab emtansine (T-DM1). The KATHERINE study compared adjuvant T-DM1 with trastuzumab alone for non-pCR HER2 positive early breast cancer and found a significant improvement in the primary endpoint, invasive disease-free survival (IDFS) of HR =0.50 (95% CI: 0.39–0.64, P<0.001) in the T-DM1 arm (8). Three-year IDFS was substantial, with an improvement of 11.3%. No data exists for patients with preoperative pertuzumab on whether T-DM1 should be used postoperatively or whether HP should be continued, but given that the improvement in IDFS in the KATHERINE trial was more substantial than that in the APHINITY trial, there seems to be a consensus that T-DM1 is the first recommendation for non-pCR cases, regardless of the subgroup.

For postoperative therapy after pCR, the CSCO Breast Cancer guidelines recommend HP as the first and trastuzumab alone as the second. Japanese guidelines have not addressed this point at this time. In Japanese clinical practice, opinions are divided on whether pertuzumab is necessary for all patients who achieve pCR. Based on the difference in efficacy according to lymph node status in the APHINITY trial described above, there is an opinion that patients without node metastasis at initial diagnosis should be switched to trastuzumab monotherapy if they achieve pCR.

Moreover, the Japanese guidelines also feature trastuzumab monotherapy as an option for elderly patients with HER2-positive early-stage breast cancer, based on the RESPECT trial.

The RESPECT trial compared postoperative chemotherapy plus trastuzumab with trastuzumab alone in patients with stage I–IIIA HER2-positive early-stage breast cancer aged 70–80 years with tumors 0.5 cm or larger in diameter. The trial enrolled 275 patients, and the 3-year disease-free survival rate was 89.5% for trastuzumab alone and 93.8% for chemotherapy plus trastuzumab (HR =1.36; 95% CI: 0.72–2.58; P=0.51) (9). The study results did not meet the prespecified non-inferiority margin and did not demonstrate the non-inferiority of trastuzumab alone. However, because of the large difference in the quality of life between the two groups and the loss of survival at 3 years of less than 1 month without chemotherapy, the Japanese guidelines include adjuvant trastuzumab alone as a weakly recommended option for elderly patients who cannot tolerate chemotherapy.

Triple-negative breast cancer (TNBC)

It is impressive that the CSCO's level 1 recommendation for neoadjuvant treatment of TNBC includes the simultaneous use of anthracycline and taxane, such as docetaxel + doxorubicin + cyclophosphamide (TAC) and doxorubicin + docetaxel (AT). In the postoperative period, sequential administration of anthracycline and taxane, including dose-dense therapy, is the first recommendation of CSCO for high-risk patients with TNBC. In Japan, concurrent use of anthracycline and taxane is rarely used owing to poor tolerability; therefore, concurrent anthracycline and taxane regimens are not included in the Japanese guidelines. No distinction was found between preoperative and postoperative regimens, and a dose-dense regimen is strongly recommended for patients with HER2-negative breast cancer at a high risk of recurrence, regardless of ER status.

The CSCO Breast Cancer guidelines have adopted some new evidence for TNBC, including platinum regimens, immune checkpoint inhibitors, and olaparib for pathogenic or likely pathogenic variants of breast cancer susceptibility gene (BRCA).

The Japanese guidelines have also added recommendations and statements on these topics to the 2022 update. In the new Japanese guidelines, the use of carboplatin is strongly recommended, based on a meta-analysis performed independently. On the other hand, the use of pembrolizumab is currently weakly recommended because the overall survival benefit of pembrolizumab in KEYNOTE-522 has not yet

been determined, and there are concerns about immune-related adverse events (10). Currently, carboplatin and pembrolizumab are not approved by insurance for early-stage TNBC in Japan, but their approvals are expected in the near future, and the perioperative treatment of TNBC is expected to change dramatically.

Multiple lines of evidence and increasing complexity were observed in non-pCR cases after neoadjuvant chemotherapy for TNBC. Based on the results of the CREATE-X trial (11), which showed a disease-free survival (DFS) improvement of HR =0.58 (95% CI: 0.39–0.87) with adjuvant capecitabine, there is a worldwide consensus on adjuvant capecitabine for non-pCR cases of TNBC. However, pembrolizumab should be continued postoperatively when we use pembrolizumab in neoadjuvant chemotherapy, according to the regimen of KEYNOTE-522. Event-free survival for subgroups based on residual cancer burden (RCB) were also reported in this trial. The pembrolizumab arm was significantly better than the control arm in the RCB-2 population, while there was no difference in RCB-0, 1, and 3 (12). This result suggests that non-pCR does not negate pembrolizumab efficacy. It is unclear whether pembrolizumab improves prognosis by neoadjuvant use or both neoadjuvant and adjuvant use. But, current evidence suggests that it is reasonable to continue pembrolizumab in the postoperative period for non-pCR TNBC patients as described above. The usefulness of pembrolizumab after surgery in RCB-0, 1, and 3 subgroups is a topic for future discussion. The benefit of adding capecitabine to pembrolizumab during the adjuvant period is unknown.

Regarding postoperative poly (ADP-ribose) polymerase (PARP) inhibitors for high-risk patients with BRCA mutations, the OlympiA trial investigated efficacy of olaparib (13). For patients with TNBC, a tumor diameter >2 cm or positive lymph nodes were required for patients who received adjuvant therapy, and non-pCR patients were eligible for those who received preoperative chemotherapy. In the intention-to-treat (ITT) population, including patients with hormone receptor-positive and hormone receptor-negative, a significant improvement in IDFS was reported with olaparib addition (HR =0.58, 95% CI: 0.41–0.82; P<0.001). The improvement in IDFS with olaparib among TNBC subgroup was HR =0.56 (95% CI: 0.43–0.73), of which HR =0.57 (95% CI: 0.41–0.79) among non-pCR TNBC population. There is no data on whether we should use olaparib or capecitabine for patients with non-pCR TNBC when BRCA mutations are present. The GEICAM-CIBOMA study examined the add-on benefit of adjuvant capecitabine in patients with TNBC and failed to demonstrate any benefit of capecitabine in ITT analysis. In the subgroup analysis, there was a significant improvement in the non-basal phenotype (HR =0.53, 95% CI: 0.31–0.91; P=0.022), but no benefit was observed in the basal phenotype (HR =0.94, 95% CI: 0.70–1.27) (14). Patients with TNBC with BRCA mutations mainly exhibit the basal phenotype. In patients with metastatic breast cancer with BRCA mutation after anthracycline and taxane treatment, olaparib significantly improved progression-free survival (PFS) compared to chemotherapy with a physician's choice, including capecitabine, suggesting that olaparib should be preferred in postoperative therapy for patients with BRCA mutations. Therefore, it is reasonable to prioritize the use of olaparib over capecitabine in postoperative therapy for patients with BRCA mutations. The adjuvant use of olaparib has not yet been approved by health insurance in Japan, and the Japanese guidelines only mention the efficacy of adjuvant olaparib in a statement. It is unknown whether pembrolizumab or olaparib is preferred in patients with BRCA mutations and whether there are combination options. It is also noteworthy that the CSCO guidelines suggest the use of capecitabine for 1 year as an adjuvant treatment option for TNBC patients, based on the results of the SYSUCC-001 trial.

HR-positive HER2 negative breast cancer

A notable change in the perioperative treatment of HR-positive and HER2-negative breast cancer in both the Japanese and Chinese guidelines is the addition of postoperative abemaciclib. The CSCO lists adjuvant abemaciclib as the primary recommendation, and the Japanese guidelines also strongly recommend it.

In Japan, the abemaciclib adjuvant is covered by insurance only for patients who meet the eligibility criteria of cohort 1 of the monarchE trial (15). Cohort 1 is eligible if they meet one of the following: (I) 4 or more lymph node metastases, or (II) patients with 1 to 3 lymph node metastases and at least one of the following: tumor diameter ≥5 cm and histological grade 3. Cohort 2 is a population of patients who meet all of the following criteria: 1 to 3 lymph node metastases, tumor diameter <5 cm, histological grade 1 or 2, and Ki67 ≥20%. Cohort 2 population had a shorter follow-up period, and no difference in the number of IDFS events has been observed in previous reports. Furthermore, the evaluation of Ki67 expression is not standardized worldwide, and Ki67 expression was centrally determined

in a monarchE study. In United States, the Food and Drug Administration (FDA) approved the indication for postoperative abemaciclib only for the Ki67 high subgroup of cohort 1, but Ki67 must be determined by an approved companion diagnostic test. In these circumstances, the Japanese guidelines recommend the use of postoperative abemaciclib for patients who meet the cohort 1 eligibility criteria for monarchE regardless of Ki67 expression.

A unique treatment option in the Japanese guidelines is adjuvant S-1 for ER-positive HER2-negative breast cancer. This was based on the results of the POTENT trial (16). The POTENT trial is an open-label, randomized phase III trial that evaluated the benefit of adjuvant S-1 for 1 year in patients with stage I-IIIB, ER-positive, HER2-negative early-stage breast cancer (with additional conditions for Stage I). The primary endpoint, IDFS, significantly improved in the S-1 + endocrine therapy group (HR =0.63, 95% CI: 0.49–0.81; P=0.0003). The monarchE study included high-risk patients, and the POTENT study included moderate-to-high-risk patients. Currently, adjuvant S-1 is not approved by Japanese health insurance, but after approval, patients and physicians will consider which to use, S-1 or abemaciclib, according to the patient's medical costs and risk of recurrence. In addition, the Oncotype DX is scheduled to be covered by Japanese insurance in the near future. A future question to be answered is how to consider the Recurrence Score of Oncotype DX when selecting abemaciclib or S-1.

Closing comments

Japanese guidelines were formatted to answer the clinical questions. For example, CQ21 states, "*What is recommended as secondary endocrine therapy when an aromatase inhibitor alone is used as primary therapy for postmenopausal hormone receptor-positive HER2-negative metastatic or recurrent breast cancer*?"; the question states, "*Combination therapy with fulvestrant and a CDK4/6 inhibitor is strongly recommended*." Furthermore, this recommendation was accompanied by the degree of recommendation: strength of recommendation: strong, strength of evidence: strong, and agreement rate: 100% (31/31). This clinical question format is a major difference from the CSCO guidelines.

In this article, we discuss some of the differences between the JBCS Clinical Practice Guidelines and the CSCO Breast Cancer Guidelines regarding perioperative drug therapy. Perioperative drug therapy is aimed at curative treatment, therefore we should try to keep intensity of treatments. No significant differences between races have been reported in the efficacy and toxicity of perioperative drug therapies. However, in recent years, several drugs for patients with metastatic breast cancer have been reported to cause adverse events of different severities and frequencies in Asian and Western populations. Examples include interstitial lung disease with trastuzumab-deruxtecan and skin disorders with alpelisib. Quality of life is important especially in the treatment of recurrent disease, adverse drug events are a major factor in decreasing the quality of life. Therefore, it is desirable to build evidence in Asia instead of citing western data. The role of the CSCO and the JBCS seems important for this purpose, and cooperation in future clinical trials between Asian countries is expected.

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