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Comparison of the efficacy and safety of the EC-T (epirubicin/cyclophosphamide followed by docetaxel) and TCb (docetaxel/carboplatin) neoadjuvant regimens in early TOP2A-normal stage II-III breast cancer

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This study aimed to compare the efficacy and safety of the EC-T (4 cycles of epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2, followed by 4 cycles of docetaxel 75 mg/m^2) and TCb (6 cycles of docetaxel 75 mg/m^2, intravenous drip (ID), day 1 + carboplatin AUC 6, ID, day 1) neoadjuvant regimens in patients with TOP2A-normal stage II-III breast cancer. This study analyzed 280 patients enrolled from three studies registered with ClinicalTrials.gov (NCT03140553, NCT03154749, NCT03507465) with early TOP2A-normal stage II-III breast cancer who received neoadjuvant chemotherapy, including 100 patients who received the EC-T regimen and 180 patients who received the TCb regimen. The primary endpoint was the ratio of RCB 0/1 (residual cancer burden 0/1) after neoadjuvant chemotherapy. The secondary endpoint was the safety of the two groups. There was no significant difference in the ratio of RCB 0/1 between the two groups (23% vs. 23.9%, p=0.614). Among the triple-negative breast cancer patients, the efficacy did not differ between the two groups (40% vs. 32%, p=0.52). Among the lymph node metastasis patients, the efficacy of the EC-T group was significantly better than that of the TCb group (14% vs. 2.6%, p=0.03). Regarding the side effects, the incidence of grade 3/4 anemia was higher in the EC-T group than in the TCb group (21.0% vs. 8.33%, p=0.002), while the incidence of grade 3/4 neutropenia was higher in the EC-T group than in the TCb group (17% vs. 14.44%, p=0.570), and the incidence of grade 3/4 thrombocytopenia was low in each group (EC-T group: 6 % and TCb group: 7.22%, p=0.697). In the EC-T group, grade 3/4 nausea and vomiting occurred in 5 patients. The EC-T group showed a higher rate of grade 3/4 myalgia than the TCb group (7% and 4.44%, respectively, p=0.363). To conclude, the TCb regimen can be used as an alternative regimen for TOP2A-normal stage II-III breast cancer patients in neoadjuvant chemotherapy. However, in patients with node-positive tumors, EC-T is still recommended. Though no difference of grade 3/4 thrombocytopenia in two groups, grade 4 thrombocytopenia caused by the carboplatin-containing regimen should be taken seriously.

Key words: TOP2A-normal, epirubicin, docetaxel, neoadjuvant, residual cancer burden

Anthracyclines were first used in breast cancer in the 1950s. Although they may cause major blood-related toxicity and cardiotoxicity, they are currently the most widely used chemotherapy drugs in breast cancer patients [1]. Meta-analyses on data obtained from 123 studies have shown that early breast cancer patients can benefit from docetaxel or anthracyclines [2], and the sensibility to anthracyclines varies according to molecular type in breast cancer patients. Therefore, it is possible to avoid unnecessary treatment if patients who are insensitive to anthracyclines are screened out by molecular markers.

The gene that encodes TOP2A is located at 17q 12q-21 and plays a key role in cell division [3]. TOP2A gene amplification often predicts a worse prognosis and stronger tumor aggressiveness in breast cancer patients [4]. A large number of clinical trials have shown that although abnormal expression of the TOP2A gene may imply a poor prognosis, it can also improve the efficacy of anthracyclines [5, 6], suggesting that more patients with a normal TOP2A gene may be exempted from anthracycline chemotherapy. Previous studies have shown that in breast cancer patients, the proportion of TOP2A-normal patients is nearly 80% [7, 8], and the

percentage of TOP2A gene amplification is only 12–24% [5, 8, 9]. There is currently a lack of relative data on whether breast cancer patients with normal expression of TOP2A can benefit from anthracyclines.

Neoadjuvant chemotherapy can predict the efficacy of drugs in patients with breast cancer earlier; it is increasingly used in patients with early breast cancer. RCB can predict the prognosis of each molecular subtype by assessing residual tumors in the breast and axilla after neoadjuvant chemotherapy [10]. It can more accurately predict the prognosis of patients who have not achieved pCR after neoadjuvant chemotherapy, which is a great supplement to the current evaluation system after neoadjuvant chemotherapy. Therefore, this study aims to compare the efficacy of neoadjuvant chemotherapy with anthracyclines and non-anthracyclines in patients with TOP2A-normal breast cancer from three prospectively clinical trials (NCT03140553, NCT03154749, NCT03507465). NCT03140553 was a randomized trial of TCH (Docetaxel/Carboplatin/Trastuzumab) Versus EC-TH (Epirubicin/Cyclophosphamide followed by Docetaxel/Trastuzumab) as Neoadjuvant Treatment for HER2-Positive Breast Cancer. NCT03154749 was a phase II prospective randomized trial of docetaxel in combination with carboplatin (TCb) versus EC followed by docetaxel as neoadjuvant chemotherapy for triple-negative, early-stage breast cancer. NCT03507465 was a randomized trial of Letrozole Plus Low-Dose Metronomic Capecitabine versus EC-T (Epirubicin/Cyclophosphamide Followed by Docetaxel) as Neoadjuvant Therapy for ER+/HER2-negative Breast Cancer. We enrolled the participants with normal TOP-2A from these clinical trials.

Patients and methods

Patients. Based on the data from three studies registered with ClinicalTrials.gov (NCT03140553, NCT03154749, NCT03507465), a total of 280 breast cancer patients with normal TOP2A expression and who received neoadjuvant chemotherapy at Guangdong Provincial People's Hospital were enrolled and included in the study. Inclusion criteria were as follows: 1) Thick needle-proven primary carcinoma (breast cancer) with normal expression of TOP2A; 2) Imaging confirmed as stage II–III breast cancer; 3) Age 18–70 years old; 4) No distant metastasis; and 5) Good bone marrow reserve and heart functions. Exclusion criteria were as follows: 1) Sentinel lymph node biopsy before chemotherapy; 2) Other locations of tumors in the past 5 years; and 3) Relevant antitumor treatment.

Chemotherapy regimen. A total of 180 patients received the TCb regimen (75 mg/m^2 docetaxel, ID, day 1 + carboplatin AUC6, ID, day 1), and 100 patients received EC-T (4 cycles of epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2, followed by 4 cycles of docetaxel 75 mg/m^2). Seventy-five HER2+ patients were also treated with Herceptin (8 mg/kg Herceptin for the first time, 6 mg/m^2 maintenance dose on day 2). All patients received 300 μg/day of G-CSF prophylactic treatment on days 2 and 3 after chemotherapy. The dose of chemotherapy was adjusted according to the inspection results on the first day of each scheduled chemotherapy. When neutrophils, hemoglobin, platelets, and other non-blood-related adverse reactions showed the toxicity of 3 or more degrees (according to the guidelines of RECIST 1.1), chemotherapy was delayed by one week. B-ultrasound was made for staging evaluation before and after neoadjuvant chemotherapy.

Clinical pathological assessment. The kits used for TOP2A gene detection (TOP2A FISH pharmDx) and HER2 gene detection (HER2 FISH pharmDx) were obtained from DAKO, and fluorescence in situ hybridization was performed strictly in accordance with the operating instructions. Under the microscope, the orange fluorescence represents the TOP2A or HER2 gene probe signal, and green fluorescence represents the chromosome 17 probe signal. The TOP2A state was determined based on the ratio of the mean number of TOP2A gene probe signals per cell to the mean number of chromosome 17 probe signals. When the ratio of the TOP2A gene probe signal to the chromosome 17 probe signal is between 0.8 and 2.0, the TOP2A gene is in a normal state. By the IHC method, the critical value of ER (estrogen receptor) and PgR (progesterone receptor) interpretation is 10% tumor cell staining; HER2 (human epidermal growth factor receptor 2)-positive is defined as IHC+++ or IHC++, FISH-positive; HER2-negative is defined as IHC 0–+ or IHC++, FISH-negative; and HER2 critical is IHC++, with FISH representing the critical value [11]. High expression of Ki67 is defined as ≥15%, and low expression of Ki67 is defined as <15%. According to the results of immunohistochemistry, breast cancer is divided into five types: Luminal A, Luminal B (HER2–), Luminal B (HER2+), HER2+, and triple-negative. Molecular subtype typing standards are as follows: Luminal A: ER- and/or PR-positive, HER2-negative, Ki67 <15%; Luminal B (HER2–): ER- and/or PR-positive, HER2-negative, Ki67 ≥15%; Luminal B (HER2+): ER- and/or PR-positive, HER2-positive, Ki67 ≥15%; HER2+: ER- and PR-negative, HER2-positive; and triple-negative: ER-, PR- and HER2-negative.

Statistical analysis. The primary endpoint of this study was the RCB 0/1. Although pCR and RCB appear to be suboptimal prognostic indicators for breast cancer, the extent of RCB is a significant prognostic biomarker [10]. The RCB scoring system is mainly based on the largest diameter of the residual tumor bed, the cellularity of the tumor bed, and the number and size of metastatic lymph nodes after neoadjuvant chemotherapy, among which pCR is judged as RCB 0. According to the scoring system, the cutoff point of RCB I and RCB II is 1.36, the cut-off point of RCB II and RCB III is 3.28 [12]. The patient's RCB index is obtained after two doctors interpret pathological sections without intervention, which are reviewed by a pathologist. We used the chi-square test to analyze the choice of chemotherapy regimen and clinical

features and the association between molecular markers and the acquisition of RCB 0/1. Two-sided p<0.05 in the statistical test results was considered statistically significant.

Results

We totally analyzed 369 TOP2A-normal breast cancer patients who received neoadjuvant therapy from 3 clinical trials (NCT03140553, NCT03154749, NCT03507465); excluding 52 patients with TOP2A amplification or TOP2A deletion, 29 patients who received neoadjuvant endocrine therapy, 8 patients who did not undergo surgery at our center. Finally, 280 patients with TOP2A-normal breast cancer who received neoadjuvant chemotherapy were analyzed. Among them, 100 received EC-T and 180 received TCb (Figure 1). The median age was 44 years, of which 172 (61.4%) patients underwent a mastectomy and 108 (38.6%) received breast-conserving surgery. The clinicopathological features of the patients are shown in Table 1. A total of 75 HER2-positive patients were treated with trastuzumab.

Efficacy Response. The proportion of patients with RCB 0/1 in the two groups was 23% (EC-T group) and 23.9% (TCb group, p=0.614). There was no significant difference between the two groups.

Exploratory studies found no significant difference in efficacy between the two chemotherapy regimens for any of the breast cancer subgroups (including tumor size, tumor histological grade, hormone receptor status, Ki67 expression, and menopausal status), apart from nodal status (Figure 2). Among the triple-negative breast cancer patients, the efficacy of the TCb group was not superior to that of the EC-T group (p=0.52). In patients with lymph node metastasis, the efficacy of the EC-T group was significantly better than that of the TCb group (p=0.03). The recurrence-free survival analysis between the EC-T group and TCb group was examined by using the Kaplan-Meier method with the log-rank test. The median follow-up was 41.5 months. There was no significant difference between the two groups in recurrence-free survival (RFS, p=0.848, Figure 3).

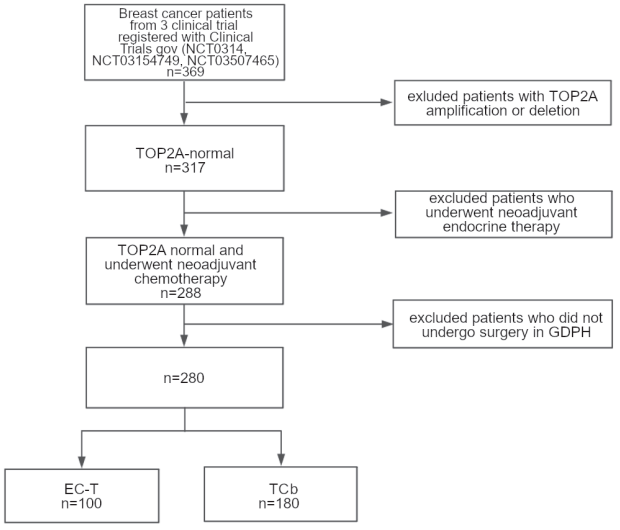

Figure 1. Study flowchart. GDPH – Guadong Provincial People`s Hospital, EC-T – epirubicin/cyclophosphamide followed by docetaxel, TCb – docetaxel/carboplatin

Table 1. Patient characteristics.

Characteristic	Anthracycline	Non-anthracycline
Menstrual status		
Premenopause	57 (57%)	108 (60%)
Postmenopause	43 (43%)	72 (40%)
Grade		
1	4 (4%)	6 (4%)
2	58 (58%)	87 (48%)
3	38 (38%)	87 (48%)
Tumor size (cm)		
≤2	6 (6%)	18 (10%)
>2, ≤5	71 (71%)	148 (82%)
>5	23 (23%)	14 (8%)
Lymph node status		
Positive	50 (50%)	77 (43%)
Negative	50 (50%)	103 (57%)
Stage		
α	87 (87%)	168 (93%)
β	13 (13%)	12 (7%)
Molecular subtyping		
Luminal A	10 (10%)	15 (8%)
Luminal B (Her2–)	43 (43%)	68 (38%)
Luminal B (Her2+)	13 (13%)	30 (17%)
Her2+	9 (9%)	22 (12%)
TNBC	25 (25%)	45 (25%)
ER status		
Negative	31 (31%)	70 (39%)
Positive	69 (69%)	110 (61%)
PgR status		
Negative	45 (45%)	82 (46%)
Positive	55 (55%)	98 (54%)
HER2 status		
Negative	78 (78%)	127 (71%)
Positive	22 (22%)	53 (29%)
Ki67		
High	66 (66%)	126 (70%)
Low	34 (34%)	54 (30%)
Surgical treatment		
Mastectomy	65 (65%)	107 (59%)
Lumpectomy	35 (35%)	73 (41%)
RCB		
0/1	23 (23%)	43 (23.9%)
2	67 (67%)	121(67.2%)
3	10 (10%)	16 (8.9%)

Abbreviations: ER – estrogen receptor, PgR – progesterone receptor, HER2 – human epidermal growth factor receptor 2

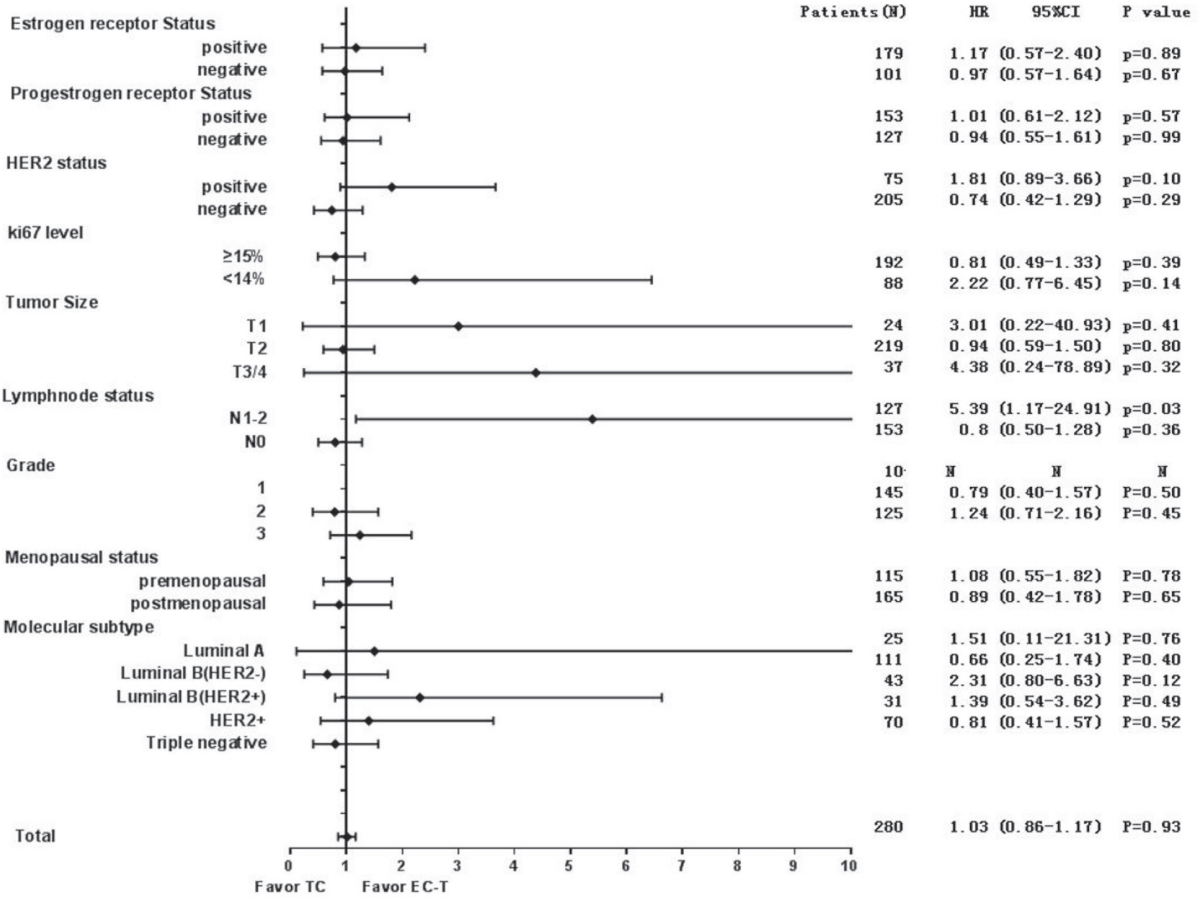

Figure 2. Forest plot shows proportional hazards models for RCB0/1 according to estrogen receptor status, progesterone receptor status, Ki67, HER2, tau, BCL-2 status, tumor size, lymph node status, malignancy grade, menopausal status, and molecular subtype. EC-T – epirubicin/cyclophosphamide followed by docetaxel, TC – docetaxel/carboplatin, HER2 – human epidermal growth factor receptor 2, tau – a microtubule-associated protein

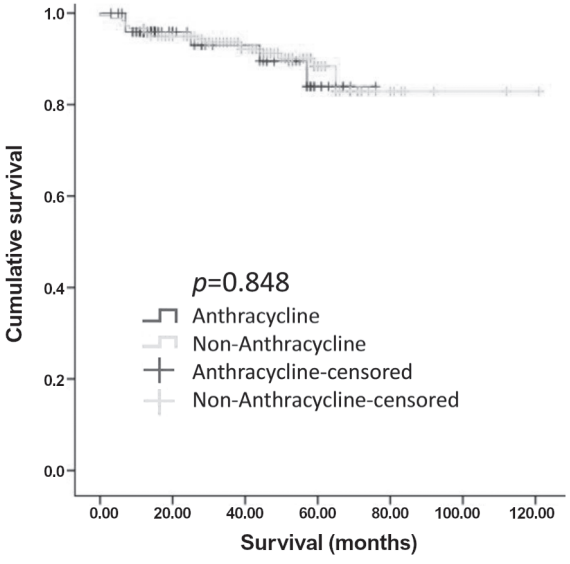

Figure 3. Comparison of RFS (recurrence-free survival) between Anthracycline- and Non-Anthracycline group.

Toxicity. In terms of hematologic toxicity, despite the routine use of G-CSF prophylactic treatment in both arms, grade 3–4 neutropenia still occurs, and our study shows that the incidence of grade 3–4 neutropenia was higher in the EC-T group than in the TCb group (17% and 14.44%, respectively, p=0.570). Regarding the side effects, the incidence of grade 3/4 anemia was higher in the EC-T group than in the TCb group (21.0% vs. 8.33%, p=0.002). The incidence of grade 3–4 thrombocytopenia was low in each group (EC-T: 6% and TCb: 7.22%, respectively, p=0.697). However, 2 patients suffered grade 4 thrombocytopenia and delayed chemotherapy in the TCb group. One patient in the TCb group experienced grade 3 liver damage. No severe cardiac damage was detected during chemotherapy in both groups.

As for nonhematologic toxicity, both groups of patients tolerated the chemotherapy regimens well. In the EC-T group, grade 3/4 nausea and vomiting occurred in 5 patients, no one showed grade 3/4 nausea and vomiting in the TCb group. The EC-T group showed a higher rate of grade 3/4 myalgia than the TCb group (7% and 4.44%, respectively, p=0.363, Table 2).

Discussion

In this study, 280 patients were finally analyzed from three clinical trials, of which 100 patients received the EC-T regimen with neoadjuvant chemotherapy and 180 patients received the TCb regimen with neoadjuvant chemotherapy. There was no significant difference in the ratio of RCB 0/1 between the two groups (23% for EC-T group vs. 23.9% for TCb group, p=0.614). This result confirmed that the anthracycline-based regimen is not the only option in the neoadjuvant chemotherapy treatment of patients with normal TOP2A.

Previous studies have shown that patients with triple-negative and HER2+ breast cancer who achieved pCR after neoadjuvant chemotherapy had a better prognosis, whereas in patients with luminal breast cancer, the predictive effect of pCR was significantly lower [13], with a pCR of only 12–16% [14]. Our previous report showed that luminal patients receiving the TCb regimen with neoadjuvant chemotherapy had a pCR of only 7–12% [15]. There were good prognoses for HR+/HER2– patients who achieved pCR or RCB-I, among whom 5 years of RFS were 88% and 100%, respectively [10]. For patients who cannot obtain pCR, RCB can better predict their prognosis and chemotherapy efficacy. In breast cancer patients excluding HR+/HER2–, the prognosis of RCB 0 was not better than that of RCB-I, and the prognosis of RCB 0/1 was significantly better than that of RCB 2/3 [10]. Therefore, this study used RCB 0/1 as the primary endpoint after neoadjuvant chemotherapy and hoped to explore the association between RCB 0/1 and prognosis at a later date. It is also important to note that using the RCB scoring system may increase the burden on the pathologist. In this study, the RCB score was carefully judged by three doctors, including a review by a pathologist.

Previous studies have shown that paclitaxel combined with carboplatin can achieve significant efficacy and good tolerance in breast cancer patients [16–18]. In this study, two groups of patients obtained a similar RCB 0/1 ratio. In the subgroup analysis, triple-negative breast cancer patients were more likely to benefit from the TCb regimen. GeparSixto trial has shown that in patients with the triple-negative type, using carboplatin in neoadjuvant chemotherapy can achieve a higher rate of complete pathologic response [17]. Among lymph node-positive patients, the EC-T regimen was significantly better than the TCb regimen (p=0.03). Although a great deal of research has shown that the addition of carboplatin to standard neoadjuvant chemotherapy for TNBC significantly improves pCR rates, there is still no direct evidence that TCb neoadjuvant chemotherapy is superior to EC-T in triple-negative patients. In this study, the efficacy of the TCb group was not superior to that of the EC-T group (p=0.52) among the triple-negative breast cancer patients, Moreover, it should be taken seriously when using a non-anthracycline regimen in node-positive patients.

Table 2. Toxicity.

Grade 3/4 Advent event	Anthracycline n (%)	Non-Anthracycline n (%)	p-value
Neutropenia	17 (17.00)	26 (14.44)	0.570
Leucopenia	13 (13.00)	4 (2.22)	<0.001
Anemia	21 (21.00)	15 (8.33)	0.002
Thrombocytopenia	6 (6.00)	13 (7.22)	0.697
ALT	–	1 (0.56)	0.643
Fever	3 (3.00)	–	0.045
Nausea/Vomiting	5 (5.00)	–	0.005
Constipation	1 (1.00)	–	0.357
Diarrhea	2 (2.00)	–	0.127
Myalgia	7 (7.00)	8 (4.44)	0.363
Bone pain	3 (3.00)	–	0.045
Fatigue	2 (2.00)	2 (1.11)	0.619
Dyspnea	–	–	–
Cough	–	–	–
Neuropathy	3 (3.00)	3 (1.67)	0.670
Cardiac impairment	–	–	–

In terms of hematologic toxicity, the anthracycline-containing regimen may have a higher rate of 3/4 neutropenia than the other group (17% vs. 14.44%, p=0.570). In the TCb group, 2 patients had severe thrombocytopenia and delayed chemotherapy. Although the incidence of grade 3/4 thrombocytopenia was low in each group, attention must be paid to the patients who experienced grade 3/4 thrombocytopenia in the TCb group. Regarding nonhematologic toxicity, the incidence of grade 3–4 adverse events was low, while the subjective expression of discomfort (including grade 1/2 abdominal pain, fatigue, hand and foot soreness, and muscle pain) was higher, which might be related to patient complaints (patient reported) [19]. The incidence of hand and foot soreness after sequential docetaxel was 3% in EC-T chemotherapy, while it was 1.67% in the TCb group, and most of the adverse reactions occurred after the end of the fifth chemotherapy cycle (the first time receiving docetaxel chemotherapy), which is similar to the results of the DBCG07-READ test [20]. The possible causes are as follows: 1. EC-T has a longer chemotherapy cycle than the TCb regimen; 2. The dose of docetaxel in the EC-T regimen exceeds that of the TCb regimen. The EC-T group showed a higher rate of grade 3/4 myalgia than the TCb group (7% and 4.44%, respectively) though the incidence of each group is low. To solve this problem, in addition to wearing ice gloves and elastic stockings [21], acupuncture treatment was used for peripheral nerve pain caused by taxanes in our study [22], and patients generally have significant relief of symptoms after one week of treatment.

This study was based on three prospectively clinical trials (NCT03140553, NCT03154749, NCT03507465). However,

the imbalance between the two groups may also cause bias in results. In addition, there have been few studies that selected RCB 0/1 as the endpoint, and more trial verification is needed. The study also required long-term survival follow-up to verify differences in efficacy between the two groups.

In summary, the TCb regimen may be an alternative neoadjuvant chemotherapy regimen for breast cancer patients with normal TOP2A. In this study, the TCb regimen achieved a similar ratio of RCB 0/1 to the EC-T regimen, and the adverse effects were relatively mild. However, more attention is still required for the toxicity of thrombocytopenia caused by carboplatin.

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