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Phase III study of TAC and TP regimens as neoadjuvant chemotherapy in patients with triple-negative breast cancer

Hanguang Ruan[1], Juan Xiong[2], Meng Wu[2]

[1] Department of Oncology, The Third Hospital of Nanchang, Nanchang 330002, China
[2] Department of Radiation Oncology, The Cancer Hospital of Jiangxi Province, Nanchang 330029, China

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Abstract ***Objective:*** This study aimed to compare the efficacy and safety of neoadjuvant chemotherapy with TAC and TP regimens of triple negative breast cancer (TNBC). ***Methods:*** A total of 102 patients with TNBC were confirmed by histopathology. They were divided into TAC group (52 cases) and TP group (50 cases). Group TAC: Docetaxel 75 mg/m^2 or paclitaxel (taxol liposome) 135 mg/m^2 on d1, pirarubicin 40 mg/m^2 or epirubicin 75 mg/m^2 on d2, cyclophosphamide 600 mg/m^2 on d1; Group TP: Docetaxel 75 mg/m^2 or paclitaxel (taxol liposome) 135 mg/m^2 on d1, cisplatin 30 mg/m^2 on d2–d4, with 21 days as a cycle. All patients underwent operation after 2–4 cycles of chemotherapy. The short-term effects and toxic and adverse effects were evaluated. ***Results:*** In TAC group, 5 cases (9.6%) had pathological complete release (pCR), 35 cases (67.3%) partial release (PR), 9 cases (17.3%) stable disease (SD), and the response rate (RR) was 76.9%. In TP group, 4 cases (8%) had pCR, 32 cases (64%) PR, 5 cases (10%) SD, and RR was 72%. In 102 patients, 12 patients with tumor progression after 2 cycles of chemotherapy, included 3 cases in TAC group, 9 cases in TP group. In TAC group, 2 cases occurred atrial premature contraction; while 3 cases developed grade 2 renal injury in TP group. In TAC group, grade 3–4 hematologic toxicity and alopecia was significantly higher than that in TP group, but grade 3–4 gastrointestinal reaction rate in TP group was significantly higher than TAC group. ***Conclusion:*** TAC and TP regimens all had certain efficacy in the neoadjuvant chemotherapy for TNBC, and the toxicity reactions can be tolerated.

Key words triple-negative breast carcinoma (TNBC); neoadjuvant chemotherapy; short-term efficacy; toxicity reaction

Triple-negative breast carcinoma (TNBC) refers to any breast cancer that does not express the genes for estrogen receptor (ER), progesterone receptor (PR) and Her2/neu. In recent years, preoperative neoadjuvant chemotherapy has been widely used in the treatment of breast cancer, its role has gradually been confirmed [1, 2]. Effect of neoadjuvant chemotherapy before operation in TNBC than other types of breast cancer is more obvious, but the chemotherapy and cycle number selection remains controversial. This study compared the efficacy and side effects of TNBC with TAC and TP regimens in the neoadjuvant chemotherapy, and provided a guidance for clinical treatment.

Correspondence to: Hanguang Ruan. Email: rhguang@163.com

Materials and methods

Patients

From October 2009 to May 2012, 102 patients with primary TNBC (stage IIB–IIIB) were enrolled in our study. Among them, 5 were males, 97 were females, aged 25–71 years with a median age of 51 years. All patients were confirmed by needle biopsy and detected the expression of ER, PR and HER-2 by immunohistochemistry before neoadjuvant therapy. The PS was 0–2 score. Liver, lung CT and radionuclide bone imaging showed no distant metastasis in all patients. Fifty-two patients received TAC regimen, and 50 cases received TP regimen. The patients characteristics were shown in Table 1.

Therapy methods

Group TAC: Docetaxel 75 mg/m^2 or paclitaxel (taxol liposome) 135 mg/m^2 on d1, pirarubicin 40 mg/m^2 or epirubicin 75 mg/m^2 on d2, cyclophosphamide 600 mg/m^2 on d1; Group TP: Docetaxel 75 mg/m^2 or paclitaxel (taxol

Table 1 Patient characteristics

Characteristic	TAC group (n = 52)	TP group (n = 50)	P
Sex			
Male	3	2	0.679
Female	49	48	
Age (years)			
≥ 35	20	18	0.797
< 35	32	32	
N stage			
N0	12	11	
N1	15	17	0.852
N2	25	22	
Pathologic type			
Invasive ductal cancer	22	25	
Invasive lobular cancer	20	18	0.675
Others	10	7	
Clinic stage			
IIB	15	16	
IIA	18	16	0.933
IIIB	19	18	

liposome) 135 mg/m^2 on d1, cisplatin 30 mg/m^2 on d2–d4, with 21 days as a cycle. All drugs were treated by intravenous drip. Before chemotherapy, patients were examined blood, ECG, liver and renal function and the score of tumor marker examination and general situation. Patients were treated with 5-HT3 receptor antagonists before chemotherapy to prevent gastrointestinal reaction, dexamethasone to prevent allergic reaction, ECG and catheter. The TP group was given proper hyperhydration and diuresis. Evaluation the effect of each cycle to decide whether to continue the next cycle of chemotherapy. The neoadjuvant chemotherapy would terminate if patients had tumor progression. Application of drugs to enhance blood cells and supporting therapy for patients with myelosuppression before the next cycle of chemotherapy, until the number of blood cells reached the requirement.

Efficacy evaluation

The short-term efficacy was evaluated according to response evaluation criteria in solid tumors (RECIST1.1). The size of breast lesions and axillary lymph nodes were examined by clinical palpation and breast ultrasonography. Efficacy evaluation include complete response (CR), partial response (PR), stability disease (SD) and progressive disease (PD). CR also include pathological complete response (pCR) and clinical complete response (cCR). The response rate (RR) was calculated as pCR + PR.

Toxic and side effects

Toxic and side effects were evaluated according to WHO classification standards of antitumor drug adverse reaction. Including hematological, gastrointestinal, alopecia, heart, kidney function indicators and were divided into 0–4. Each cycle were assessed toxic and side effects.

Statistic analysis

SPSS 13.0 software package was used for statistical analysis. χ^2 test was used to compare the difference between the two groups. $P < 0.05$ was considered to be statistically different.

Results

Short-term efficacy

All patients were completed 2 to 4 cycles of chemotherapy. In TAC group, 5 cases (9.6%) had pathological complete release (pCR), 35 cases (67.3%) partial release (PR), 9 cases (17.3%) stable disease (SD), and the response rate (RR) was 76.9%. In TP group, 4 cases (8%) had pCR, 32 cases (64%) PR, 5 cases (10%) SD, and RR was 72%. Compared with TP group, pCR in TAC group was higher, but the difference had no statistically significant (χ^2 = 0.083, P = 0.774). The RR in TAC group and TP group was 76.9% and 72%, respectively. There was no significant difference in RR between two groups (χ^2 = 0.325, P = 0.568). A total of 12 cases occurred tumor progression after 2 cycles of chemotherapy (3 cases in TAC group, 9 cases in TP group), they were treated with operation and terminated neoadjuvant chemotherapy. The other patients were treated with operation after 4 cycles of therapy.

Toxic and side effects assessment

In TAC group, 2 cases occurred atrial premature contraction; while 3 cases developed grade 2 renal injury in TP group. In TAC group, grade 3–4 hematologic toxicity and alopecia was significantly higher than that in TP group, but grade 3–4 gastrointestinal reaction rate in TP group was significantly higher than TAC group, the differences were statistically significant ($P < 0.05$). There were no significantly different in thrombocytopenia, diarrhea and the incidence of aminotransferase elevations between two groups ($P > 0.05$; Table 2).

Discussion

TNBC is a research focus in the field of breast cancer recently. At present, there is no uniform guidelines. This study compared the short-term effects and toxic and side effects in different chemotherapy regimens for patients with TNBC, and provide reliable theoretical basis for the future treatment. Patients with TNBC were hormone receptor negative, which resulting in a lack of hormone therapy and targeted drugs. Chemotherapy has become an important part of the treatment, many studies show that TNBC patients are more sensitive to chemotherapy.

Table 2 Comparison of toxic and side effects between two groups

Toxic and side effects	TAC group (n = 52)				TP group (n = 50)				χ^2	P
	1	2	3	4	1	2	3	4		
Blood toxicity	8	12	13	19	18	22	8	2	18.158	0.000
Hemoglobin	6	9	9	14	15	19	6	1	15.810	0.000
Leukopenia	8	10	12	9	14	15	4	0	13.730	0.000
Thrombocytopenia	3	5	3	2	5	1	0	0	3.132	0.007
Gastrointestinal	19	23	4	6	7	8	13	22	26.649	0.000
Nausea, vomiting	8	21	2	4	7	8	11	20	17.245	0.000
Diarrhea	5	10	3	2	5	7	8	3	2.386	0.122
High transaminase level	10	12	1	0	6	3	3	0	3.323	0.068
Alopecia	5	10	16	21	17	23	6	4	26.845	0.000

With neoadjuvant chemotherapy, the pCR of TNBC patients was significantly higher than that of hormone receptor positive breast cancer, and the pCR increasing can improve the prognosis. The traditional single-agent or combination chemotherapy is an important method in the treatment of TNBC, especially the chemotherapy with anthracycline and taxane [3, 4]. Liedtke [5] showed that the pCR rate in TNBC group and non-TNBC group was 22% and 11%, respectively. In our study, 9 cases had pCR, 67 cases PR, pCR rate was 8.8%, RR was 74.5%. The pCR rate was lower than the previous reports, probably because of small number of cases, different chemotherapy regimens and chemotherapy cycles. Yi [6] conducted a randomized controlled study of a paclitaxel efficacy in patients with positive nodes of breast cancer patients, 1500 cases of lymph node positive breast cancer patients were randomly divided into two groups, one group received 4 cycles of doxorubicin plus cyclophosphamide chemotherapy, then received paclitaxel chemotherapy for 4 cycles of adjuvant chemotherapy in the other. One group was treated with 4 cycles of doxorubicin plus cyclophosphamide. Results showed a survival following paclitaxel chemotherapy was better than no paclitaxel chemotherapy patients (P = 0.002), and chemotherapy containing paclitaxel for patients with TNBC sequential may bring higher survival benefit. Our study showed that two groups of patients with paclitaxel for neoadjuvant chemotherapy, RR were 79.6% and 72%, respectively. RR rate in anthracycline group was slightly higher than that of non-anthracycline group, but no statistically significant difference was found (P = 0.568). Therefore, the taxol medicaments had efficiency in patients with TNBC, when combined chemotherapy with anthracycline, the efficiency is more likely to improve.

Recent studies of TNBC focuses on BRCA1 gene, more and more evidences show it has close correlation with TNBC. BRCA1 related breast cancer is caused by mutation of BRCA1 gene instability, 80% of the hereditary breast cancer with BRCA1 mutation would have a poor prognosis [7–9]. Researches showed cisplatin had high efficiency to patients with TNBC [10, 11], especially to patients with BRCA1 gene mutations. Yi *et al* [6] reported that the pCR of TNBC patients treated with platinum based chemotherapy was 23%–90%, which was higher than that of the anthracycline and taxane chemotherapy scheme (19%–34%). Further study is still needed because of the limited cases alloted. In TP group, the pCR rate was 8.0%, PR rate and RR was 64% and 72%, respectively. In TAC group, the pCR rate was 9.6%, PR rate and RR rate was 67.3% and 76.9%, respectively. Nine patients had tumor progression in TP group, while 3 cases in TAC group. In this study, short-term efficacy results were inconsistent with some previous reports, the possible cause is BRCA1 gene mutations in TNBC patients. And the BRCA1 gene detection was not performed for all patients, so we did not know if the mutation rate was correlated with the negative results, and it need further research.

At present, the chemotherapy play an important role in the treatment of breast cancer, especially in advanced breast cancer. In consideration of the short-term effect and long-term survival of patients with chemotherapy, toxic and side effects and quality of life also can not be ignored [12]. The adverse reactions in this study were evaluated from 5 aspects, including hematology, gastrointestinal tract, alopecia, heart, and kidney function. In TAC group, 2 cases occurred atrial premature contraction; while 3 cases developed grade 2 renal injury in TP group. In TAC group, grade 3–4 hematologic toxicity and alopecia was significantly higher than that in TP group, but grade 3–4 gastrointestinal reaction rate in TP group was significantly higher than TAC group (P < 0.05). Possible reason for the TAC group contained the anthracycline. The gastrointestinal adverse reactions in TP group were significantly higher than those in TAC group (P < 0.05). In this study, patients in the TAC group had more serious adverse reactions than in TP group, but they could tolerate, and this result was consistent with previous reports. At present, there is no uniform standard for patients with TNBC, combining molecular biological detection with individual treatment may be one of the research direction in the future.

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