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Investigation of paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab in HER2-positive breast cancer

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Summary

Objective: This study aims to observe the curative effects and safety of paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab on HER2-positive breast cancer. *Materials and Methods:* Forty-two patients with HER2-positive breast cancer were included into this study. These patients underwent paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy for four courses of treatment. Paclitaxel (80 mg/m^2) and carboplatin (AUC 1.5) were administered via i.v. g.t.t., d1, repeated every week. Three weeks was considered as one course of treatment, and there were 12 weeks in total. At the same time, trastuzumab (Herceptin) one-cycle therapy was combined. Its efficacy and adverse reactions were evaluated, and the major observational indicator was pathological complete remission (pCR). *Results:* A total of 41 patients successfully underwent paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy for four courses of treatment, and the total clinical effective rate was 97.6%. Clinical complete remission (CR) was achieved by 25 patients (59.5%), partial remission (PR) of the tumor was achieved by 16 patients (38.1%), and pCR was achieved by 23 patients (54.8%). Adverse reactions included bone marrow suppression and hair loss, and no toxic and adverse reactions of the heart were observed. *Conclusion:* In the neoadjuvant chemotherapy of HER-2-positive breast cancer, paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy for four courses of treatment achieved better efficacy and tolerance.

Key word: Paclitaxel plus CarboPlatin; Trastuzumab; Breast cancer; Neoadjuvant Therapy; HER2.

Introduction

Neoadjuvant chemotherapy of breast cancer is carried out before partial treatment of surgery plus radiotherapy, and systemic chemotherapy has been considered as the first step in treating breast cancer. Initially, neoadjuvant chemotherapy was only used for the standard treatment of locally advanced breast cancers that are not applicable for surgery [1]. In recent years, neoadjuvant chemotherapy has been increasingly applied in all stages of breast cancer. Application of trastuzumab in the adjuvant therapy for HER2-positive breast cancer has been the golden standard. Forty-two patients with human epidermal growth factor receptor (HER2)-positive breast cancer, who were admitted by the Department from June 2013 to March 2015, underwent paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy, and achieved better efficacy.

Materials and Methods

Forty-two patients with HER2-positive breast cancer, who were admitted at the Department of Breast Cancer in Baotou Cancer Hospital, Inner Mongolia, from June 2013 to March 2015, were selected as study objects. All patients underwent hollow-bore needle puncture and qualitative diagnosis by pathologic histology. All patients were female; and their age ranged from 31 to 68 years old, with a median age of 45.6 years. Eastern Cooperative Oncology Group (ECOG) physical status score was ≤ 1. Furthermore, 29 patients had left breast cancer and 13 patients with right breast cancer. Thirty-nine patients suffered from invasive ductal carcinoma and three patients suffered from invasive lobular carcinoma. Twenty-seven patients were diagnosed with Stage II breast cancer and 15 patients suffered from Stage III breast cancer. The immunohistochemistry of any estrogen receptor and progesterone receptor were implemented. All patients underwent axillary lymph node puncture or sentinel lymph node biopsy before chemotherapy, and axillary lymph node metastasis was observed in 34 patients (Table 1).

After puncture and qualitative diagnosis, 42 patients underwent paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy for four courses of treatment. Paclitaxel (80 mg/m^2) was used to dissolve 5% of 250 ml of glucose, which was administered *via* i.v. g.t.t. for six hours. Carboplatin (AUC 1.5) was used to dissolve 5% of 250 ml of glucose, which was administered *via* i.v. g.t.t. for 30-60 minutes. At the same time, trastuzumab one-cycle therapy was combined with the first dosage of 4 mg/kg. After the second week, the dosage was changed into 2 mg/kg *via* i.v. g.t.t., d1, repeated every week. Three weeks were considered as one course of treatment. The plan was to carry out four courses of treatment (12 weeks). Routine pretreatment and preventive vomit-stopping were performed. On the day before chemotherapy, routine blood examination and biochemical examination (all items) were carried out. In the first week, preventive leukocyte increase was not performed. After the second week, whether preventive and therapeutic leukocyte increase would be performed or not was determined according to the results of the biochemical examination. G-CSF was the commonly used drug via subcutaneous injection, 300 μg, d4. Leukocyte increase aims to maintain white blood cell count/absolute neutrophil count at

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Table 1. — *Analysis of neoadjuvant chemotherapy's efficacy.*

	Cases	OR (CR+PR) (%)	SD (%)	pCR (%)	*p* value
TNM staging					
Groups					
IIA	3	3 (2+1) (100)	0	2 (66.7)	
IIB	17	17 (12+5)(100)	0	11 (64.7)	
IIIA	16	15 (10+5)(93.8)	1(6.2)	9 (56.3)	
IIIB	4	4 (1+3) (100)	0	1 (25)	
IIIC	2	2 (0+2) (100)	0	0	
Pathology					>0.05
Invasive dutal carcinoma	39	38 (24+14) (97.4)	1 (2.6)	22 (56.4)	
Invasive lobular carcinoma	3	3 (1+2) (100)	0	1 (33.3)	
Lymph node metastasis					>0.05
Positive	34	33 (18+(10+5)*) (97.1)	1 (2.9)	16 (47.1)	
Negative	8	8 (7+1) (100)	0	7 (87.5)	

Note: (10+5) means 15 patients with PR; among them, 10 patients with lymph node metastasis becoming negative and 5 patients with Lymph node metastasis still on.*

Table 2. — *Main adverse reactions of neoadjuvant chemotherapy.*

Adverse reactions	0-2°(cases)	3-4°(cases)
Neutrophil decrease	31	11
Digestive tract reactions	13	0
Toxic side effects of heart	0	0
Peripheral nerve damage	2	0
Rash	1	0
Liver function damage	1	0
Alopecia	3	39

2.0-10/1.0-8.0×10^9/L, respectively. The dosage of drugs for leukocyte increase was adjusted according to the results of routine blood examinations. At the end of each cycle, color Doppler ultrasound examination for mammary glands was performed. At the end of every two cycles, MRI for mammary glands, electrocardiogram (ECG), and color Doppler ultrasound examination for the heart were carried out. Under auxiliary diagnosis by color Doppler ultrasound examination and MRI for mammary glands, the tumor was relieved and chemotherapy was continued. If the tumor progressed and was stable, or abnormalities were observed in cardiac function, chemotherapy was discontinued. At the end of the chemotherapy, surgery was carried out. Postoperative adjuvant therapy was performed according to National Comprehensive Cancer Network (NCCN) diagnosis and the treatment specifications of breast cancer, and trastuzumab 6 mg/ kg, one time 21 days, for one year.

This group underwent color Doppler ultrasound examination and MRI for mammary glands to measure the size of the tumor and evaluate the efficacy. Many studies suggest that MRI dynamic contrasted-enhancement technology is better than traditional ways such as clinical breast examination, Molybdenum-target X-ray photograthy, breasts ultrasound, etc. [2, 3] Efficacy was divided into four categories, according to unified standards formulated by the World Health Organization (WHO): (1) clinical complete remission (CR) indicated that the tumor completely disappears according to clinical examination; (2) clinical partial remission (PR) indicated that the size of the tumor decreased by ≥ 50%; (3) stable disease (SD) indicated that the size of the tumor decreased by < 50% or increased by < 25%; (4) progressive disease (PD) indicated that the size of the tumor increased by ≥ 25%, or new lesions occurred. Total effective rate (OR)=CR+PR [3]. Pathological complete remission (pCR) indicaterd that there were no invasive cancer cells in the primary tumor area of the surgical samples, and no cancer metastasis could be found in axillary lymph nodes.

SPSS 17.0 software was used to perform the χ^2-test for enumeration data. $P < 0.05$ was considered statistically significant.

Results

Among the 42 patients in this group, 41 patients successfully completed four courses of paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy. In 1/42 patients, SD of the tumor was achieved and the treatment was consequently discontinued after two courses of treatment, and the total clinical effective rate was 97.6%. CR was achieved by 25 patients, and the CR rate was 59.5%, while PR of the tumor was achieved by 16 patients, and the PR rate was 38.1%. Surgery was performed in three weeks after chemotherapy was completed, in which 33 patients underwent modified radical mastectomy, and nine patients underwent breast reservation radical correction. Axillary lymph nodes before neoadjuvant chemotherapy indicated that 34 patients had cancer metastasis and 28 patients were without cancer metastasis through Axillary lymph nodes after neoadjuvant chemotherapy. Among patients with CR, cancer residues were found in two patients, with tumor lesion residue in one patient and axillary lymph node cancer residue in one patient, and the rate pathological CR was 54.8%. pCR was analyzed according to TNM staging, pathological nature, and lymph node situation; and no statistical significance was identified (Table 1).

Among these adverse reactions, no heart-related adverse reactions were observed and only digestive tract reactions were found, such as mild nausea, vomiting, and diarrhea. Furthermore, 3-4° of neutrophil decrease was found in 11 patients, with an incidence rate of 26.1%. Among these patients, one patient presented with neutrophil decreasing fever; hence, the treatment was delayed for one week. Furthermore, one patient suffered from severe thrombocy-

topenia and anemia, and two patients presented with 1° and above peripheral nerve adverse reactions (Table 2).

Discussion

Neoadjuvant chemotherapy can manage the early distant metastasis of tumors through "partial to whole". Patients who previously could not receive the surgery can be applied to the surgery, and patients who would receive mastectomy can undergo feasible breast-conserving surgery. In addition, according to the size of the tumor before and after chemotherapy, changes in pathological and biological indicators intuitively allow the understanding on whether the specific tumor is sensitive and effective to chemotherapeutic drugs and schemes [4]. Furthermore, this avoids the blindness of chemotherapy, and prevents excessive chemotherapy and invalid chemotherapy. Luangdilok *et al.* [5] suggested that patients with pathological CR are obviously higher than those without pathological CR in the rate of living without this kind of disease after new adjuvant chemotherapy.

Many large-scale clinical researches about adjuvant chemotherapy for breast cancer all indicate that patients who need to receive adjuvant chemotherapy can all adopt new adjuvant chemotherapy [6]. Due to the exact curative effect of neoadjuvant chemotherapy in treating breast cancer, this approach has been adopted by more breast surgeons. With the development of the chemotherapeutic drugs, constantly looking for more effective neoadjuvant chemotherapy regimens is an important research direction. Experts in the St. Gallen meeting in 2013 recommended that neoadjuvant chemotherapy preferred those regimens containing taxanes and anthracycline. Thus, the combination or sequential application of taxanes and anthracycline has been mostly adopted in clinical practice, but there are no standardized chemotherapeutic regimens.

The overexpression of HER2 is closely correlated with strong invasion, high recurrence rate, and high mortality rate [7]. Trastuzumab aims at the humanized monoclonal antibody of HER2-positive breast cancer, and this combination chemotherapy can significantly improve disease-free survival rate and overall survival rates [8, 9]. So far, trastuzumab treatment for one year has become the international standard of treating HER2-positive breast cancer [10]. Results of the meta-analysis conducted by Valachis *et al.* [11] on patients with HER-2-positive breast cancer revealed that neoadjuvant chemotherapy added with trastuzumab can significantly increase the rate of pCR.

As for HER2-positive breast cancer, various studies on trastuzumab combined with different chemotherapy regimens have been conducted. Compared with the single chemotherapy group, the pCR rate (31.7-65.0%) of patients who received neoadjuvant chemotherapy in combination with trastuzumab was significantly higher than that in the single chemotherapy group (15.7-26.3%) [12-14].

This difference may be related to inconsistent tumor typing, staging, chemotherapy regimen, and course of treatment. In vitro tests indicated that trastuzumab has accumulation effects in combination with paclitaxel, and synergistic effects in combination with carboplatin [15]. This study selected 42 patients with HER2-positive breast cancer, and paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy was used. The clinical effective rate was 97.6% and pCR rate was 57.1%, which achieved a good therapeutic effect.

Among the adverse events of chemotherapy, cardiac function injury is the most severe adverse reaction of trastuzumab, with an incidence rate of approximately 4-6%, and its incidence rate was 27% when combined with anthracyclines [16, 17]. It is still unknown how trastuzumab causes cardiotoxicity [18]. Untill now, it has not had a uniformed rule to follow up patients after trastuzumab treatment [19]. For avoiding cardiotoxicity caused by trastuzumab, clinical guidelines advise that cardiac function evaluation should be done before treatment and once again after post-treatment three months [20]. In terms of the incidence rate of bone marrow suppression, gastrointestinal reaction, oral ulcer and alopecia, no significant differences were observed between the chemotherapy plus trastuzumab group and the single chemotherapy group [21]. As for the 42 patients that were included into this study, no digestive tract-related adverse events and heart-related adverse events were found. This is related with regimens that excluded anthracyclines. In addition, 11 patients with severe bone marrow suppression continuously received treatment after G-CSF treatment for leukocyte increase. Other adverse events were mild, and patients can be tolerant after symptomatic and supporting therapies.

In summary, the four-course treatment of paclitaxel-carboplatin one-cycle neoadjuvant chemotherapy plus trastuzumab therapy for the neoadjuvant therapy of HER2-positive breast cancer has a higher clinical effective rate and pCR rate, and no severe adverse events were found. Hence, it is an alternative neoadjuvant chemotherapy regimen that does not contain anthracycline.

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