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Clinical Research Paper

Primary safety analysis of trastuzumab after adjuvant chemotherapy in 30 Chinese Her2-positive early breast cancer patients

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Background and Objective: It has been proven that trastuzumab has clinical activity in early and advanced breast cancer with Her2-overexpression. This study analyzes the safety of trastuzumab after adjuvant chemotherapy in 30 Chinese Her2-positive early breast cancer patients. Methods: Trastuzumab was administrated after adjuvant chemotherapy every 21 days. The initial dose was 8 mg/kg, and the subsequent dose was 6 mg/kg, for four to 35 cycles (medium 18 cycles). The side effects of these patients, especially cardiotoxicity, were analyzed. Resutls: Thirty patients with Her2-positive early breast cancer were entered into the study. The average treatment period was one year (range nine weeks to two years). Two patients had shivering and fever during the first infusion with trastuzumab. Left ventricular ejection fraction (LVEF) level dropped in 18 cases after treatment with trastuzumab, half of which decreased more than 10%; however, no cardiac failure was observed. Conclusions: The post-surgical use of trastuzumab in Chinese patients with Her2-positive early breast cancer shows a satisfactory safety profile. However, the potential cardiotoxicity of trastuzumab should be carefully monitored during therapy.

In recent decades, the incidence of breast cancer has increased globally, becoming the most common malignant tumor affecting females.[1] Approximately 20%–30% of breast cancer patients are Her2 positive, and Her2 positivity is closely correlated to the poor prognosis of cancer patients.[2] Trastuzumab is a recombinant humanized monoclonal antibody against-P185 HER2. It has a close affinity to the Her2/neu protein and it alone is effective for the treatment of Her2-positive breast cancer.[3] A multi-center study overseas has confirmed that trastuzumab monoclonal antibody has a good effect on Her2-positive advanced breast cancer or as adjuvant post-operative treatment for early breast cancer. In 2006, NCCN guideline recommends the use of trastuzumab as a post-operative treatment of Her2-positive early breast cancer.[4] In this paper, we retrospectively analyzed the safety of trastuzumab in post-operative adjuvant therapy of early breast cancer when administrated via injection every three weeks.

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Patients and Methods

Patients. Thirty Her2-positive early breast cancer patients receiving trastuzumab treatment at the Department of Internal Medicine at the Sun Yat-sen University Cancer Center from April 2002 to January 2008 were included in this study. All cases were confirmed by histopathological examinations as invasive ductal carcinoma and immunohistochemistry detected Her2 (+++). Standard, 12-electrode ECG screening before medication showed no obvious abnormalities in any of the patients and all subjects had baseline value of left ventricular ejection fraction (LVEF) >55% before medication. The 30 patients were female, with a median age of 45 years (27–65 years old), with 20 pre-menopausal patients and ten post-menopausal patients (for clinical features see Table 1).

Drug administration method. The thirty subjects included in our study were all post-operative patientswho had completed adjuvant chemotherapy and/or radiation therapy prior to trastuzumab treatment. The initial dose of trastuzumab was 8 mg/kg and the secondary and subsequent maintenance dose was 6 mg/kg, administrated once every three weeks. The drug was dissolved in normal saline solution and infused into patients within 90 min. The first application of trastuzumab to patients was observed for at least six hours (that is, until 4.5 h after infusion). If no serious infusion reactions appeared after the initial application, the observation period for secondary drug administration was shortened to 2 h (i.e., until 30 min after infusion). No patients received combined drug administration.

Observation and evaluation criteria for adverse effects. Adverse effects during treatment were observed and recorded according to CTC Version 3 criteria of the NCI. Briefly, the blood pressure, pulse and body temperature before drug administration were

Table 1 **Clinical characteristics of 30 breast cancer patients**

Item	Cases	Percentage(%)
Age		
<50 years	20	66.7
≥50 years	10	33.3
Menstrual status		
Postmenopause	10	33.3
Premenopause	20	66.7
ER and/or PR		
Positive	13	43.3
Negative	17	56.6
Radiotherapy		
Left chest wall	10	33.3
Right chest wall	5	16.7
No	15	50.0
Treatment period of trastuzumab		
Less than 6 months	5	16.7
6 to 12 months	7	23.3
12 months	13	43.3
24 months	5	16.7
Previous chemotherapy drugs		
Anthracyclines	30	100
Anthracyclines and taxanes	13	43.3

ER, Estrogen receptor; PR, Progesterone.

Table 2 **Cardiac safety of 30 breast cancer patients**

	Before treatment	After treatment
Value of left ventricular ejection fraction (LVEF)		
≤45%	0	0
46%–54%	0	2
55%–64%	16	17
≥65%	14	3
Myocardial strain		
Minor	0	24
Moderate	0	0
Severe	0	0
Heart function		
Ⅰ	30	6
Ⅱ	0	24

recorded, blood routine examination, liver and kidney functions and ECG were tested every three weeks and LVEF was tested every three months. In case of LVEF decline to >10% and LVEF <50%, withdrawal of trastuzumab should be considered. According to NYHA classification criteria, patients showing stage III or IV heart failure should discontinue the application of trastuzumab. Extent of myocardial injury was determined referring to the degree of ST-T segment depression in ECG.

Results

Among the 30 cases in this study, 60.0% received treatment for ≥1 year, 23.3% for half a year and 16.7% for less than half a year. The reasons for early drug withdrawal of these patients were mainly economic difficulty or disease progression. No patients stopped treatment because of adverse effects. Overall side effects were rare, and these observed adverse effects including fever, shiver and rash, no hematological toxicity or serious cardiac events.

Intravenous infusion-related symptoms. The main side effects were shivering in one case (3.3%) and fever in two cases (6.7%), both happened during the first infusion. Upon noticing the above symptoms, trastuzumab infusion was temporarily suspended and paracetamol or benzene diphenhydramine etc., were administrated to relieve symptoms. Trastuzumab infusion resumed until completion after symptoms disappeared, and the above adverse effects did not occur again, no other serious side effects.

Cardiac safety assessment. All 30 patients received anthracycline-based chemotherapy previously, of which 13 patients used paclitaxel drugs. Previous to this study, cardiac function evaluation, ECG and echocardiography all appeared normal. Twenty-two of the 30 patients had echocardiography after trastuzumab treatment, and results showed four cases of same level LEVF and 18 cases of declined LEVF decline of, of which nine cases had >10% LEVF decline. After treatment, two patients had LEVF, respectively, <55%, 53% and 48%. Since the LEVF levels of those two patients were close to normal, with normal ECG finding and no obvious symptoms, we continued to treat them under close monitoring. After three months of treatment, their LEVF returned to normal upon examination. ECG test detected 24 cases of mild ST-T wave changes, but since there were no complaints from patients, treatment was not stopped. No symptoms of heart failure were identified among the subjects (Table 2).

Rate of adverse effects. No hematological toxicity was observed in the 30 patients; however, one case voluntarily discontinued drug trastuzumab treatment at the fourteenth administration since bone tuberculosis was detected. One patient ceased trastuzumab treatment on the tenth administration because of liver damage (CTC stage III), detected $HbsAg^+/eAg^+/cAb^+$, as the patient had liver damage before inclusion in this study (CTC stage I); thus, the liver damage might be unrelated to drug treatment. One case had lung nodules identified during a routine checkup after the seventeenth drug administration, which proved tobe bronchioloalveolar carcinoma after surgery.

Discussion

In 1987, Slamon et al.[2] established Her2 as a important prognostic factor in breast cancer in addition to tumor size, lymph node and estrogen receptors; it is also an independent prognostic factor for tumor recurrence and survival duration. In January 2005, the St. Gallen guideline points out that initial diagnosis of breast cancer needs to put Her2 expression status into consideration, i.e.,

Her2 positivity should be treated as a high-risk factor. A number of major international multi-center clinical studies published in 2005 show that post-operative administration of trastuzumab in Her2-positive early breast cancer patients can significantly reduce the risk of relapse.[5,7] Since 2006, the NCCN guideline has recommended the application of adjuvant containing trastuzumab to treat Her2-positive (IHC^{+++} or $FISH^{+}$) and lymph node-positive breast cancer patients. In breast cancer patients with Her2-positive, lymph node-negative and tumors >1 cm, trastuzumab can be used simultaneously with paclitaxel in an AC sequential paclitaxel-based adjuvant regimen, or used sequentially after completion of adjuvant chemotherapy.[4]

Trastuzumab is a humanized monoclonal antibody against Her2 with low heterogeneity and low toxicity to non-target cells; thus, it has fewer side effects, with the major side effect being cardiac adverse events, of which the incidence is fairly low. In HERA trials, the incident rate of serious cardiac toxicity in patients of the treatment group increases 0.5% when compared to the placebo group.[5] Results by B-31 and N9831 show that, the incidence of stage III and IV congestive heart failure in the trastuzumab treatment group are 4.1% and 2.9% respectively.[6] Meanwhile, the study by B-31 also confirms the potential risk factors for cardiac toxicity. The relevant factors are age >50, high blood pressure, EF value at lower than normal range; unrelated factors are diabetes, left chest wall radiation therapy, smoking, family history of heart disease and use of antihyperlipidemic drugs etc.

The result of this study via retrospectively analysis of 30 breast cancer cases is consistent with the results of overseas studies. Twenty-two cases had repeated LVEF after treatment, 18 cases (81.8%) had declined LVEF after treatment, in which nine cases declined by more than 10%. In addition, 24 out of 30 cases had ST-T wave changes during the treatment process. These results suggest that trastuzumab has certain effects on cardiac functions which should be attentively monitored during drug administration. Although no obvious heart failure events emerged during our study, given the bulk of cases reported in previous literature, medical professionals should still be well-aware of this possibility. Furthermore, only two cases of fever and shivering appeared in our study; the symptoms were mild, improved after symptomatic therapy, and did not impact the trastuzumab treatment. No toxicity on other organs was detected in this study.

Our results showed that when applying trastuzumab on Her2-positive patients as post-operative adjuvant therapy, overall, special attention should be paid to the heart and cardiac function should be closely monitored. Nevertheless, the study concludes that trastuzumab rarely damages cardiac functions, so it is safe for most patients. It is important to note, however, that this study only considers a limited number of cases and clinical observation of a larger sample is still needed.

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