

Use of trastuzumab as an adjuvant/neoadjuvant therapy in patients with HER2-positive breast cancer in China

The Nwva study

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Abstract

The aim of this study was to understand current trends in trastuzumab use in China as a neoadjuvant/adjuvant therapy for human epidermal growth factor receptor-2 positive (HER2+) breast cancer and identify factors influencing trastuzumab use.

This was a retrospective, multicenter, cross-sectional study of patients diagnosed with HER2+ breast cancer (stage I–III), between July 2013 and June 2014, at 155 hospitals in 29 provinces/cities in China. Demographic and clinical data, including tumor characteristics and details of adjuvant/neoadjuvant therapies used, were collected. Data analysis included univariate analysis, multivariate logistic regression, and subgroup analyses.

Of 4994 HER2+ patients (mean age 51.1 ± 9.9 years) included, only 29.8% received trastuzumab, with 30.5% in adjuvant therapy and 18.3% in neoadjuvant therapy. The highest rates of adjuvant trastuzumab were in Beijing (59.3%), Jiangsu (57.1%), and Ningxia (50.0%), while those of neoadjuvant trastuzumab were in Guangdong (24.8%), Beijing (14.1%), and Zhejiang (10.7%). Multivariate regression results revealed that factors associated with trastuzumab use were medical insurance cover for trastuzumab, residing locally to the hospital, more lymph node involvement, and more advanced tumor stage. Subgroup analysis revealed that patients receiving neoadjuvant therapy were likely to be younger, premenopausal and non-local, and had lymph node metastases, more advanced tumor, and progesterone receptor positive tumor.

Trastuzumab use in patients with HER2+ breast cancer is relatively low in China, especially for neoadjuvant therapy. Insurance coverage seems to be the most correlated factor that influences the use of trastuzumab in Chinese patients with HER2+ breast cancer.

Abbreviations: CIs = confidence intervals, CFDA = China Food and Drug Administration, ECOG = Eastern Cooperative Oncology Group, ER = estrogen receptor, GCP = Good Clinical Practice, HER2 = human epidermal growth factor receptor-2, HER2+ = HER2-positive, ICH = International Council on Harmonization, KPS = Karnofsky Performance Status, ORs = odds ratios, PR = progesterone receptor, SD = standard deviation.

Keywords: adjuvant therapy, breast cancer, HER2-targeted therapy, neoadjuvant therapy, trastuzumab

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1. Introduction

According to a recent study using data from the National Cancer Registry, breast cancer was the most frequently diagnosed cancer in Chinese women during 2012.^[1] Breast cancer is a heterogeneous group of diseases with several different molecular subtypes, including tumors that show expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2).^[2] Although surgery is the mainstay of treatment, the use of adjuvant (after surgery) or neoadjuvant (before surgery) therapies, including specifically targeted therapies, reduces the risk of disease recurrence and improves survival.^[3] Adjuvant and neoadjuvant therapies can improve progression-free survival and can include chemotherapy, hormonal therapy, radiotherapy, and HER2-directed therapies. There have been tremendous improvements in the efficacy and tolerability of adjuvant/neoadjuvant therapies over the last half-century,^[4] and these treatments now play a vital role in the management of breast cancer.

Approximately 20% of all breast cancers are HER2-positive (HER2+), which was historically indicative of a poor prognosis.^[5,6] The development of trastuzumab and other therapies that

target HER2, including lapatinib, pertuzumab, and trastuzumab-emtansine (T-DM1), has improved progression-free survival and overall treatment response in women with HER2+ breast cancer.^[7,8] Importantly, several meta-analyses have demonstrated that adjuvant or neoadjuvant trastuzumab can enhance the complete response rate and prolong disease-free and overall survival in patients with HER2+ breast cancer.^[9–13]

However, the use of trastuzumab has been restrained in certain regions of the world, particularly in developing countries, due to the high cost or limited availability of the drug. According to a recent publication by Strasser-Weippl et al,^[3] resource-limited countries or populations have reduced access to trastuzumab (and other adjuvant/neoadjuvant therapies) due to economic or logistical considerations. Indeed, several studies have highlighted national, regional, age-related, and racial disparities in the use of trastuzumab in the management of HER2+ breast cancer.^[14–17] However, although information is available regarding trastuzumab use in the USA, Europe, and certain other countries, no large-scale population-based surveys have been conducted in China to explore the utilization of HER2-targeted therapies in patients with HER2+ breast cancer. Therefore, the current study aims to investigate the current use of adjuvant/neoadjuvant trastuzumab therapy in patients with stage I–III HER2+ breast cancer and examine the potential factors influencing the selection of therapy.

2. Materials and methods

2.1. Study design

The Nvwa Study was a retrospective, multicenter, cross-sectional study covering 155 hospitals in 29 provinces/cities in China between July 2013 and June 2014. The registration number for this study is CBCSG024. The study was based on data extracted from patients' hospital records. A list of the number of participating hospitals by province/city is presented in Supplementary Table 1, <http://links.lww.com/MD/C234>.

The study was approved by an independent ethics committee and complied with the Declaration of Helsinki and the Good Clinical Practice (GCP) principles of the International Council on Harmonization (ICH) guidelines. The study was conducted according to the China Food and Drug Administration (CFDA) guidelines.

2.2. Patients

The study included patients diagnosed with or treated for HER2+ breast cancer. Patients had to meet the following criteria for enrollment in the study: age ≥ 18 years; had undergone surgery for breast cancer and received adjuvant/neoadjuvant therapy; had been diagnosed as HER2+ on the basis of a pathological report after the first operation and had histological and cytological documentary evidence; and had been staged lower than T4N3M0 (i.e., had breast cancer of stage I–III). Patients were excluded if they met any of the following criteria: their medical record contained data for $<75\%$ of the parameters analyzed in this study (see section below describing data collection); had pre-invasive carcinoma; had undetected, negative, or unclear HER2 status; or had declared that their information could not be used in the study. All patients included in the final analysis met the HER2+ diagnostic standard according to the *Guidelines and Specifications for the Diagnosis and Treatment of Breast Cancer in China* (2013).^[18]

2.3. Data collection

Data were extracted from the medical records, and additional information was collected through telephone conversations and other means, as necessary. The following data were collected for each patient.

2.3.1. Demographic data. Patient identifier (the initials of their name); date of birth; height; weight; method of payment for treatment (health insurance, public expenditure, self-paid, or unclear); patient address (local or nonlocal); household income; and education level.

2.3.2. Clinical data. Menstruation status (premenopausal or postmenopausal); Karnofsky Performance Status (KPS) score; Eastern Cooperative Oncology Group (ECOG) score; and Breast Imaging Reporting and Data System score.

2.3.3. Surgical data. Surgical method, including sentinel lymph node biopsy and axillary lymph node dissection (for the latter, the number of lymph nodes removed and number positive for cancer were recorded); size of primary tumor and pathological staging; receptor status (whether positive or negative for the ER, PR, and HER2); and the results of immunohistochemistry and fluorescence in situ hybridization for HER2 receptor expression.

2.3.3.1. Neoadjuvant/adjuvant therapy. Whether neoadjuvant or/and adjuvant therapy was received, and which regimen was used; whether trastuzumab was administered and how the patient paid for trastuzumab.

2.4. Subgroup analyses

2.4.1. Factors influencing use of neoadjuvant therapy. HER2-positive breast cancer, found in approximately 20% of patients, is associated with shorter disease-free survival and overall survival.^[19] However, there is strong evidence that the use of trastuzumab as a neoadjuvant therapy can improve the pathological complete response rate and prolong disease-free survival.^[20–22] A previous study identified several potential barriers to the use of neoadjuvant therapy, including patient, system, clinician, and clinical trial related factors.^[23] In the current study, we explored other potential factors that influenced the use of neoadjuvant therapy.

2.5. Statistical analysis

A descriptive statistical analysis was applied. Continuous data were analyzed by the Kolmogorov–Smirnov method to test for a normal distribution and are expressed as the mean \pm standard deviation (SD) or median (quartile, maximum value, and minimum value), as appropriate. Categorical variables are expressed as n (%). Univariate analysis (comparisons of individual factors between trastuzumab and non-trastuzumab groups) was used to identify variables that were entered into a multivariate analysis. Multivariate stepwise logistic regression analysis with backward elimination was used to identify the factors influencing the use of targeted therapy, and the results are expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). For the univariate and multivariate analyses, all patients who had received trastuzumab (whether as neoadjuvant therapy, adjuvant therapy, or both) were considered as 1 group. All statistical tests were 2-sided, and $P < .05$ was considered to indicate statistical significance. SPSS 22.0 (IBM Corp., Armonk, NY) was used for the analyses.

Table 1
Baseline demographic and clinical characteristics of the patients included in the analysis.

Parameter	Value (N = 4994)
Age, y	51.14 ± 9.88
Missing	23 (0.46%)
<35	248 (4.97%)
35–60	3835 (76.79%)
>60	888 (17.78%)
Body mass index, kg/m ²	23.36 ± 3.18
Medical insurance cover for trastuzumab	
No	4317 (86.44%)
Yes	677 (13.56%)
Patient's residence	
Missing	705 (14.12%)
Nonlocal to hospital	1471 (29.46%)
Local to hospital	2818 (56.43%)
Household income, Yuan	
Missing	4023 (80.56%)
<10,000	54 (1.08%)
10,000–30,000	276 (5.53%)
30,000–50,000	284 (5.69%)
>50,000	357 (7.15%)
Hospital classification	
Tertiary	4963 (99.38%)
Secondary	31 (0.62%)
Education level	
Missing	3521 (70.5%)
Primary school or lower	469 (9.39%)
High school	738 (14.78%)
College or higher	266 (5.33%)
Menstrual status	
Missing	495 (9.91%)
Premenopausal	2496 (49.98%)
Postmenopausal	2003 (40.11%)
Lymph node involvement	
Missing	933 (18.68%)
Negative	1901 (38.07%)
1–3 lymph nodes involved	1175 (23.53%)
≥4 lymph nodes involved	985 (19.72%)
Primary tumor stage	
Missing	416 (8.33%)
T1mi	12 (0.24%)
T1a	147 (2.94%)
T1b	278 (5.57%)
T1c	1407 (28.17%)
T2	2514 (50.34%)
T3	220 (4.41%)
Estrogen receptor-positive	2473 (49.92%)
Progesterone receptor-positive	2036 (41.11%)
Hormone receptor-positive	2648 (53.46%)
HER2 immunohistochemistry	
Missing	242 (4.85%)
Negative*	4 (0.08%)
1+	23 (0.46%)
2+	1075 (21.53%)
3+	3650 (73.09%)
HER2 fluorescence in situ hybridization	
Missing	3165 (63.38%)
Negative	20 (0.40%)
Positive	1801 (36.06%)
Critical value	8 (0.16%)
Karnofsky Performance Status score	90 (10,100)
Eastern Cooperative Oncology Group score	0 (0.3)
Breast Imaging Reporting and Data System score	4 (1.5)
Treatment	
Breast-conserving surgery	10.05%

(continued)

Table 1
(continued).

Parameter	Value (N = 4994)
Sentinel lymph node biopsy	15.76%
Neoadjuvant therapy	16.30%
Adjuvant therapy	97.70%
HER2-targeted therapy	
Yes	29.78%
No	70.22%

Data presented as mean ± SD, n (%), or median (maximum, minimum). Note that for some parameters, data were not available for all 4994 participants.

HER2 = human epidermal growth factor receptor-2.

*All 4 patients with a negative HER2 immunohistochemistry result had a positive HER2 fluorescence in situ hybridization result.

†All 20 patients with a negative HER2 fluorescence in situ hybridization result had a positive HER2 immunohistochemistry result. Note that all patients received a positive diagnosis for HER2 breast cancer using at least 1 of these 2 methods (HER2 immunohistochemistry or HER2 fluorescence in situ hybridization).

3. Results

3.1. Patients

A total of 4994 adults (mean age 51.1 ± 9.9 years) diagnosed with HER2+ breast cancer were enrolled in the study, of whom 4879 received adjuvant therapy, 814 received neoadjuvant therapy, and 724 patients received both neoadjuvant and adjuvant therapy. Among all patients included, only 29.8% (1488 patients) were administered trastuzumab therapy; 30.5% of patients receiving adjuvant therapy were given adjuvant trastuzumab (1488/4879 patients), and 18.3% of those receiving neoadjuvant therapy were given neoadjuvant trastuzumab (149/814 patients). All 149 patients who received neoadjuvant trastuzumab were also given adjuvant trastuzumab. The majority of patients (86.4%) did not have medical insurance cover for trastuzumab and over half (55.5%) were premenopausal. Detailed baseline demographics for the patients included in the analysis are presented in Table 1.

3.2. Epidemiological analysis

3.2.1. Geographical differences in the use of trastuzumab therapy. Regional differences in the use of trastuzumab therapy as an adjuvant or neoadjuvant treatment are depicted in Fig. 1. Geographical variation between provinces in the use of trastuzumab therapy was greater for neoadjuvant therapy (Fig. 1A) than for adjuvant therapy (Fig. 1B). Provinces/cities with the 3 highest rates of neoadjuvant trastuzumab therapy were Guangdong (24.8%), Beijing (14.1%), and Zhejiang (10.7%), while 10 of the 29 provinces did not use neoadjuvant trastuzumab therapy in any patients (Supplementary Table 2, <http://links.lww.com/MD/C234>). Provinces/cities with the 3 highest rates of adjuvant trastuzumab therapy were Beijing (59.3%), Jiangsu (57.1%), and Ningxia (50.0%), while those with the lowest rates were Anhui (5.0%), Guizhou (11.1%), and Gansu (12.2%).

3.2.2. Univariate analysis of factors associated with trastuzumab use. Univariate analysis revealed that patients receiving trastuzumab therapy and those not receiving trastuzumab therapy differed significantly with regard to the following factors: age, height, BMI, medical insurance cover for trastuzumab, locality of the patient's residence to the treating hospital, household income, education level, menstrual status, lymph node involvement and primary tumor stage, HER2 immunohistochem-

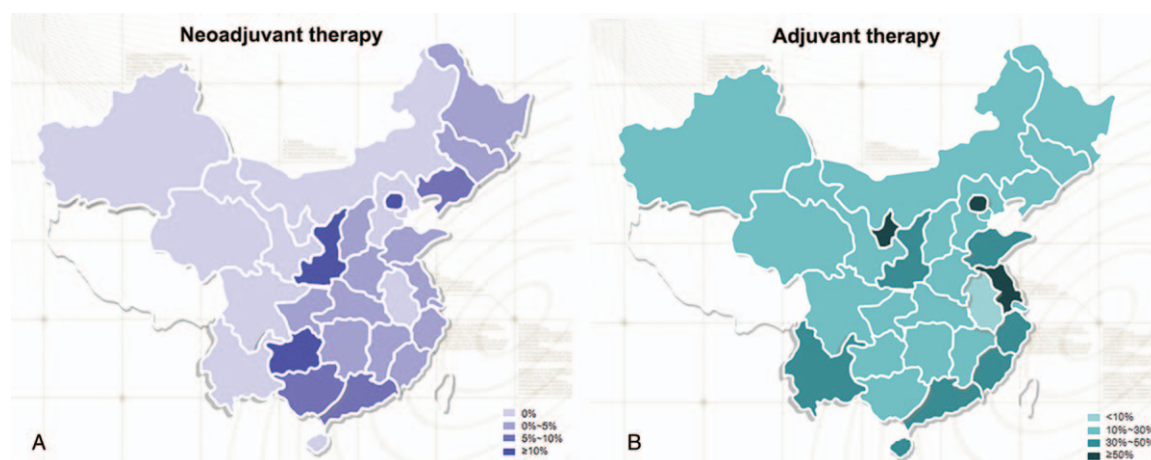


Figure 1. Use of HER2-targeted adjuvant and neoadjuvant therapy in patients with HER2+ breast cancer. (A) Proportion of patients with HER2+ breast cancer receiving neoadjuvant therapy. The percentage value refers to the proportion of all patients (in each province) with HER2+ breast cancer that received neoadjuvant therapy. (B) Proportion of patients with HER2+ breast cancer receiving adjuvant therapy. The percentage value refers to the proportion of all patients (in each province) with HER2+ breast cancer who received adjuvant therapy.

istry, KPS score, and ECOG score (all $P < .05$; Table 2). There were no significant differences between the 2 groups in weight, ER status, PR status, or hormone receptor status (Table 2).

3.3. Multivariate logistic regression analysis

Multivariate logistic regression analysis was performed to identify the factors associated with the use of trastuzumab therapy. The factors identified by the univariate analysis as differing significantly between patients treated with trastuzumab and those not treated with trastuzumab were entered into the multivariate analysis. As height and BMI, KPS, and ECOG scores are similar, only BMI and ECOG were included in multivariate analysis. As differences in policies and standard practices between hospitals of different classifications could also potentially influence our results, hospital classification (Primary, Secondary, and Tertiary as classified in China) was also included in the multivariate analysis. The factors identified by multivariate analysis as significantly associated with trastuzumab therapy are summarized in Table 3. We found that medical insurance cover for trastuzumab was strongly correlated with trastuzumab use (OR: 4.795; 95% CI: 3.416–6.631), while those living locally to the hospital were more likely to be given trastuzumab therapy than those living nonlocally (OR: 2.01; 95% CI: 1.488–2.714). Greater lymph node involvement was also associated with higher use of trastuzumab therapy (OR of 1.426 and 1.783 for ≥ 4 and 1–3 compared with no lymph node involvement, respectively). Compared with advanced tumor stage (T3), patients diagnosed at early tumor stages (T1a, T1b, T1c, and T2) were also more likely to receive trastuzumab therapy (OR: 1.186, 6.094, 2.376, 2.593, respectively). All other factors, including hospital classification, showed no significant association with trastuzumab therapy. No multicollinearity was observed between the included covariates.

3.4. Subgroup analyses

3.4.1. Factors influencing use of trastuzumab as a neoadjuvant therapy. Table 4 summarizes the demographic and clinical characteristics of patients in our study who received neoadjuvant therapy with those who did not receive neoadjuvant therapy. Compared with those who did not receive neoadjuvant therapy, patients who were given neoadjuvant therapy were more

likely to be younger, live less locally to the hospital, be premenopausal, have lymph node metastases, have more advanced tumor stage, and have PR-positive tumor (all $P < .05$; Table 4).

4. Discussion

The current study was conducted in 155 hospitals of different types and sizes that covered almost all provinces/cities of China, except Tibet. To the best of our knowledge, this is the first large-scale, multicenter study in China exploring the utilization of trastuzumab therapy in patients with HER2+ breast cancer. It is envisaged that better knowledge of the factors influencing the use of trastuzumab therapy in China will help to improve the management of patients with HER2+ breast cancer.

Breast cancer was the most common cancer diagnosed in Chinese women in 2012,^[2] and approximately 20% of those with the disease are diagnosed as HER2+. Although trastuzumab therapy is considered standard treatment for early HER2+ breast cancer,^[3] inter-country and intra-country regional variations in the use of trastuzumab therapy have been reported.^[14–16] Our findings demonstrate clear regional differences in the use of trastuzumab in China. Before June 2014, there were limited geographical regions in China that provided trastuzumab to patients with HER2+ breast cancer: Jiangsu province, Guangzhou City, and Qiangdao City. The data provided in the present study indicate that cities and provinces with patients holding medical insurance provide targeted therapy at higher rates. Hospitals treating patients with medical insurance offered trastuzumab treatment to 61.2% of patients (26 hospitals), whereas those in the same geographical areas that did not offer medical insurance-based treatment only provided targeted therapy to 24.9% of patients (129 hospitals). On the basis of the geographical data obtained by this study, patients who resided in more prosperous provinces/cities (with higher incomes) or in more populous urban settings (Beijing, Guangdong, and Zhejiang provinces) were more likely to be treated with neoadjuvant therapy. This is also true of the cities with the highest rates of adjuvant therapy: Beijing, Jiangsu, and Ningxia. All of these areas have populations with greater incomes and higher education levels, suggesting that patients with higher incomes were more likely to receive more comprehensive treatment.

Table 2**Univariate analysis of the factors associated with the use of trastuzumab therapy.**

Parameter	Trastuzumab (N=1487)	Non-trastuzumab (N=3507)	P
Age			.046
Missing, y	7 (0.47%)	16 (0.46%)	
<35	87 (5.85%)	161 (4.59%)	
35–60	1151 (77.4%)	2684 (76.53%)	
>60	242 (16.27%)	646 (18.42%)	
Body mass index, kg/m ²	23.1 ± 3.32	23.47 ± 3.11	.001
Body mass index, kg/m ²			.137
Missing	336 (22.6%)	978 (27.89%)	
<18.0	25 (1.68%)	36 (1.03%)	
18.0–25.0	839 (56.42%)	1813 (51.7%)	
>25.0	287 (19.3%)	680 (19.39%)	
Medical insurance cover for trastuzumab			<.001
No	1073 (72.16%)	3244 (92.50%)	
Yes	414 (27.84%)	263 (7.50%)	
Patient's residence			<.001
Missing	154 (10.36%)	551 (15.71%)	
Nonlocal to hospital	380 (25.55%)	1091 (31.11%)	
Local to hospital	953 (64.09%)	1865 (53.18%)	
Household income, Yuan			<.001
Missing	1170 (78.68%)	2853 (81.35%)	
<10,000	12 (0.81%)	42 (1.2%)	
10,000–30,000	55 (3.7%)	221 (6.3%)	
30,000–50,000	82 (5.51%)	202 (5.76%)	
>50,000	168 (11.3%)	189 (5.39%)	
Hospital classification			.138
Tertiary	1474 (99.13%)	3489 (99.49%)	
Secondary	13 (0.87%)	18 (0.51%)	
Education level			<.001
Missing	1004 (67.52%)	2517 (71.77%)	
Primary school or lower	112 (7.53%)	357 (10.18%)	
High school	238 (16.01%)	500 (14.26%)	
College or higher	133 (8.94%)	133 (3.79%)	
Menstrual status			.002
Missing	83 (5.58%)	412 (11.75%)	
Premenopausal	827 (55.62%)	1669 (47.59%)	
Postmenopausal	577 (38.8%)	1426 (40.66%)	
Lymph node involvement			.004
Missing	294 (19.77%)	639 (18.22%)	
Negative	511 (34.36%)	1390 (39.64%)	
1–3 lymph nodes involved	378 (25.42%)	797 (22.73%)	
≥4 lymph nodes involved	304 (20.44%)	681 (19.42%)	
Primary tumor stage			<.001
Missing	94 (6.32%)	322 (9.18%)	
T1mi	1 (0.07%)	11 (0.31%)	
T1a	38 (2.56%)	109 (3.11%)	
T1b	109 (7.33%)	169 (4.82%)	
T1c	463 (31.14%)	944 (26.92%)	
T2	741 (49.83%)	1773 (50.56%)	
T3	41 (2.76%)	179 (5.1%)	
Estrogen receptor positive	723 (48.88%)	1750 (50.36%)	.342
Progesterone receptor positive	632 (42.79%)	1404 (40.40%)	.118
Hormone receptor positive	785 (53.11%)	1863 (53.61%)	.747
HER2 immunohistochemistry			.002
Missing	17 (1.14%)	225 (6.42%)	
Negative	1 (0.07%)	3 (0.09%)	
1+	4 (0.27%)	19 (0.54%)	
2+	380 (25.55%)	695 (19.82%)	
3+	1085 (72.97%)	2565 (73.14%)	
Karnofsky Performance Status score	90 (10,100)	90 (10,100)	<.001
Eastern Cooperative Oncology Group score	0 (0.3)	0 (0.2)	.031

Data presented as mean ± SD, n (%), or median (maximum, minimum). Note that for some parameters, data were not available for all 4994 participants.

HER2 = human epidermal growth factor receptor-2.

Table 3**Multivariate logistic regression analysis of the factors associated with the use of trastuzumab therapy.**

Parameter	Odds ratio (95% CI)	P
Medical insurance cover for trastuzumab		
No	1.000	
Yes	5.231 (3.865–7.080)	<.001
Patient's residence		
Nonlocal to hospital	1.000	
Local to hospital	1.921 (1.473–2.506)	<.001
Lymph node involvement		
Negative	1.000	
1–3	1.622 (1.235–2.130)	<.001
≥4	1.232 (0.925–1.642)	.154
Primary tumor stage*		
T3	1.000	
T1a	1.565 (0.622–3.939)	.342
T1b	5.359 (2.448–11.731)	<.001
T1c	2.474 (1.306–4.687)	.005
T2	2.598 (1.401–4.817)	.002
HER2 immunohistochemistry		
3+	1.000	
negative	1.638 (0.140–19.151)	.694
1+	0.219 (0.023–2.113)	.189
2+	1.554 (1.176–2.054)	.002

CI = confidence interval.

* Patients diagnosed in stage T1mi and household incomes were not entered into the multivariate logistic regression analysis due to the low number of cases.

The rate of trastuzumab use in developed countries has increased progressively during the past decade.^[24,25] An important finding of the present study was that although more than 97% of patients with HER2+ breast cancer were given adjuvant therapy, only around 30% received trastuzumab therapy. The main factors revealed by the current study as predicting the use of trastuzumab therapy in China were medical insurance cover for trastuzumab, residing locally to the hospital, more lymph node involvement, and primary tumor stage.

Using certain assumptions (including the rate of HER2+ breast cancer), 1 recent study has estimated that Western Europe and the USA procure enough trastuzumab to treat virtually all patients with HER2+ breast cancer, indicating widespread use of this adjuvant therapy in developed countries.^[15] By comparison, many Eastern European countries appeared not to buy sufficient quantities of trastuzumab to treat all patients who might require it,^[15] suggesting that less economically developed regions of the world may show lower use of HER2-targeted therapies. A recent survey of physicians in Mexico, Turkey, Russia, Brazil, and the USA suggested that there were several barriers to the use of trastuzumab in patients with HER2+ breast cancer, such as a lack of insurance coverage, a lack of drug availability at the hospital/clinic, and a prohibitive cost to the patient.^[14] Regional differences within Sweden in the utilization of trastuzumab have also been reported, with the underlying reasons suggested to include differing interpretations in clinical practice, budget-related issues, and variations in coordination, experience, and training.^[16] The present study found that more than two-thirds of patients with HER2+ breast cancer in China did not receive HER2-targeted therapy, in stark contrast to the situation in Western Europe and the USA, and more in keeping with observations made in countries that are less well economically developed. Further studies are merited to compare the use of adjuvant and neoadjuvant HER2-targeted therapy between China, Europe, and the USA.

Economic factors might be one of the most important considerations in the decision to use trastuzumab therapy in

patients with HER2+ breast cancer in China. This is illustrated by the observation that patients with medical insurance cover for trastuzumab were much more likely to be given trastuzumab therapy than those without; indeed, the presence or absence of medical insurance cover for trastuzumab was by far the strongest predictor of trastuzumab therapy use. This is consistent with previous studies suggesting that treatment costs are an important factor determining the administration of trastuzumab and related agents.^[14–16] Particularly concerning observations were that only 14% of patients in the present study held medical insurance cover for trastuzumab and that only a quarter of those without medical insurance were administered trastuzumab therapy. However, due to the retrospective nature of this study, we were unable to collect sufficient information regarding the patients' household income: as many of the patients' records did not include data for household income, we did not include this factor in the multivariate analysis in order to avoid potential bias.

Interestingly, women who had to travel for their treatment were less likely to receive trastuzumab therapy. The underlying reasons for this observation remain unknown, although it is possible that those patients living nonlocally to the hospital may have resided in less prosperous areas and had lower levels of income, limiting their ability to afford the costs of adjuvant treatment. Other factors affecting the use of trastuzumab therapy included lymph node involvement and later tumor stage at diagnosis. The latter findings may indicate that a patient is more willing to accept, or the physician more willing to recommend, trastuzumab therapy when the disease is more advanced.

As a cross-sectional study, the current research has some limitations. The variables selected for the analysis were mostly based on the patients' hospital records, which may have introduced some bias in the analyses of the relationships between the various factors and trastuzumab use. In addition, data were missing for many of the variables analyzed, particularly household income. Incomplete datasets, which may be encountered in retrospective observational studies such as this one, are another potential source of bias whose direction and effect might

Table 4**Comparison of demographic and clinical characteristics of patients who received neoadjuvant therapy with non-neoadjuvant therapy.**

Parameter	Neoadjuvant group (N=814)	Non-neoadjuvant group (N=4180)	P
Age, y			.014
Missing	0 (0%)	23 (0.55%)	
<35	55 (6.76%)	193 (4.62%)	
35–60	631 (77.52%)	3204 (76.65%)	
>60	128 (15.72%)	760 (18.18%)	
Height, cm	158.73 ± 5.45	158.95 ± 5.31	.341
Weight, kg	59.26 ± 8.65	59.2 ± 9.06	.876
Body mass index, kg/m ²	23.5 ± 3.18	23.32 ± 3.18	.189
Medical insurance cover for trastuzumab			.280
No	694 (85.26%)	3623 (86.67%)	
Yes	120 (14.74%)	557 (13.33%)	
Patient's residence			<.001
Missing	79 (9.71%)	626 (14.98%)	
Nonlocal to hospital	306 (37.59%)	1165 (27.87%)	
Local to hospital	429 (52.7%)	2389 (57.15%)	
Household income, Yuan			.401
Missing	694 (85.26%)	3329 (79.64%)	
<10,000	4 (0.49%)	50 (1.2%)	
10,000–30,000	30 (3.69%)	246 (5.89%)	
30,000–50,000	41 (5.04%)	243 (5.81%)	
>50,000	45 (5.53%)	312 (7.46%)	
Education level			.151
Missing	584 (71.74%)	2937 (70.26%)	
Primary school or lower	62 (7.62%)	407 (9.74%)	
High school	128 (15.72%)	610 (14.59%)	
College or higher	40 (4.91%)	226 (5.41%)	
Menstrual status			.011
Missing	51 (6.27%)	444 (10.62%)	
Premenopausal	455 (55.9%)	2041 (48.83%)	
Postmenopausal	308 (37.84%)	1695 (40.55%)	
Lymph node involvement			<.001
Missing	104 (12.78%)	829 (19.83%)	
Negative	276 (33.91%)	1625 (38.88%)	
1–3	217 (26.66%)	958 (22.92%)	
≥4	217 (26.66%)	768 (18.37%)	
Primary tumor stage			<.001
Missing	132 (16.22%)	284 (6.79%)	
T1mi	3 (0.37%)	9 (0.22%)	
T1a	34 (4.18%)	113 (2.7%)	
T1b	32 (3.93%)	246 (5.89%)	
T1c	135 (16.58%)	1272 (30.43%)	
T2	385 (47.3%)	2129 (50.93%)	
T3	93 (11.43%)	127 (3.04%)	
Estrogen receptor positive	377 (46.83%)	2096 (50.52%)	.056
Progesterone receptor positive	297 (36.99%)	1739 (41.91%)	.009
Hormone receptor positive	405 (50.44%)	2243 (54.05%)	.06
HER2 immunohistochemistry			.401
Missing	16 (1.97%)	226 (5.41%)	
Negative	1 (0.12%)	3 (0.07%)	
1+	4 (0.49%)	19 (0.45%)	
2+	165 (20.27%)	910 (21.77%)	
3+	628 (77.15%)	3022 (72.3%)	
KPS score	90 (10,100)	90 (10,100)	.007
ECOG score	0 (0.1)	0 (0.3)	<.001
HER2-targeted therapy			.432
No	581 (71.38%)	2926 (70.00%)	
Yes	233 (28.62%)	1254 (30.00%)	

Data presented as mean ± SD, n (%), or median (maximum, minimum). ECOG = Eastern Cooperative Oncology Group, FISH = fluorescence in situ hybridization, HER2 = human epidermal growth factor receptor-2, KPS = Karnofsky Performance Status

not be well estimated. Well-designed questionnaires will help to reduce bias in future studies.

In conclusion, the current study has analyzed the factors affecting the use of trastuzumab as an adjuvant/neoadjuvant

therapy for HER2+ breast cancer in China. The results show that the main factors influencing the use of trastuzumab therapy in patients with HER2+ breast cancer were medical insurance cover for trastuzumab, household income, locality of the patient's

residence to the hospital, and specific disease-related factors (lymph node metastasis status and primary tumor stage). It is hoped that highlighting these variations in trastuzumab therapy will be of help to future efforts to standardize the use of trastuzumab in the management of breast cancer in China.

Author contributions

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