Original Article

Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer: A real-world retrospective study in Chinese patients

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Abstract

Objective: To assess the long-term effectiveness and safety of trastuzumab in adjuvant therapy for Chinese patients with early-stage human epidermal growth factor 2 (HER2)-positive breast cancer in a real-world setting.

Methods: This retrospective observational study analyzed the medical records of HER2-positive breast cancer patients between 2000 and 2012 at the Chinese Academy of Medical Sciences. Patients who received adjuvant chemotherapy alone or adjuvant chemotherapy followed by/combined with trastuzumab were included. The Kaplan-Meier method was used to estimate disease-free survival (DFS) and overall survival (OS). Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using the Cox regression model.

Results: Of the 1,348 patients analyzed, 909 received chemotherapy alone and 439 received chemotherapy plus trastuzumab. The 3-year, 5-year and 10-year DFS rates were 83.70%, 76.38% and 68.94%, respectively, in the chemotherapy-alone cohort, and 90.21%, 86.19% and 83.45% in the chemotherapy plus trastuzumab cohort. The 3-year, 5-year and 10-year OS rates were 96.10%, 91.40% and 81.88% in the chemotherapy-alone cohort, and 98.17%, 94.91% and 90.01% in the chemotherapy plus trastuzumab cohort. The chemotherapy plus trastuzumab group had a significantly lower risk of disease recurrence and death than the chemotherapy-alone group (DFS: HR=0.50, 95% CI, 0.37–0.68; P<0.001; OS: HR=0.53, 95% CI, 0.34–0.81; P=0.004) after adjusting for covariates. In the 439 patients treated with trastuzumab, multivariate analysis suggested that lymph node positivity, higher T stages, and hormone receptor-negative status were significantly associated with higher risks of disease recurrence, and lymph node positivity and hormone receptor-negative status were significantly associated with higher risks of death. Grade 3/4 adverse events (incidence ≥1%) were more common in patients receiving trastuzumab (54.44% *vs.* 15.73%).

Conclusions: Early-stage HER2-positive breast cancer patients treated with trastuzumab plus adjuvant chemotherapy have a significant survival benefit compared with chemotherapy-alone in real-world settings. Lymph node positivity, hormone receptor-negative status, and higher T stages may be associated with higher risks of recurrence, and effective therapy for patients with these factors is required.

Keywords: Adjuvant therapy; breast cancer; HER2; trastuzumab; risk factors

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Introduction

Breast cancer is the most common malignancy in females worldwide. An estimated 1.38 million (10.9%) new cases of breast cancer occur annually, resulting in 450,000 deaths. The incidence of breast cancer in China is 21.6 per 100,000, and the mortality rate is 5.7 per 100,000 women (1). Breast cancer was the most commonly diagnosed cancer in female Chinese (2). Breast cancer is a heterogeneous disease which can have an early onset. Surgery has been the primary treatment strategy for breast cancer, but many patients experience recurrence or distant metastasis leading to treatment failure eventually. Even early breast cancer has been suggested to be a systemic disease (3,4). The importance of adjuvant therapy for early breast cancer is gradually being recognized (5,6).

Human epidermal growth factor 2 (HER2) oncogene amplification occurs in 15%–25% of all breast cancers. It is associated with aggressive tumor growth and consequent high rates of recurrence and mortality (7,8). Trastuzumab, a monoclonal antibody that inhibits the extracellular domain of HER2, improves survival and quality-of-life in patients with HER2-positive breast cancer. Several studies have shown that the addition of trastuzumab to adjuvant chemotherapy significantly improves disease-free survival (DFS) and overall survival (OS) and reduces the risk of recurrence and death (9-11). At a median of 2 years follow-up, the HERceptin Adjuvant (HERA) trial showed that 1-year of adjuvant treatment with trastuzumab significantly improved DFS and OS in women with HER2-positive early breast cancer as compared with those who did not receive trastuzumab (12). A significant benefit was still observed at 4 years with an improved DFS (13), and at 11 years with improved DFS and OS (14). Subgroup analysis from clinical trials showed that the benefits associated with trastuzumab were independent of tumor size and lymph node positivity (15,16).

Due to the relatively short follow-up periods and strict eligible criteria, results from clinical trials may not be entirely applicable to daily clinical practice. Although several retrospective analyses have demonstrated the prognostic advantage of trastuzumab administration, data are usually derived from studies with small numbers of patients and short follow-up durations. In China, data on the long-term effectiveness of adding trastuzumab to adjuvant therapy in HER2-positive early breast cancer in real-world clinical practice are scarce.

We performed a retrospective study with up to 17 years' follow-up data to determine the long-term survival and safety profiles of adjuvant chemotherapy plus sequential/concurrent trastuzumab compared with adjuvant chemotherapy alone in patients with early-stage HER2-positive breast cancer.

Materials and methods

Study population

This retrospective, observational study collected and screened the medical records of patients with HER2-positive breast cancer at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from January 2000 to December 2012. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Eligible patients had HER2-positive breast cancer and were aged >18 years with an Eastern Cooperative Oncology Group (ECOG) score ≤1 and had received non-metastatic surgery for primary invasive breast cancer. Patients with left ventricular ejection fraction (LVEF) ≥ 55% were eligible. For patients with bilateral breast-infiltrating cancer, only those with two-sided HER2-positive lesions were selected. In terms of the tumor-node-metastasis (TNM) classification, histology, clinical stage, and Ki67 protein of two-sided patients, higher grades/stages in either side of HER2-positive lesions will be labeled in any patients. The hormone receptor status was labeled positive if there was hormone receptor positivity in lesions on either side.

The main exclusion criteria were: 1) any history of invasive ipsilateral or contralateral breast cancer; 2) females undergoing chemotherapy, radiotherapy, anti-HER2 treatment (e.g. with trastuzumab, lapatinib), biological therapy, or immunotherapy; or 3) those with serious heart disease or discomfort or any other serious diseases that could interfere with treatment. Patients were divided into two cohorts according to the use of trastuzumab. The chemotherapy plus trastuzumab group included patients who received chemotherapy followed by or combined with trastuzumab, and the chemotherapy-alone group consisted of patients who received chemotherapy alone.

Data collection and assessment

Trastuzumab was administered intravenously mainly as a 3-

week regimen in patients with primary early breast cancer following surgery, (neo)adjuvant chemotherapy, and radiotherapy (if applicable). Patients received trastuzumab in a loading dose of 8 mg/kg per body weight initially, and then a maintenance dose of 6 mg/kg once every 3 weeks for 1 year, or as a weekly regimen with an initial dose of 4 mg/kg and subsequent maintenance doses of 2 mg/kg weekly for 1 year.

HER2-positivity was defined as grade 3+ staining intensity by immunohistochemistry (IHC), or confirmation of *HER2* gene amplification by fluorescence *in situ* hybridization (FISH). Data collected at baseline included demographic, clinical pathologic, molecular feathers, and adjuvant therapies. Tumor staging was performed according to the 2002 American Cancer Research Joint Committee (AJCC) Breast Cancer Staging Standard (6th edition), with the staging determined by the diameter of the largest invasive tumor for those with multiple lesions (2 or more lesions in a single quadrant of the breast) or multiple central lesions (2 or more lesions in the same breast with different quadrants). LVEF was measured by echocardiography or multiple-gated acquisition scanning.

Follow-up and outcome assessments

Patients were followed up via phone calls or at visits once every 3–4 months for the first 2 years after surgery, then once every 6 months (between 2 and 5 years), and thereafter once yearly (after 5 years) following surgery. The follow-up period was up to December 2017. An event was defined as a new primary breast cancer, a first recurrence, distant relapse, or death from any cause. The primary endpoint was DFS, which was defined as the time from the start of initial treatment to the first event. Secondary endpoints included OS (defined as the time from the date of treatment to death from any cause or loss of follow-up) and adverse events (AEs) which were graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events, version 3.0 (17).

Statistical analysis

Continuous variables were expressed as $\overline{x}\pm s$ and categorical variables as percentages. The Kaplan-Meier method was used to estimate DFS and OS rates. The log-rank test was used to assess differences between groups. Hazard ratio (HR) and 95% confidence interval (95% CI) were estimated by using the Cox proportional hazard model. A two-sided P<0.05 was considered statistically significant. All data were analyzed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) and R software (Version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' characteristics

A total of 1,348 females with HER2-positive early breast cancer were were finally analyzed, including 909 patients in the chemotherapy-alone group and 439 patients in the chemotherapy plus trastuzumab group. The patients' baseline characteristics are shown in *Table 1*. Patients in chemotherapy-alone group were older, with higher proportions of progesterone receptor-positive (PR+) and hormone receptor-positive (HR+) statuses, and a lower proportion received radiotherapy. Among the 439 trastuzumab-treated patients, 280 patients received concurrent trastuzumab, 151 patients received sequential trastuzumab, and 8 patients' the scheduling of trastuzumab in combination therapy was unknown.

Survival outcomes

During a median follow-up of 79.16 (range: 5.02–247.62) months for the 1,348 patients, 319 (23.66%) DFS events were observed, including 253 (18.77%) in the chemotherapy -alone cohort, and 66 (4.90%) in the chemotherapy plus trastuzumab cohort. The 3-year, 5-year, and 10-year DFS rates were 83.70%, 76.38% and 68.94%, respectively, in the chemotherapy-alone cohort, and 90.21%, 86.19% and 83.45%, respectively, in the chemotherapy plus trastuzumab cohort (*Figure 1*). Chemotherapy plus trastuzumab significantly lowered the risk of recurrence in comparison with chemotherapy-alone (HR=0.50, 95% CI, 0.37–0.68; P<0.001). The 3-year, 5-year, and 10-year DFS rates for concurrent and sequential trastuzumab administration were shown in *Figure 2*. HRs for DFS between the chemotherapy-alone and chemotherapy plus trastuzumab cohorts were consistent across subgroups (*Table 2*).

In all 1,348 patients, 165 (12.24%) breast cancer deaths occurred during follow-up, including 135 (10.01%) in the chemotherapy-alone cohort, and 30 (2.22%) in the chemotherapy plus trastuzumab cohort. The 3-year, 5-year, and 10-year OS rates were 96.10%, 91.40% and 81.88%, respectively, in the chemotherapy-alone cohort, and 98.17%, 94.91% and 90.01%, respectively, in the chemotherapy plus trastuzumab cohort (*Figure 3*).

Table 1 Main baseline characteristics in chemotherapy alone and chemotherapy plus trastuzumab cohorts

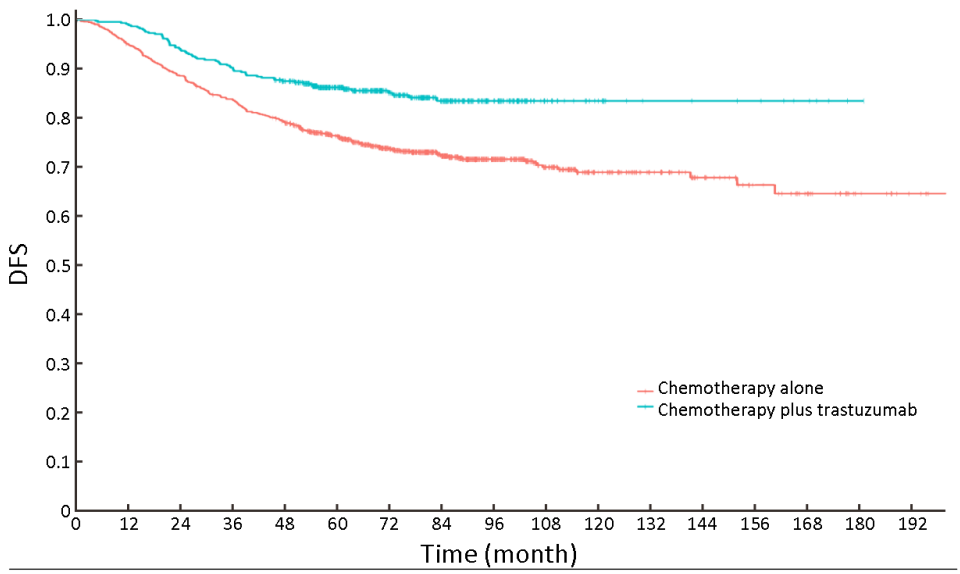
Characteristics	Chemotherapy alone (n=909) [n (%)]	Chemotherapy plus trastuzumab (n=439) [n (%)]	P
Age (year)			0.012
<40	156 (17.16)	91 (20.73)	
40–50	324 (35.64)	178 (40.55)	
≥50	429 (47.19)	170 (38.72)	
Lymph node			0.479
N0	440 (48.40)	197 (44.87)	
N1	237 (26.07)	120 (27.33)	
N2	115 (12.65)	67 (15.26)	
N3–N4	117 (12.87)	55 (12.53)	
Histology type			<0.001
I	11 (1.21)	7 (1.59)	
I–II	454 (49.94)	224 (51.03)	
II–III	276 (30.36)	165 (37.59)	
IDC	139 (15.29)	28 (6.38)	
Others	29 (3.19)	15 (3.42)	
Tumor stage			0.083
T1	441 (48.51)	232 (52.85)	
T2	430 (47.30)	197 (44.87)	
T3–T4	34 (3.74)	8 (1.82)	
Unknown	4 (0.44)	2 (0.46)	
Tumor clinical stage			0.743
0	22 (2.42)	14 (3.19)	
I	226 (24.86)	108 (24.60)	
II	421 (46.31)	194 (44.19)	
III–IV	240 (26.40)	123 (28.02)	
Neoadjuvant treatment			0.834
No	771 (84.82)	375 (85.42)	
Yes	138 (15.18)	64 (14.58)	
Chemotherapy			<0.001
A no T	160 (17.60)	24 (5.47)	
T no A	51 (5.61)	139 (31.66)	
T plus A	592 (65.13)	258 (58.77)	
Others	8 (0.88)	1 (0.23)	
Unknown	98 (10.78)	17 (3.87)	
Radiotherapy			0.047
No	495 (54.46)	213 (48.52)	
Yes	414 (45.54)	226 (51.48)	
ER status			0.271
Negative	427 (46.97)	221 (50.34)	
Positive	482 (53.03)	218 (49.66)	
PR status			0.027

Table 1 (*continued*)

Table 1 (*continued*)

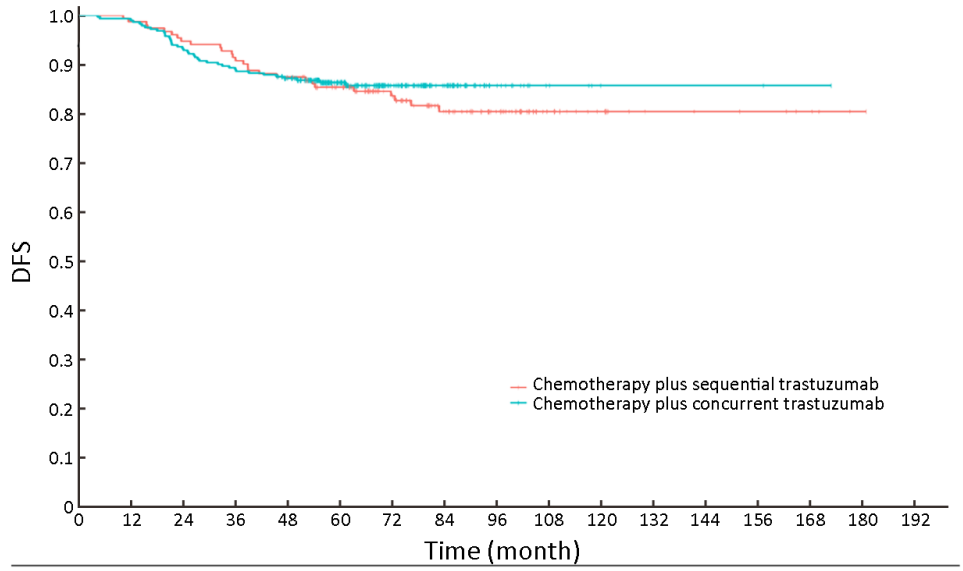
Characteristics	Chemotherapy alone (n=909) [n (%)]	Chemotherapy plus trastuzumab (n=439) [n (%)]	P
Negative	400 (44.00)	222 (50.57)	
Positive	509 (56.00)	217 (49.43)	
Hormone receptor status			0.009
Negative	313 (34.43)	184 (41.91)	
Positive	596 (65.57)	255 (58.09)	
Ki67			<0.001
≤14	116 (12.76)	61 (13.90)	
>14	367 (40.37)	258 (58.77)	
Unknown	426 (46.86)	120 (27.33)	
Trastuzumab treatment			–
Sequential	–	151 (34.40)	
Concurrent	–	280 (63.78)	
Unknown	–	8 (1.82)	

IDC, infiltrating ductal carcinoma; A, anthracyclines; T, taxanes; ER, estrogen receptor; PR, progesterone receptor.



Treatment cohorts	3-year	5-year	10-year
Chemotherapy alone cohort (n=909)			
No. of events	148	213	250
Disease-free survival rate (%)	83.70	76.38	68.94
95% confidence interval (%)	81.33–86.13	73.66–79.21	65.39–72.68
Chemotherapy plus trastuzumab cohort (n=439)			
No. of events	43	60	66
Disease-free survival rate (%)	90.21	86.19	83.45
95% confidence interval (%)	87.47–93.03	83.00–89.50	79.68–87.39

Figure 1 Kaplan-Meier curves of disease-free survival (DFS) in chemotherapy-alone and chemotherapy plus trastuzumab cohorts (P<0.0001).



Treatment cohorts	3-year	5-year	10-year
Chemotherapy plus sequential tratuzumab cohort (n=151)			
No. of events	12	22	27
Disease-free survival rate (%)	91.39	85.32	80.38
95% confidence interval (%)	87.02–95.98	79.84–91.19	73.83–87.51
Chemotherapy plus concurrent trastuzumab cohort (n=280)			
No. of events	30	38	39
Disease-free survival rate (%)	89.29	86.30	85.69
95% confidence interval (%)	85.74–92.98	82.33–90.45	81.60–89.99

Figure 2 Kaplan-Meier curves of disease-free survival (DFS) in concurrent trastuzumab and sequential trastuzumab cohorts. Analysis based on data excluding 8 patients with unknown scheduling of trastuzumab.

Chemotherapy plus trastuzumab significantly lowered the risk of death in comparison with chemotherapy-alone (HR=0.53, 95% CI, 0.34–0.81; P=0.004). The 3-year, 5-year, and 10-year OS rates for concurrent and sequential trastuzumab administration were shown in *Figure 4*. HRs for OS between the chemotherapy-alone and chemotherapy plus trastuzumab cohorts were consistent across subgroups (*Table 2*).

Risk factors for breast cancer recurrence and death in patients treated with trastuzumab

In the 439 early-stage breast cancer patients who were treated with trastuzumab, multivariable analysis showed that lymph node positivity, higher T stages, and hormone receptor-negative status were significantly associated with higher risks of disease recurrence, and lymph node positivity and hormone receptor-negative status were significantly associated with higher risks of death (*Table 3*).

Safety

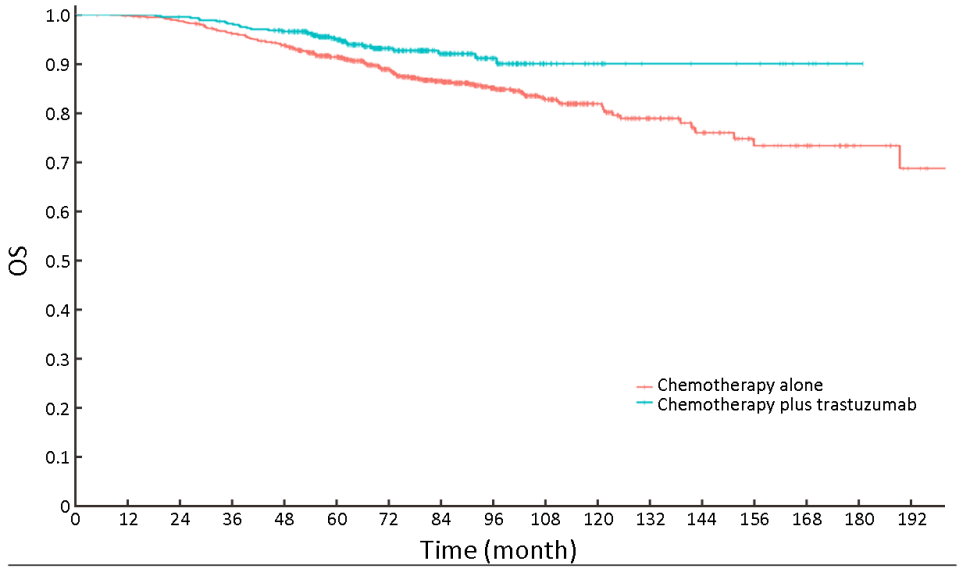
AEs occurred more frequently in the trastuzumab group. In the chemotherapy plus trastuzumab cohort, the most frequent AEs were thrombocytopenia (100%), neutropenia (69.93%), nausea and vomiting (69.70%), leukopenia (69.25%), and hair loss (38.04%), while nausea and vomiting (56.33%), leukopenia (27.61%), and neutropenia (27.61%) were the most frequent AEs in the chemotherapy-alone cohort. Grade 3/4 AEs (incidence ≥ 1%) were more common in the chemotherapy plus trastuzumab cohort (54.44% *vs*. 15.73% with chemotherapy -alone; P<0.001). These AEs were resolved after dosage adjustment and/or drug suspension. No patients discontinued treatment due to AEs.

Twelve patients in the chemotherapy plus trastuzumab cohort developed cardiac symptoms, two of whom experienced palpitations and a greatly decreased LVEF. One patient who received combined adjuvant

Table 2 Overall and subgroups HRs for DFS and OS with chemotherapy alone and chemotherapy plus trastuzumab treatment

Variables	DFS			OS		
	n/N*	HR**	95% CI	n/N*	HR**	95% CI
Overall	317/1,342	0.50	0.37–0.68	164/1,342	0.53	0.34–0.81
Age (year)						
<40	76/246	0.39	0.22–0.70	39/246	0.21	0.08–0.56
40–50	106/497	0.46	0.26–0.78	55/497	0.42	0.21–0.83
≥50	135/599	0.60	0.37–0.96	70/599	0.65	0.33–1.29
Lymph node						
Negative	89/637	0.44	0.23–0.83	39/637	0.42	0.16–1.10
Positive	228/705	0.53	0.37–0.74	125/705	0.53	0.33–0.86
Tumor stage						
T1	140/673	0.53	0.35–0.82	64/673	0.65	0.35–1.23
T2	154/627	0.46	0.30–0.71	86/627	0.41	0.22–0.74
T3–T4	23/42	1.56	0.46–5.29	14/42	0.71	0.08–6.62
Tumor clinical stage						
0–I	47/370	0.45	0.22–0.94	18/370	0.48	0.14–1.67
II	131/615	0.56	0.35–0.89	60/615	0.53	0.27–1.04
III–IV	139/357	0.50	0.32–0.80	86/357	0.43	0.24–0.77
Neoadjuvant treatment						
No	247/1,141	0.49	0.35–0.68	129/1,141	0.47	0.29–0.78
Yes	70/201	0.61	0.34–1.09	35/201	0.51	0.22–1.17
Chemotherapy						
A no T	60/184	0.80	0.30–2.11	31/184	0.24	0.03–1.82
T no A	32/189	0.37	0.16–0.85	9/189	0.49	0.12–2.02
T plus A	211/849	0.46	0.33–0.66	117/849	0.48	0.30–0.77
Radiotherapy						
No	129/702	0.49	0.30–0.79	57/702	0.38	0.16–0.89
Yes	188/640	0.49	0.33–0.72	107/640	0.58	0.35–0.95
ER status						
Negative	165/645	0.46	0.31–0.69	92/645	0.51	0.30–0.89
Positive	152/697	0.53	0.35–0.80	72/697	0.49	0.25–0.97
PR status						
Negative	162/618	0.50	0.34–0.75	85/618	0.56	0.33–0.98
Positive	155/724	0.44	0.27–0.70	79/724	0.39	0.19–0.80
Hormone receptor status						
Negative	132/494	0.53	0.34–0.81	72/494	0.61	0.34–1.09
Positive	185/848	0.45	0.29–0.68	92/848	0.39	0.21–0.75
Ki67						
≤14	33/177	0.55	0.20–1.48	15/117	0.49	0.14–1.71
>14	137/624	0.43	0.28–0.65	74/624	0.48	0.27–0.86

HR, hazard ratio; DFS, disease-free survival; OS, overall survival; A, anthracyclines; T, taxanes; ER, estrogen receptor; PR, progesterone receptor; 95% CI, 95% confidence interval; *, event number/patient number. Six patients were excluded for multi-factor analysis due to missing relevant data, and then 1,342 patients were analyzed; **, HRs and 95% CI were derived from multivariable proportional hazards regression model with adjustment for the potential confounders such as age, hormone receptor status, chemotherapy, radiotherapy, neoadjuvant treatment, tumor stage, lymph node, tumor clinical stage and Ki67. Subgroup analyses for chemotherapy and Ki67 were based on data excluding patients with unknown or other status.



Treatment cohorts	3-year	5-year	10-year
Chemotherapy alone cohort (n=909)			
No. of events	35	76	124
Overall survival rate (%)	96.10	91.40	81.88
95% confidence interval (%)	94.90–97.40	89.60–93.30	78.69–85.21
Chemotherapy plus trastuzumab cohort (n=439)			
No. of events	8	21	30
Overall survival rate (%)	98.17	94.91	90.01
95% confidence interval (%)	96.93–99.44	92.80–97.07	96.04–94.16

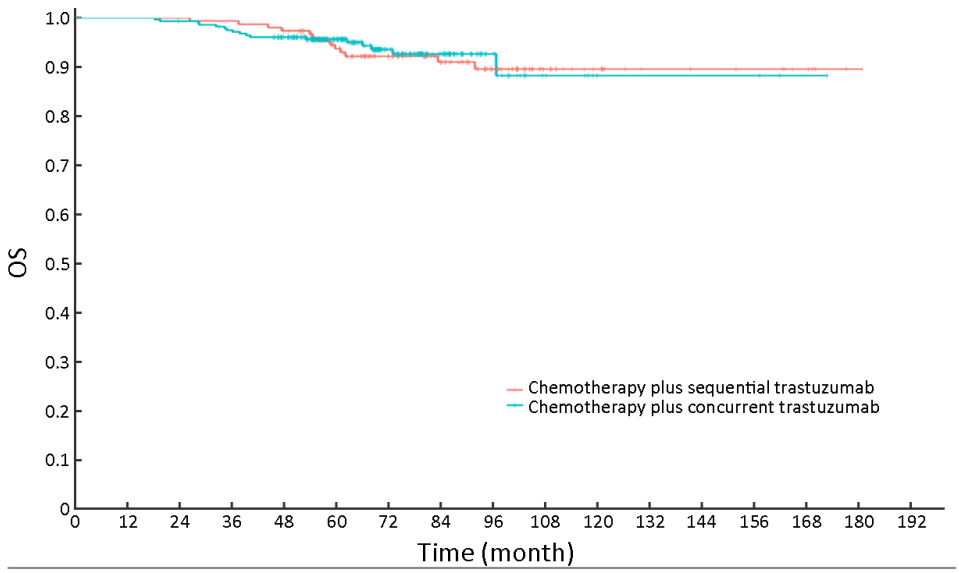
Figure 3 Kaplan-Meier curves of overall survival (OS) in chemotherapy-alone and chemotherapy plus trastuzumab cohorts (P=0.0028).

chemotherapy [taxotere (TXT) + carboplatin] plus trastuzumab was found to have a decreased LVEF of 56% (20% reduction), which was reversible upon withdrawal of trastuzumab. In this patient, trastuzumab was re-administered after the completion of chemotherapy and no adverse effects were observed. The LVEF of the other patients who received combined adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab) and supplementary weekly administration of trastuzumab was decreased to 50% (12% reduction). The cardiac symptoms were relieved after the weekly dosage of trastuzumab was reduced from 120 mg to 100 mg. In the remaining 10 patients with cardiotoxicity, palpitations (5 cases), tachycardia (2 cases), ventricular premature beats (2 cases), and sinus arrhythmia (1 case) were reported. Of the patients in chemotherapy-alone cohort, only two had palpitations (with adjuvant chemotherapy regimens of TXT plus epirubicin and TXT plus cisplatin, respectively), and no significant cardiac adverse effects were reported in the remaining patients. During the study period, no instances of congestive heart failure (CHF) related to treatment were reported.

Discussion

The long-term effectiveness of combined trastuzumab in adjuvant chemotherapy for Chinese patients with HER2-positive early breast cancer is unclear. This study demonstrated favorable survival outcomes and a manageable safety profile with trastuzumab given in addition to adjuvant chemotherapy for HER2-positive early breast cancer in Chinese real-world clinical practice over a period up to 20 years.

A previous meta-analysis has reported that DFS and OS rates were significantly favorable in patients with HER2-positive early breast cancer who received trastuzumab-containing regimens (18). In our study, the benefit of trastuzumab was associated with a better DFS and OS in the overall cohort and this benefit was consistent across subgroups. Younger HER2-positive patients (<40 years of



Treatment cohorts	3-year	5-year	10-year
Chemotherapy plus sequential tratuzumab cohort (n=151)			
No. of events	1	9	13
Overall survival rate (%)	99.34	3.72	89.57
95% confidence interval (%)	98.05–100	89.83–97.79	84.13–95.36
Clhemotherapy plus concurrent trastuzuumab cohort (n=280)			
No. of events	7	12	17
Overall survival rate (%)	97.50	95.64	88.23
95% confidence interval (%)	95.70–99.30	93.26–98.09	79.53–97.89

Figure 4 Kaplan-Meier curves of overall survival (OS) in concurrent trastuzumab and sequential trastuzumab cohorts. Analysis based on data excluding 8 patients with unknown scheduling of trastuzumab.

age) may benefit more in DFS and OS with the addition of trastuzumab to adjuvant chemotherapy. The GHEA study (19), which retrospectively analyzed the records of 1,002 who were treated with sequential adjuvant trastuzumab, reported similar results but the median follow-up in this study was 32 months as compared with 69.9 months in the chemotherapy plus trastuzumab cohort in our study. Another retrospective evaluation of HER2-positive early breast cancer treated with or without trastuzumab in routine clinical practice between 2006 and 2008 also showed that treatment that did not include trastuzumab was associated with an increased risk of recurrence; however, the number of patients involved in this analysis (n=128) was small (20). The results of our analysis align with those in HER2-positive patients reported by Inwald *et al*. (21) who showed that those treated with chemotherapy and/or endocrine therapy without trastuzumab had worse OS than the control groups. Our evaluation of trastuzumab in routine clinical practice was conducted in 1,348 HER2-positive patients, and it showed that regardless of whether trastuzumab was administered concurrently or sequentially, it significantly improved DFS and OS.

Despite the obvious survival benefits in patients treated with the combination of chemotherapy and trastuzumab, patients with lymph node positivity, hormone receptor-negative status, and higher T stage were found to have a greater risk of recurrence. Previous research has suggested that young age may be an independent risk factor for disease recurrence and death (22,23). Lymph node positivity and hormone receptor status have also been considered as important prognostic factors for HER2-positive breast cancer patients (24,25). A more effective treatment is needed for those patients with a high risk of recurrence or death in future clinical practice.

This retrospective study also reported the safety of

Table 3 Risk factors associated with breast cancer DFS and OS in 439 early-stage breast cancer patients treated with trastuzumab

Risk factors	DFS (n=66)*		OS (n=30)*	
	HR**	95% CI	HR**	95% CI
Lymph node				
Negative	Reference		Reference	
Positive	3.71	2.01–6.85	4.30	1.65–11.24
Tumor stage				
T1	Reference		–	
T2	0.90	0.54–1.49	–	–
T3–T4	4.44	1.56–12.64	–	–
Hormone receptor status				
Positive	Reference		Reference	
Negative	1.74	1.07–2.83	2.32	1.10–4.89

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; *, event number; **, HRs and 95% CI were derived from multivariable proportional hazards regression model with mutually adjustment. For example, the HR of DFS for lymph node was estimated in the multivariate model with adjustments for tumor stage and hormone receptor status. The HR of DFS for hormone receptor status was adjusted for the tumor stage and lymph node in the model. For DFS, two patients were excluded from the regression model because of the unknown of the tumor stage.

trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer, showing that it is both feasible and well-tolerated in routine clinical practice. The cardiac safety of trastuzumab in our study appeared to be better than that reported in previous studies: other studies have shown that in trastuzumab-treated breast cancer patients, 4.7% developed cardiac insufficiency, with 1% of patients experiencing serious adverse reactions that led to trastuzumab withdrawal (26). However, in our study, the incidence of cardiovascular AEs was very low, and no patients developed CHF. This may be due to younger patients in our study, and treatment differences by physicians. A previous study also showed that concurrent or sequential administration of trastuzumab and anthracyclines is safe for adjuvant treatment of HER2-positive breast cancers (27), which is similar to our observations.

Our study has important strengths. The results were obtained in a large series of patients, all treated according to standard guidelines in the same institute and with a long follow-up period, which enabled us to capture the majority of late recurrences. Our results have demonstrated the real-world benefit of trastuzumab in patients with various types of HER2-positive breast cancer. We consider these results are clinically meaningful to present day clinical practice in China as they demonstrate the effectiveness and safety of trastuzumab. And they also provide some useful statistics for future studies.

Our study also has substantial limitations. Because of its retrospective nature, several biases need to be taken into account when interpreting the findings. As a single center, retrospective analysis reporting hospital information system data, extrapolation of the results should be undertaken with caution. The unbalanced baseline characteristics, especially the heterogeneity of adjuvant regimens, could have potentially affected clinical outcomes. Nevertheless, it appears that trastuzumab is effective regardless of the type of chemotherapeutic regimens received previously. For patients with HER2-positive breast cancer, anthracycline adjuvant therapy has been found to be associated with a better prognosis than non-anthracycline-based chemotherapy (28-31). In addition, the follow-up time for the chemotherapy-alone and chemotherapy plus trastuzumab regimens in our study was different; fewer patients received trastuzumab and medical records were non-standardized in earlier years. Only 49 of 290 patients received trastuzumab from January 2001 to December 2007, which is in line with the real-world use of trastuzumab in China.

Conclusions

This study suggests that early-stage HER2-positive breast cancer patients can significantly benefit from the use of trastuzumab with adjuvant chemotherapy in real-world clinical settings. Effective therapy is needed for patients at increased risk of recurrence or death such as those with lymph node positivity, hormone receptor-negative status,

or higher T stages.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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