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Original Article

A multicenter real-world study comparing the clinical equivalence of trastuzumab biosimilar HLX02 and reference trastuzumab in the treatment of HER-2-positive breast cancer

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Abstract: As the first trastuzumab biosimilar introduced in China, there are few studies on the clinical application of HLX02, especially in combination with other antitumour drugs, for the treatment of HER-2-positive breast cancer. A multicenter retrospective study was conducted in three hospitals in China to select patients with HER-2-positive breast cancer who met the inclusion criteria and received HLX02 or the reference trastuzumab. Ninety-six patients diagnosed with HER-2-positive breast cancer were finally included and divided into two groups and treated with HLX02 or the reference trastuzumab. The results showed no significant differences in pathological complete response (70.0% vs. 76.2%; P=1.000) and overall response rate (91.9% vs. 94.9%; P=0.673) between the two groups. Kaplan-Meier survival curves also showed no significant difference in time-to-event variables between the two groups (log-rank P=0.48). Safety was also comparable in both groups. In conclusion, among patients with HER2-positive breast cancer, HLX02 demonstrated equivalent efficacy and safety to its reference trastuzumab, both in neoadjuvant chemotherapy and in postoperative adjuvant therapy. However, clinical equivalence studies between HLX02 and the original trastuzumab drug remain challenging. Future research should focus on the clinical exchange between biosimilars and original drugs, as well as the extrapolation of biosimilars' indications.

Keywords: HLX02, trastuzumab, biosimilar, breast cancer, real-world study

Introduction

By 2020, breast cancer had become the most common cancer in the world, replacing lung cancer, and the main cause of cancer-related death in women due to its high global incidence of 2.26 million new cases (https://www.iarc.who.int/faq/latest-global-cancer-data-2020-qa). Approximately 20% of breast cancers express human epidermal growth factor receptor-2 (HER-2), which means that the tumour cells are more malignant, progress faster, and are more likely to metastasize and recur, while conventional radiotherapy and chemotherapy have low specificity. Thus, the diagnosis and treatment of HER-2-positive breast cancer has become a research hotspot [1, 2]. The advent of trastuzumab (Herceptin®, Genentech/Roche, Inc.), which has targeted patients with HER-2-positive breast cancer, has significantly improved their prognosis by specifically acting on HER-2 on the surface of cancer cells [3, 4]. Nevertheless, the high cost and limited availability of trastuzumab preclude its use by many eligible patients, especially in developing countries, such as China [5, 6].

The advent of biosimilars has not only introduced alternatives with similar clinical effectiveness to that of the original drugs but also reduced the cost of medication for patients [7]. Biosimilars are biological products that are similar in quality, safety and efficacy to the approved reference product for therapeutic use (https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview).

HLX02 (Zercepac®, Henlius, Inc.) was the first China-manufactured, globally evaluated trastuzumab biosimilar, and several recent studies have shown that HLX02 has similar safety, efficacy, tolerability and immunogenicity to its reference trastuzumab (RTZ) [8-10]. Nevertheless, due to the large molecular weight and complex molecular structure of biosimilars, they cannot reach the exact same level as the original drug in terms of active ingredients, structure and function [11].

A phase III trial compared the efficacy of HLX02 and RTZ combined with docetaxel in patients with recurrent or metastatic HER-2-positive breast cancer, showing that HLX02 and RTZ had equivalent efficacy and adverse events [10]. However, due to the strict inclusion and exclusion criteria set in the premarketing clinical randomized controlled study (RCT), although the internal authenticity of the study itself has been improved, the external authenticity is poor, which limits the practical application and promotion of the research results [12]. In actual clinical practice, the condition of HER-2-positive breast cancer patients is usually heterogeneous, and they may need to be treated together with other drugs, such as pertuzumab [13]. Moreover, based on the fact that the development of biosimilars in China is only in the beginning stages, many ordinary people, and even doctors and pharmacists, do not completely understand biosimilars and even worry about their efficacy and safety [14]. Thus, real-world research on biosimilars is encouraged in China to further improve the relevant biosimilar systems. As the first trastuzumab biosimilar marketed in China, it is necessary to conduct a comprehensive clinical evaluation of whether HLX02 achieves clinical consistency with the original drug from a real-world perspective and thus provide an evidence-based basis for the clinical replacement of biosimilars in China.

Materials and methods

Study design and patients

Clinical characteristics of patients were collected retrospectively from three tertiary level-A hospitals in Guangdong Province, China, between August 2020 and August 2022. This was a retrospective, observational cohort study so a waiver of informed consent was obtained. This study was approved by the Guangdong Provincial Hospital Association and the Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University. The major inclusion criteria were (a) patients with a pathological diagnosis of HER-2-positive breast cancer and (b) patients who had received at least one cycle of the RTZ or HLX02 chemotherapy regimen. The major exclusion criteria were (a) patients who had previously been treated in other hospitals; (b) patients with incomplete medical records or missing detailed data; (c) patients with other cancers; (d) patients who used RTZ concomitantly with HLX02; and (e) patients with renal failure or requiring hemodialysis.

Study variables

Data collected from the patient's medical records included clinical characteristics at diagnosis, such as age, weight, height, clinical stage, Eastern Cooperative Oncology Group performance status (ECOG PS), lymph node status, estrogen receptor status, progesterone receptor status, number of lymph node metastases, presence of distant organ metastases, and Ki67 level. We calculated the numbers of people receiving neoadjuvant chemotherapy and neoadjuvant chemotherapy combination regimens. Clinical staging was classified into stages I to IV using the tumor-node-metastasis (TNM) staging system [15].

Treatment and dosing information

In neoadjuvant chemotherapy or adjuvant chemotherapy, when trastuzumab was used, all patients received an 8 mg/kg RTZ or HLX02 intravenous loading dose in the first cycle and then received 6 mg/kg combined with other antineoplastic agents every 3 weeks. The treatment cycle and the number of follow-up targeted treatments varied according to the patient's disease stage, response to initial chemotherapy and individual treatment tolerance. Most patients were planned to receive six cycles of neoadjuvant chemotherapy or adjuvant chemotherapy and to then continue to receive trastuzumab targeted therapy for one year.

Assessments and definition of outcomes

For patients receiving neoadjuvant chemotherapy, clinical response was assessed according to the Miller-Payne system classification,

whereas for patients receiving postoperative adjuvant chemotherapy, response was assessed based on imaging reports following Response Evaluation Criteria in Solid Tumors (RECIST), and treatment-related adverse events were recorded [16, 17]. Adverse events were graded based upon National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 grading.

The primary patient outcome was pathologic complete response (pCR), defined as the absence of invasive tumor cells in the breast tissue and in axillary lymph nodes, regardless of whether there was residual ductal carcinoma in situ (DCIS). The secondary outcomes were overall response rate (ORR), progression-free survival (PFS), and the incidence of each adverse reaction. The ORR was defined as the sum of the complete response (CR) and partial response (PR) rates. Progression-free survival (PFS) was defined as the time from the start of chemotherapy to disease progression, including any recurrence or death from any cause. Patients without documented disease progression or death at the time of the final analysis were censored at the date of the last follow-up, with a cutoff date of 1 August 2022. We defined a significant decrease in left ventricular injection fraction (LVEF) as a decrease of ten percentage points from baseline or an absolute drop of less than 50%.

Statistical analysis

The Shapiro-Wilk test was used to determine whether continuous variables were normally distributed, and continuous variables that followed a normal distribution were described as the mean, standard deviation, median, and interquartile range. Differences between categorical variables were assessed using the chi-square test or Fisher's exact test, and differences between continuous variables were assessed using Student's t test or the Mann-Whitney U test. In addition, subgroup analysis of efficacy parameters was performed according to chemotherapy modality (preoperative neoadjuvant chemotherapy versus postoperative adjuvant chemotherapy).

PFS was analyzed using the Kaplan-Meier method, and the log-rank test was used to identify variables that were statistically significant. Univariate and multivariate analyses were performed with the Cox proportional hazards regression model to determine the effect of drug type on PFS. In multivariate analysis, factors with $P < 0.1$ were preferentially included, and if all factors had $P > 0.1$, age, weight, height, clinical stage, lymph node status, estrogen receptor status, progesterone receptor status, number of lymph node metastases, presence of distant organ metastases, and Ki67 level were included to observe the effect of drug type on PFS. Hazard ratios (HR) and their 95% confidence interval (95% CI) were presented. All statistical analyses were performed using R Version 4.1.1, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 204 patients were obtained from the hospital database. After excluding the patients who did not meet the inclusion criteria, 96 patients were finally included in the retrospective study, all of whom were female patients, including 37 patients receiving HLX02 treatment and 59 patients receiving RTZ treatment (**Figure 1**). The baseline demographic and disease characteristics of the patients are shown in **Table 1**. No significant differences in age, weight, height, clinical stage, Eastern Cooperative Oncology Group performance status (ECOG PS), lymph node status, estrogen receptor status, progesterone receptor status, number of lymph node metastases, presence of distant organ metastases, Ki67 level, number of people receiving neoadjuvant chemotherapy, or neoadjuvant chemotherapy combination regimens were noted between the two groups (all $P > 0.05$).

Efficacy results

In the entire patient population, 31 (32.3%) patients received neoadjuvant chemotherapy, including 10 in the HLX02 group and 21 in the RTZ group. The neoadjuvant chemotherapy combination regimens of the two groups was different according to the actual clinical situation, but there was no significant difference between the two groups (P=0.824) (**Table 2**). In the neoadjuvant chemotherapy population, 7 (70.0%) patients in the HLX02 group and 16 (76.2%) patients in the RTZ group achieved pCR. In the HLX02 group, 1 (10.0%) patient

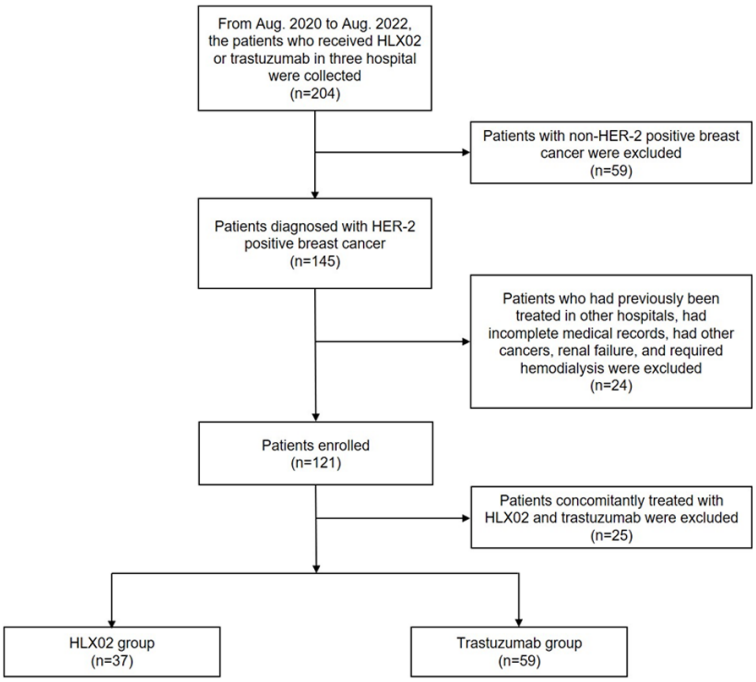

Figure 1. Screening patient flow chart.

developed disease progression after receiving the 5th course of neoadjuvant chemotherapy, but overall, there was no significant difference in the efficacy of neoadjuvant chemotherapy between the two groups (P=1.000) (**Table 2**).

All patients received postoperative adjuvant therapy, with 37 in the HLX02 group and 59 in the RTZ group. Patients who had received prior neoadjuvant chemotherapy required only dual-targeted trastuzumab and pertuzumab after surgery, and the other postoperative patients received 4 cycles of doxorubicin plus cyclophosphamide followed by taxanes combined with trastuzumab and pertuzumab. In the entire patient population, 90 (93.7%) and 84 (87.5%) patients achieved overall response and complete response, respectively, with 34 (91.9%) and 32 (86.5%) patients achieving overall response and complete response in the HLX02 group and 56 (94.9%) and 52 (88.1%) patients achieving overall response and complete response in the RTZ group. There was no significant difference in the efficacy of adjuvant chemotherapy between the two groups (P > 0.05) (**Table 3**).

In the survival analysis, the median (range) follow-up time for the entire patient population was 11 (3-24) months. The median (range) follow-up times were 11 (3-21) and 12 (3-24) months in the HLX02 and RTZ groups, respectively. During the follow-up period, a total of 4 (4.2%) patients exhibited disease progression, including 2 (5.4%) patients in the HLX02 group and 2 (3.4%) patients in the RTZ group. Given that no patient died during the entire treatment period or follow-up period, only PFS curves were plotted, and Kaplan-Meier estimation described the recurrence status between the two groups. The results of the log-rank test showed no significant difference in recurrence status between the two groups (P=0.48), whereas the median PFS was not achieved in either group (**Figure 2**). Both univariate [HR: 0.503 (95% CI: 0.708, 3.579), P=0.493] and multivariate Cox proportional hazards regression models [HR: 0.708 (95% CI: 0.001, 5.935), P=0.241] showed no effect of drug type on PFS.

Safety results

In the entire patient population, a total of 9 (9.4%) patients experienced grade 3 or greater adverse events, with 3 (8.1%) in the HLX02 group and 6 (10.2%) in the RTZ group. Among the population with grade 3 or greater adverse events, 2 patients treated with HLX02 developed grade 3 or greater myelosuppression compared with 5 patients in the RTZ group, 1 patient in the HLX01 group developed severe diarrhoea, and 1 patient in the RTZ group developed severe drug-induced liver injury leading to temporary discontinuation of the targeted agent.

In addition, a total of 8 (8.3%) patients developed infusion-related reactions, with 4 (10.8%) patients in the HLX02 group and 4 (6.8%) patients in the RTZ group, exhibiting dizziness, headache, fear of cold, chills and other symptoms during infusion, but there was no significant difference between the two groups (P=0.707).

Table 1. Demographical characteristics and clinical data of the patients

Variables	HLX02 (n=37)	RTZ (n=59)	*P* value
Demographics			
Age (y, Mean ± SD)	54.27 ± 11.66	51.27 ± 10.13	0.186
Weight (kg)	59.38 ± 9.19	58.51 ± 8.63	0.643
Height (cm)	157.73 ± 3.92	156.21 ± 5.06	0.123
Clinical stage			0.971
I	8 (21.6)	12 (20.3)	
II	20 (54.1)	34 (57.6)	
III	7 (18.9)	9 (15.3)	
IV	2 (5.4)	4 (6.8)	
ECOG PS ≥ 3	3 (8.1)	3 (5.1)	0.673
Nodal status			0.213
Positive	14 (37.8)	30 (50.8)	
Negative	23 (62.2)	29 (49.2)	
Estrogen receptor			0.731
Positive	20 (54.1)	34 (57.6)	
Negative	17 (45.9)	25 (42.4)	
Progesterone receptor			0.238
Positive	17 (45.9)	20 (33.9)	
Negative	20 (54.1)	39 (66.1)	
Number of lymph node metastasis ≥ 2	8 (21.6)	21 (35.6)	0.147
Distant organ metastasis			1.000
Yes	2 (5.4)	4 (6.8)	
No	35 (94.6)	55 (93.2)	
Ki67 (%)	45.05 ± 23.14	46.47 ± 24.54	0.778
Receive neoadjuvant chemotherapy	10 (27.0)	21 (35.6)	0.382

Data are n (%) unless otherwise indicated. Abbreviations: SD, standard deviation; ECOG PS, astern Cooperative Oncology Group performance status.

Table 2. Efficacy outcomes of neoadjuvant chemotherapy of two groups

	HLX02 (n=10)	RTZ (n=21)	*P* value
Clinical response			1.000
pCR	7 (70.0)	16 (76.2)	
pPR	2 (20.0)	5 (23.8)	
PD	1 (10.0)	0 (0.0)	
Neoadjuvant chemotherapy regimens			0.824
ACTHP[a]	1 (10.0)	4 (19.1)	
TCH[b]	2 (20.0)	2 (9.5)	
TCbHP[c]	4 (40.0)	6 (28.6)	
THP[d]	3 (30.0)	7 (33.3)	
TH[e]	0 (0.0)	2 (9.5)	

Data are n (%). [a]ACTHP: doxorubicin, cyclophosphamide, taxane, trastuzumab, and pertuzumab. [b]TCH: taxane, cyclophosphamide, and trastuzumab. [c]TCbHP: taxane, carboplatin, trastuzumab, and pertuzumab. [d]THP: taxane, trastuzumab, and pertuzumab. [e]TH: taxane and trastuzumab. Abbreviations: pCR, pathological complete response; pPR, pathological partial response; PD, progressive disease.

It is worth noting that hypertension was reported in 2 patients in the HLX02 group and none in the RTZ group, but no statistically significant difference was observed between the two groups (P=0.146). A total of 2 patients reported decreased LVEF, which was a specific adverse reaction of trastuzumab, with 1 patient in the HLX02 group and 1 in the RTZ group, and there was no significant difference between the two groups (P=1.000). Overall, there were no significant differences in reported adverse events between the two groups (all P > 0.05) (**Table 4**).

Discussion

Biopharmaceuticals provide efficient treatment for cancer patients,

Table 3. Efficacy outcomes of postoperative adjuvant therapy of two groups

	HLX02 (n=37)	RTZ (n=59)	*P* value
Overall response (CR+PR)	34 (91.9)	56 (94.9)	0.673
CR	32 (86.5)	52 (88.1)	0.943
PR	2 (5.4)	4 (6.8)	
SD	1 (2.7)	1 (1.7)	
PD	2 (5.4)	2 (3.4)	

Data are n (%). Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

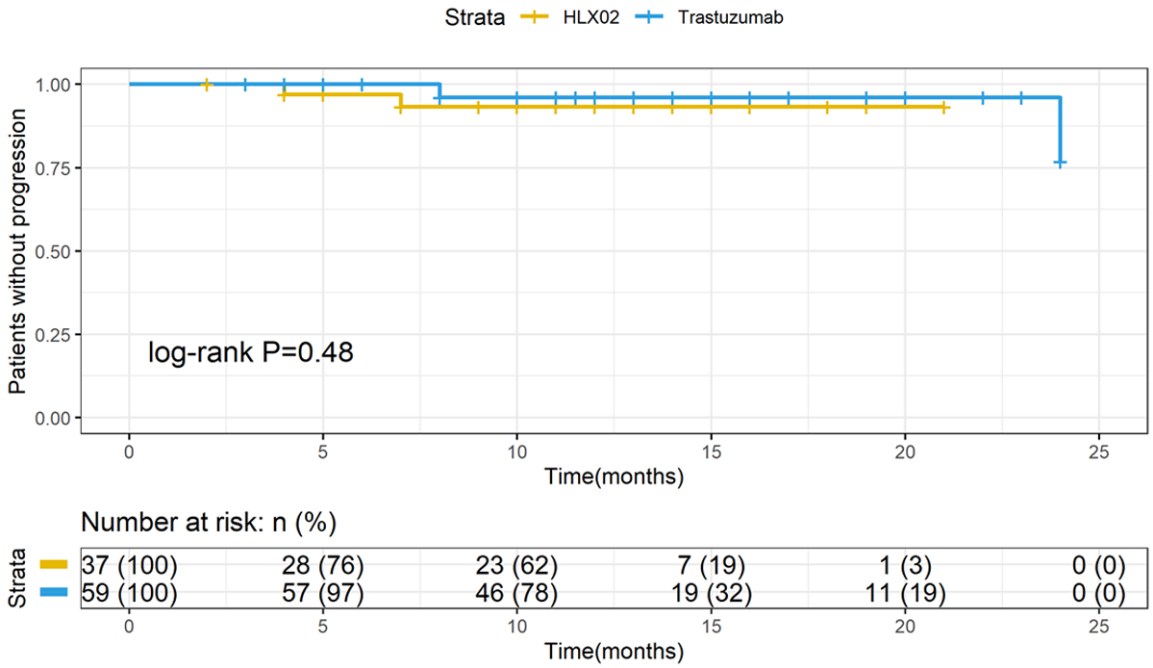

Figure 2. Kaplan-Meier survival curves for progression-free survival.

but the high cost often limits their availability for patients, so the introduction of biosimilars in clinical practice is necessary to sustainably reduce the burden of medical care, especially in developing countries such as China. Treatment using biosimilars is not only a direct cost saving method but also motivates the clinical use of new therapies and drugs [18]. It has also previously been shown that HLX02 is more economical than RTZ in the treatment of HER-2-positive breast cancer and can allow more patients to access treatment [19]. Therefore, more attention should be given to the application of HLX02 in the real world to further evaluate whether it is equivalent to RTZ in terms of clinical effectiveness and safety.

This study evaluated the efficacy and safety of HLX02 versus RTZ in the treatment of patients with HER-2-positive breast cancer based on multicenter real-world clinical data. As an evaluation indicator of neoadjuvant chemotherapy for breast cancer, pCR is one of the prognostic factors to determine whether patients have clinical long-term survival benefit, and ORR is also one of the clinical endpoints for comparative studies of antitumour biosimilars because of its rich information and sufficient sensitivity [20]. The results of this study showed that there was no significant difference in pCR (70.0% in the HLX02 group and 76.2% in the RTZ group) and ORR (91.9% in the HLX02 group and 94.9% in the RTZ group) between HLX02 and RTZ in the treatment of HER-2-positive breast cancer. In addition, the results of this study showed that there was no significant difference in efficacy, survival outcomes or adverse events between HLX02 and RTZ in the treatment of

Table 4. Adverse events of two groups

Adverse event	HLX02 (n=37)	RTZ (n=59)	*P* value
Number of TEAEs[a]	113	182	
TEAEs ≥ Grade 3	3	6	
Infusion-related reaction	4 (10.8)	4 (6.8)	0.707
Leukopenia	12 (32.4)	26 (44.1)	0.257
Neutropenia	7 (18.9)	15 (25.4)	0.461
Anemia	3 (8.1)	8 (13.6)	0.522
Increased alanine aminotransferase	11 (29.7)	23 (40.0)	0.356
Increased aspartate aminotransferase	11 (29.7)	21 (35.6)	0.553
Increased alkaline phosphatase	6 (16.2)	8 (13.6)	0.720
Insomnia	6 (33.3)	9 (38.9)	0.899
Decreased appetite	10 (27.0)	12 (20.3)	0.448
Nausea	4 (10.8)	6 (10.2)	0.920
Vomit	1 (2.7)	4 (6.8)	0.646
Diarrhea	6 (16.2)	7 (11.9)	0.544
Chest discomfort	7 (18.9)	4 (6.8)	0.100
Palpitation	2 (5.4)	3 (5.1)	1.000
Headache	1 (2.7)	2 (3.4)	1.000
Arthralgia	1 (2.7)	2 (3.4)	1.000
Myalgia	3 (8.1)	2 (3.4)	0.370
Hypertension	2 (5.4)	0 (0.0)	0.146
Fever	1 (2.7)	5 (8.5)	0.401
Infections	6 (16.2)	9 (15.2)	0.899
Stomatitis	3 (8.1)	3 (5.1)	0.673
Rash	5 (13.5)	7 (11.9)	0.812
Decreased LVEF	1 (2.7)	1 (1.7)	1.000

Data are n (%) unless otherwise indicated. [a]TEAEs were coded using the Medical Dictionary for Regulatory Activities version 21.1 coding dictionary. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Abbreviations: TEAE, treatment-emergent adverse event; LVEF, left ventricular injection fraction.

HER-2-positive breast cancer with neoadjuvant chemotherapy or postoperative adjuvant therapy. These results also further showed that HLX02 had equivalent clinical efficacy and safety to RTZ, similar to the results of the phase III clinical trial conducted by Xu et al. [10]. In addition to analyzing the primary and secondary outcome measures, this study also compared outcome measures such as CR and PR between the HLX02 group and RTZ group. The results showed that there was no significant difference in CR or PR between the two groups.

Compared with the previous Phase 3 clinical trial conducted by Xu et al. [10], this study included more diversified clinical data that was in line with the heterogeneous characteristics of clinical practice, including the population of neoadjuvant chemotherapy, the clinical stage of the disease, and the combination regimens. Because the patient population included in this study was also treated with pertuzumab, a targeted agent that can be combined with trastuzumab for HER-2 positive breast cancer, thereby significantly improving the clinical benefit of patients [21, 22], this work is one of the few real-world studies that has shown for the first time that the trastuzumab biosimilar HLX02 combined with pertuzumab has similar efficacy and safety to RTZ combined with pertuzumab in HER-2 positive breast cancer patients. Importantly, we also compared the safety profiles of the two drugs and found no differences between HLX02 and RTZ, especially with regard to infusion-related reactions, diarrhoea of any grade, and cardiotoxicity. This is an important finding, since the use of RTZ has historically been associated with an increased risk of cardiotoxicity [3].

To date, an increasing number of new trastuzumab biosimilars have been gradually developed and have begun to enter phase I or phase III clinical trials, such as SIBP-01 and HL02 [23, 24]. Nevertheless, it is important to note that clinical interchange of biosimilars with original drugs and extrapolation of biosimilar indications is more common in clinical practice. Especially for the indication extrapolation of biosimilars, the difference in immunogenicity response among populations with different indications may bring potential drug safety hazards to patients with indications extrapolated by biosimilars (https://www.cde.org.cn/main/news/viewInfoCommon/d92c65-07a57bee9ccfc5baa1ee87fda9). Therefore, for the trastuzumab biosimilar HLX02, future studies should focus on the clinical interchange between biosimilars and original drugs as well as the extrapolation of indications for biosimilars. Notably, a recently published study report-

ed that HLX02 also showed good therapeutic effect in HER-2-positive gastric cancer [25].

HLX02 was brought to market in China in August 2020, so the number of patients using this drug is still relatively small. Moreover, because strict exclusion criteria were set in this study, few patients met the inclusion criteria. To include as many eligible patients as possible, this study selected multiple hospitals to conduct a multicenter real-world study. Due to the short marketing time of HLX02 and the current follow-up time of patients having reached 2 years, this study will continue to follow the patients to further evaluate the clinical equivalence and safety of HLX02 versus RTZ.

Limitations of this study should be noted. First, it was a retrospective study with a relatively small sample of patients using HLX02, a trastuzumab biosimilar newly marketed in China, and patients were followed for only 2 years. Therefore, attention must be paid to its intrinsic limitations to avoid a misleading and potentially harmful application of its results. However, sharing our data and experience is also helpful in the choice of clinical medication, as patients are recruited from multiple centers and thus provide more representative evidence. Second, given the need to enhance the homogeneity of the study population, patients receiving both HLX02 and RTZ were excluded from this study, which also included only Asian populations. Thus, future studies should include patients with clinical interchange between the biosimilars and original drugs as well as patients of other ethnicities. Finally, the patients received trastuzumab and other antitumour drugs, such as pertuzumab, at the same time. Therefore, it could not be determined whether some adverse events were caused by trastuzumab. However, we recorded all adverse events from the medical records of patients in the two groups and performed statistical analysis. The results showed that there was no statistically significant difference in adverse events between the two groups.

Conclusions

In conclusion, in the treatment of HER-2-positive breast cancer, the trastuzumab biosimilar HLX02 has equivalent clinical efficacy and safety to the original drug, especially in combination with pertuzumab, while HLX02 is more cost-effective and can be used as an important therapeutic strategy to reduce the medical burden. However, clinical equivalence studies between HLX02 and the original trastuzumab drug remain challenging, particularly involving the clinical interchange of biosimilars with the original drugs and extrapolation of biosimilar indications.

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Each patient signed an informed consent form at the initiation of diagnosis, allowing for further clinical research and publication using the clinical records.

Disclosure of conflict of interest

None.

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