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ORIGINAL RESEARCH

Delayed Cardiac Dysfunction During Prolonged Use of Trastuzumab for the Treatment of HER2-Positive Metastatic Breast Cancer

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Background: Cardiotoxicity is the most concerning side effect of trastuzumab in HER2-positive metastatic breast cancer. However, data on the delayed cardiac safety of long-term trastuzumab are rare.

Patients and Methods: A retrospective review of patients with HER2-positive breast cancer receiving trastuzumab for more than 24 months in a metastatic setting was conducted. Patients with medical records of regular assessment of the left ventricular ejection fraction (LVEF) and serum brain natriuretic peptide (BNP) level were included. The incidence of cardiac events and possible predictive factors were analyzed.

Results: A total of 75 patients were eligible for the current cardiac safety analyses. The median trastuzumab exposure was 50 (range: 29–114) cycles. By the cut-off time, the median follow-up time for cardiotoxicity was 34.0 (range: 26.0–41.9) months. The median timing of occurrence of a decrease in LVEF was 8.3 months after follow-up, mostly occurring within the third year from the initiation of trastuzumab. The cumulative incidence of LVEF decline was 10.7% (n=8) after 24-month trastuzumab. Patients with a history of anthracycline administration had a higher incidence of LVEF reduction (13.0% vs 3.6%, p=0.006). Five patients recovered soon after the cessation of trastuzumab. One patient died from congestive heart failure. BNP elevations were noted in 42.7% of patients, but elevated BNP levels could not identify patients with cardiotoxicity.

Conclusion: Of the patients who had received long-term trastuzumab for more than 24 months, delayed cardiotoxicity was observed in only a small subset, and was reversible in most of them. Elevation of serum BNP could not predict cardiotoxicity. Less frequent LVEF monitoring could be considered during long-term use of trastuzumab.

Keywords: cardiotoxicity, long-term, trastuzumab, HER2-positive

Introduction

HER2-positive metastatic breast cancer (MBC) is considered incurable, but the development of anti-HER2 drugs with different mechanisms has led to an unprecedented improvement in prognosis for patients with this disease.[1–4] Trastuzumab, as the first humanized anti-HER2 monoclonal antibody, has been the backbone in the treatment of HER2-positive breast cancer patients since its approval in 1998. Until now, trastuzumab-based chemotherapy in first-line treatment has obtained a median progression-free survival (PFS) of 18.7–24.3 months,[5,6] and the median overall survival (OS) has been prolonged to approximately 5 years, or even longer.[4–8] Unlike the established principle of stopping and switching to other cytotoxic drugs after disease progression on chemotherapy, the continuation of trastuzumab is acceptable and effective in HER2-positive MBC,[9,10] and a plethora of subsequent trastuzumab-based treatment options are available through first- and later-line treatment. In a metastatic setting, trastuzumab is always continuously used in

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combination with chemotherapy or other anti-HER2 drugs during multiple lines of treatment and a duration of trastuzumab treatment for MBC lasting for more than 2 years is very common. However, it remains unclear whether the long-term administration of trastuzumab for MBC could be countered by concerns over its cardiac safety.

The toxicity of trastuzumab is generally mild, and cardiotoxicity is the most concerning side effect.[11] The cardiotoxicity of trastuzumab is dose independent and usually reversible.[12] The cardiac safety of 1-year trastuzumab as neoadjuvant and adjuvant treatment has been reported in a series of large-scale trials.[13–15] Regular left ventricular ejection fraction (LVEF) monitoring every 3 months is recommended during 1-year trastuzumab. However, when trastuzumab is combined with different chemicals, patients are faced with different risks of cardiac dysfunction. For example, the risk of cardiac dysfunction was 7% for patients with trastuzumab monotherapy, but this risk rose to 12% for patients with trastuzumab plus paclitaxel after extensive exposure to anthracycline; the risk of cardiac dysfunction was as high as 27% when trastuzumab was used concurrently with anthracycline.[14–16] In addition, the incidence of all grades of cardiac events was higher after 2-year trastuzumab than after 1-year trastuzumab in the HERA study (7.7% vs 4.4%).[13]

Data on the delayed cardiac safety of long-term trastuzumab-based treatment (more than 2 years) for MBC are rare. Moreover, few studies have explored the utility of serum biomarkers in the detection of cardiotoxicity.[17] Here, we report on the study of delayed cardiac safety of long-term trastuzumab-based treatment using ultrasonography, and explore the potential of serum brain natriuretic peptide (BNP) to monitor cardiac safety in patients with HER2-positive MBC in routine clinical practice.

Patients and Methods

Patients and Data Collection

We performed a retrospective review on the electronic medical charts of consecutive women with HER2-positive metastatic breast cancer receiving trastuzumab-based treatment during March 2017 to May 2023 in the National Cancer Hospital & Shenzhen Hospital. Patients were included if the cumulative time of receiving trastuzumab was 24 months or longer in a metastatic setting. Patients who had received (neo)adjuvant trastuzumab were included, but the treatment period did not count toward to the cumulative time of receiving trastuzumab. Then, baseline characteristics at the time point of 24-month trastuzumab were retrieved, including cardiovascular and cancer treatment history. The sum of lines of treatments added to trastuzumab was at least 2, including chemotherapy and other anti-HER2 drugs. Regular assessment of LVEF by echocardiography and measurement of serum BNP (every 3 months) after 24-month trastuzumab were required. Patients were followed until death or the end of follow-up period (November 30th, 2023). The Institutional Review Board of the National Cancer Hospital & Shenzhen Hospital approved the retrospective study with approval no. KYKT2024-11-1. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Cardiac Evaluation

Follow-up was conducted from the time point at which patients had finished 2-year trastuzumab treatment to death or the cut-off time. LVEF was assessed by echocardiography at the time of 24-month trastuzumab and every 3 months thereafter. Cardiac events were defined as: a decrease in the ejection fraction of 10% compared with the baseline, an LVEF of less than 50% at any time, or symptoms of congestive heart failure (CHF). Blood samples were collected at the same time. BNP assessments were coupled with LVEF measurement on the Elecsys platform. All values of BNP >125 pg/mL were considered elevated. The time to cardiac events was calculated from the date of 24-month trastuzumab for MBC to the first occurrence of cardiotoxicity or the date of the last follow-up.

Statistical Analyses

Patient characteristics were summarized using descriptive statistics. Continuous variables were presented as means with standard deviations. Mean LVEFs at different time points were compared using a *t*-test. Receiver operating characteristics (ROC) curve analyses were used to investigate the ability of BNP to distinguish between patients with and without a significant LVEF decline. OS was estimated using the Kaplan–Meier method. OS refers to the time interval from the

first recurrence to death from any cause. Data analyses were performed using SPSS 26.0. Values of $p<0.05$ were considered to be statistically significant.

Results

Baseline Characteristics

Between March 2017 and May 2023, 202 patients with HER2-positive MBC were identified, 98 of whom had received at least 24 months of trastuzumab. Among them, 11 patients had no baseline LVEF and BNP measurements, and 12 had no regular LVEF and BNP measurements taken during trastuzumab treatment. Finally, 75 patients were eligible for the current analyses. Baseline characteristics at the time of 24-month trastuzumab are listed in Table 1. Possible risk factors for cardiotoxicity at baseline were as follows: 22 patients (29.3%) had comorbidities (17 with hypertension, three with diabetes, five with hypercholesterolemia, and two with cardiac disorder), 46 patients (61.3%) had received anthracycline chemotherapy, and 44 (58.7%) had a history of chest radiation (23 of them on the left side). One patient had a smoking history and another had a body mass index (BMI) >30 kg/m^2. By the cut-off time on November 30th, 2023, the median follow-up for cardiotoxicity was 34.0 (range: 26.0–41.9) months. The median OS for this group of patients was as long as 78.8 (range: 52.6–105.1) months (Figure 1).

Exposure to Trastuzumab and Concomitant Drugs

By the cut-off time, 27 deaths were observed, and 25 patients were continuing to receive trastuzumab-based therapy. The treatment history of the 75 HER2-positive patients in a metastatic setting is shown in Table 2. The median trastuzumab exposure was 50 (range: 29–114) cycles and the median duration was 39 (range: 33.1–44.9) months in the metastatic

Table 1 Demographic and Characteristics of All Included Patients

Characteristic	**(n=75)**
	No. of Patients (%)
Age at enrollment (years)	
Median	49
Range	30–75
Comorbidity	22 (29.3)
Diabetes mellitus	3 (4.0)
Hypertension	17 (22.7)
Cardiac disorder	2 (2.7)
Hypercholesterolemia	5 (6.7)
HR status	
ER positive	35 (46.7)
PR positive	27 (36.0)
(Neo)adjuvant trastuzumab	26 (34.7)
Median duration of (neo)adjuvant trastuzumab (months)	12
Anthracycline	
Yes	46 (61.3)
Radiation of the chest	44 (58.7)
Left side	23 (30.7)
Right side	21 (28.0)
BMI at baseline (kg/m^2)	
<25	64 (85.3)
25–30	10 (13.3)
>30	1 (1.3)
Smoking	
Yes	1 (1.3)

Abbreviations: HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; BMI, body mass index.

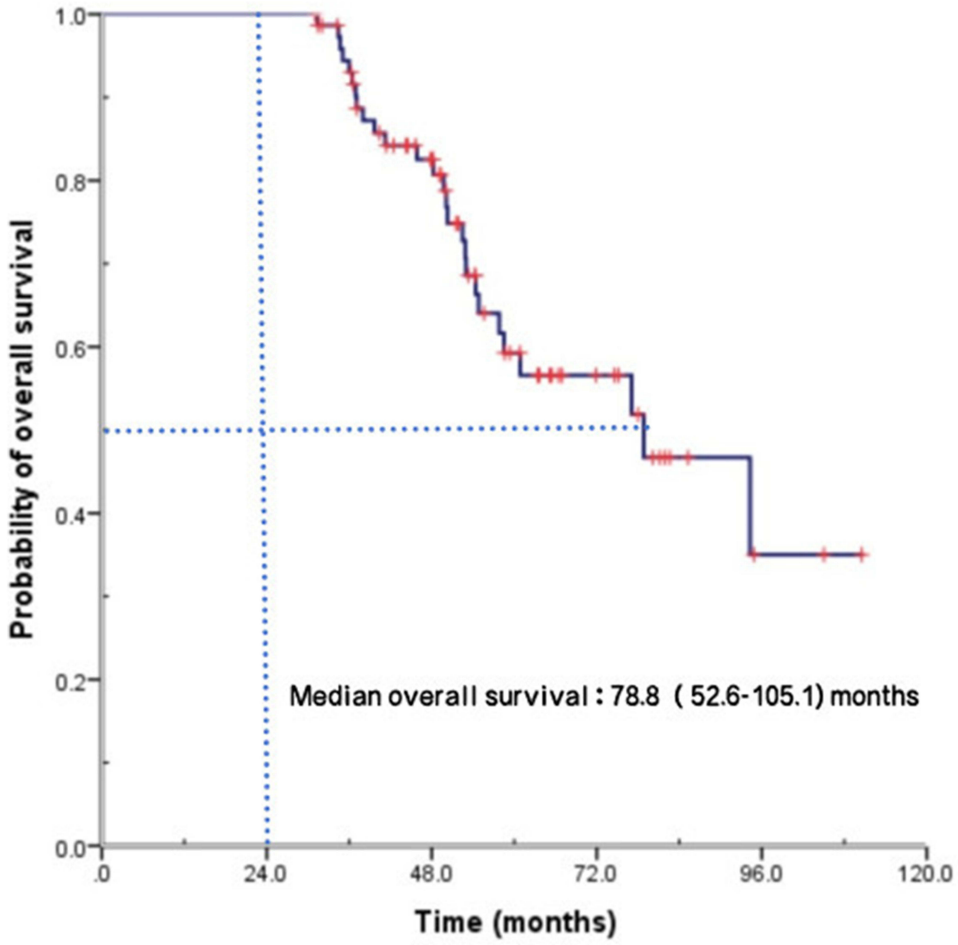

Figure 1 Estimation of overall survival for patients who received more than 24-month trastuzumab-based chemotherapy, censored on the date of last follow-up.

setting. In addition, 26 patients (34.7%) had already received 12-month trastuzumab in (neo)adjuvant setting. Trastuzumab was temporarily discontinued once or more throughout the course of their treatment in 61.3% of patients. However, 88.0% of them received trastuzumab consecutively for at least 24 months, 40.0% of patients received trastuzumab without interruption for at least 36 months, and the longest duration of continuous trastuzumab was 69 months. Reasons for stopping trastuzumab included physician's decision (n=18), coronavirus (n=8), cardiotoxicity

Table 2 Treatment History of the 75 HER2-Positive Patients in a Metastatic Setting

Cumulative Duration of Trastuzumab Administration for MBC (Months)	Number or Median (Range)
24–36	30
36–48	27
>48	18
Interruption of trastuzumab	
Yes	45
No	30

(*Continued*)

Table 2 (Continued).

Cumulative Duration of Trastuzumab Administration for MBC (Months)	Number or Median (Range)
Maximum duration of trastuzumab continuous administration for MBC (months)	
<24	9
24–36	36
36–48	18
>48	12
Median trastuzumab exposure (cycles)	50 (29–114)
Previous cardiotoxicity during first 2 years of trastuzumab	
Yes	4
No	0
Median lines of anti-HER2 treatment	4 (1–15)
Anti-HER2 treatment	
Pertuzumab	26
Lapatinib	36
Neratinib	1
Pyrotinib	64
Trastuzumab emtansine	9
Others	4
Number of combined chemotherapy drugs	4 (1–11)

Abbreviation: MBC, metastatic breast cancer.

(n=12), and patient's request (n=8). Trastuzumab was given combined with chemotherapy in all eligible patients, and the median cumulative number of combined cytotoxic drugs was 4 (range: 1–11), including taxane, capecitabine, gemcitabine, elibulin, vinorelbine, and so on. Dual blockade of HER2 was common, and concomitant anti-HER2 agents included pertuzumab (n=26), lapatinib (n=36), pyrotinib (n=64), and neratinib (n=1). Furthermore, 13 patients had received antibody–drug conjugates in later-line treatment.

Cardiac Events and Recovery

Of the 75 patients who were eligible for the current analyses, two patients had a decrease in LVEF of ≥10% during the previous 2-year trastuzumab treatment. By the date of 24-month trastuzumab, almost all patients had a baseline LVEF ≥50%, apart from one (LVEF 46%) who had experienced a rupture of an aortic sinus aneurysm and who recovered later. Mean baseline LVEF at the time of 24-month trastuzumab was 66.3%. The change in mean LVEF during the following treatment with trastuzumab is shown in Figure 2A. The overall mean LVEF values remained stable throughout the treatment. By the cut-off time on November 30th, 2023, the mean LVEF was 69.5%. Cardiac events and cardiac biomarker changes are shown in Table 3. The cumulative incidence of an LVEF drop was 10.7% (n=8). Patients with a history of anthracycline administration (n=46) had a higher incidence of LVEF drop (13.0% vs 3.6%, p=0.006) than those without such a history. All of these patients had received 1–8 cycles of anthracycline, and three of them concurrently with trastuzumab, and none of them demonstrated a significant drop in LVEF after receiving anthracycline. There were no differences in the distribution of chest radiation, BMI, or cardiovascular complications between patients with and those without an LVEF drop (data not shown).

The median timing of occurrence of the LVEF decrease was 8.3 months after follow-up; LVEF drops almost always (7/8) occurred within the third year after trastuzumab initiation in the metastatic setting (Figure 2B). Two asymptomatic patients continued trastuzumab, and the LVEF returned to normal within 3 months during subsequent follow-up.

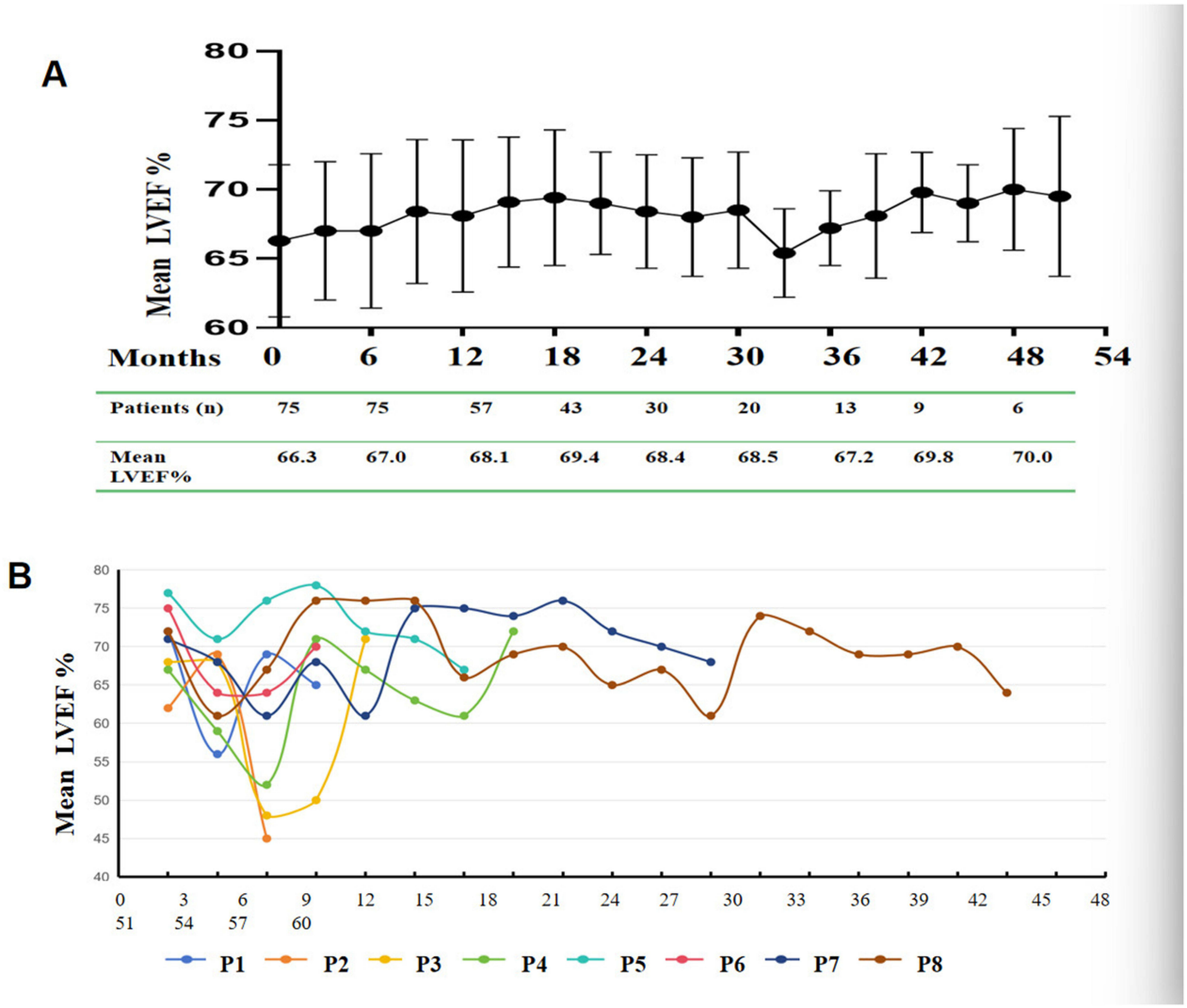

Figure 2 Time course of LVEF. (**A**) Trend line of change of mean LVEF during treatment after 24-month trastuzumab-based chemotherapy. (**B**) Time course of drops and recoveries in LVEF for eight patients who developed cardiac dysfunction.
Abbreviation: LVEF, left ventricular ejection fraction.

Trastuzumab was discontinued in six cases with suspected symptoms (palpitations or chest tightness), two of whom were diagnosed with acute CHF. One recovered to a normal level 6 months later, but eventually died from disease progression, and the other patient died from acute CHF within 1 month. The cardiact dysfunction for all the 8 patients recovered within 6 months after discontinuation of trastuzumab. Trastuzumab was resumed in two patients, neither of whom experienced another LVEF decline.

Serum Cardiac Biomarkers

Overall, seven of the 75 patients had increased BNP during the previous 2-year trastuzumab treatment and four of them still had persistently elevated BNP values at baseline. During the follow-up, BNP elevations were noted in 32 of 75 breast cancer patients (42.7%). BNP elevation was observed throughout the follow-up, with the yearly incidence of BNP elevation being 26.7% (20/75), 27.5% (14/51), 33.3% (10/30), 30.8% (4/13), and 50% (2/4) in year 3, year 4, year 5, year 6, and year 7–8 after trastuzumab initiation, respectively. However, only five patients with elevated BNP concentrations had an LVEF decline at the same time. Moreover, 27 patients with elevated BNP maintained normal

Table 3 Cardiac Events and Cardiac Biomarkers for Metastatic Breast Cancer After 24-Month Trastuzumab-Based Chemotherapy

Cardiac Markers	**(n=75)**
	No. of Patients (%)
Maximum LVEF decrease from baseline, n (%)	
≥10%	8 (10.7)
Symptomatic heart failure	2 (2.7)
Cardiac-related death	1 (1.3)
Median timing of incidence of LVEF decrease since initiation of trastuzumab (months)	32.3
Incidence of elevated BNP level	32 (42.7)

Abbreviations: LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide.

LVEF values throughout the study period, including one with cardiac symptoms. Three patients with an LVEF drop had normal BNP levels.

The highest BNP value during follow-up or the highest value recorded up to the date of the cardiac event (if any) was used. ROC curve analyses indicated that elevated BNP levels did not identify patients with a later LVEF drop, with an area under the curve (AUC) of 0.643 (95% CI 0.42–0.86) (shown in supplementary appendix Figure S1) and a Youden index of 0.38 at the optimal cut-off value of BNP (514.5 pg/mL). The variability of mean BNP values at each time point was very high, so it is not suitable to compare mean BNP values between different time points. A slight and temporary elevation of BNP fell back automatically in 14 patients, irrespective of the use of trastuzumab. Meanwhile, consistent increases in the BNP level declined quickly after discontinuation of trastuzumab in five patients. BNP elevations were also observed in a few particular situations with no LVEF drop: severe infections (n=2), myocardial infarction (n=1), rupture of an aortic sinus aneurysm (n=1), and chronic renal inefficiency (n=1).

Discussion

This study comprehensively evaluated the delayed cardiac safety profiles after 2-year trastuzumab for MBC in real-life clinical settings in China. Among the 75 women included in the study, eight (10.7%) developed at least one cardiac event during follow-up. Two developed CHF, one of whom died from CHF. In addition, serum BNP elevations were observed in more than 42.7% of patients, but were not associated with LVEF decline.

Cardiotoxicity is the major concern during treatment with trastuzumab. Trastuzumab monotherapy carries an incidence of cardiac dysfunction ranging from 2% to 9%.[18] The mechanism underlying this is still unclear.[19] HER2 signaling is critical for cardiac physiology in adults, especially with regard to cardiac pressure overload and damage.[20] However, compared to other monoclonal antibodies and oral small-molecule tyrosine kinase inhibitors against HER2 (eg pertuzumab or pyrotinib), trastuzumab is associated with the most frequent occurrence of cardiac dysfunction, especially when it is used concurrently with anthracycline.[12,18] A preclinical study indicates that trastuzumab significantly impairs the contractile and calcium handling properties but does not induce cardiomyocyte death.[21] It is not yet sufficient to explain the mechanism of development of cardiac dysfunction following trastuzumab therapy.

Data on the cardiac safety of long-term trastuzumab-based treatment in MBC are rare and the incidence of cardiac event varies in previous reports. In the CLEOPATRA study on first-line treatment of HER2-positive MBC, the median treatment cycle of trastuzumab was 15 cycles in the trastuzumab and placebo groups, and the incidence of all-grade left ventricular systolic dysfunction was 8.6% at the time of the 30-month follow-up.[5] In another study, the incidence of asymptomatic LVEF decline was only 3.0% with a 21-month follow-up.[22] But in a retrospective study from the MD Anderson Cancer Center, the incidence of all grades of cardiac events was 28% with a median follow-up time of 32.6 months.[23] The difference in the incidence of cardiotoxicity could be attributed to the baseline characteristics of the enrolled population, the method used to evaluate treatment-induced cardiac toxicity, the time of trastuzumab treatment

and follow-up, and so on. In our study, we used the definition of a cardiac event that has commonly been used in previous clinical trials for patients receiving trastuzumab therapy.[5] The median trastuzumab exposure was 50 (range: 29–114) cycles in this study, and the incidence of a cardiac event after 2-year trastuzumab was 10.7% with a median follow-up time of 34 months. This is the first study to focus on delayed cardiotoxicity in patients who had received 2-year trastuzumab for MBC. Similarly to the retrospective study from the MD Anderson Cancer Center,[23] the enrolled population in our study is a typical representation of clinical practice, with high exposure to anthracyclines (61.3%), prolonged exposure to trastuzumab (median 39 months), and undergoing multiple regimens of chemotherapy. However, the incidence of cardiac events in our cohort is much lower than that of the MD Anderson Cancer Center (28%), and most of these (87.5%) were reversible without the intervention of a cardiologist. One of the reasons for this may be that almost all the patients in our study had a normal baseline LVEF value, which means that patients who could maintain a normal LVEF level after 2-year trastuzumab may be no more vulnerable to trastuzumab, and maintain a low incidence of cardiac events during the following treatment. Bouwer et al also reported that the cumulative incidence of cardiotoxicity increased minimally after the first 2-year use of trastuzumab for MBC.[24] Similar results were also observed in other reports.[25–27] In a preclinical study, pluripotent stem cell-derived cardiomyocytes generated from patients who experienced severe cardiac dysfunction after trastuzumab were more vulnerable to trastuzumab treatment compared to those from patients who did not experience cardiac dysfunction after trastuzumab.[21] Hence, we propose that since trastuzumab-related cardiotoxicity usually occurs early in a small population after the initiation of trastuzumab, less frequent LVEF monitoring should be considered at a later time, especially in patients who have successfully completed adjuvant trastuzumab. More data are needed for further confirmation.

Cardiotoxicity is an important and irreversible side effect of anthracyclines. Concurrent administration of anthracyclines and trastuzumab is correlated with unacceptably high rates of cardiotoxicity.[28] As previously reported, the risk of trastuzumab-associated cardiac dysfunction appears to be higher in anthracycline-treated patients.[29] Our study obtained similar results, with patients with a history of anthracycline administration also experiencing a higher incidence of delayed cardiac dysfunction (13.0% vs 3.6%, p=0.006).

On the other hand, LVEF decline is considered a late manifestation of cardiotoxicity, and thus monitoring of cardiotoxicity primarily based on LVEF may fail to detect subtle alterations in left ventricular function.[30,31] Heart failure may even occur with normal LVEF.[32] Moreover, many patients with LVEF drops during trastuzumab treatment do not develop cardiac failure. Similar cases are also observed in our cohort. Therefore, there is still a need for more sensitive and specific markers. Serum cardiac biomarkers such as BNP are promising in detecting earlier subclinical cardiotoxicity and play an important complementary role in identifying cardiotoxicity and predicting prognosis.[32] However, in our study, elevation of BNP was observed in 42.7% of patients after regular testing. ROC analysis showed no association between the elevation of BNP and LVEF drop. A transient and slight elevation in BNP was very common (14/32). Another point to be remarked upon is that serum levels of BNP could be easily affected by age, sex, body weight, infection, or chronic kidney disease.[33] Moreover, one patient in this study with both significantly increased BNP level and cardiac symptoms had a normal LVEF value. The huge differences in susceptibility between LVEF and BNP in identifying trastuzumab-related cardiotoxicity hinder the further use of BNP in predicting cardiotoxicity.

In this study, we focus on evaluating patients after at least 2 years of trastuzumab treatment and present a view of the delayed cardiac side effects of prolonged trastuzumab therapy for MBC in clinical practice. This study is limited by its small sample size and retrospective nature, but the data provide a useful complement to the safety profile of trastuzumab in daily practice. The relatively low incidence of cardiac events and favorable prognosis of this cohort of patients indicate that the long-term use of continuous trastuzumab is feasible and efficient.

Conclusion

Cardiotoxicity was observed in only a small subset of patients after long-term trastuzumab. Elevation of serum BNP was common, but it could not predict cardiotoxicity. Less frequent LVEF monitoring could be considered during long-term use of trastuzumab.

Data Sharing Statement

The data supporting the results in the manuscript are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the institutional review boards of the National Cancer Hospital & Shenzhen Hospital with approval no. KYKT2024-11-1. Owing to the retrospective and non-interventional nature of the study, informed consent was waived by the institutional review boards for those participants who were deceased. Patients who were still alive after the initiation of this study were informed of the study objectives for data collection.

Consent for Publication

All authors approved the version submitted for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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