Int J Clin Exp Med 2019;12(8):10039-10047
www.ijcem.com /ISSN:1940-5901/IJCEM0096486

Original Article

Therapeutic effects of trastuzumab combined with anthracyclines in metastatic breast cancer

Tao Li, Xiaoming Ma, Anwen Huang

Department of General Surgery, Shibei Hospital, Shanghai, China

Received May 5, 2019; Accepted July 5, 2019; Epub August 15, 2019; Published August 30, 2019

Abstract: Objective: The aim of the current study was to evaluate therapeutic effects and safety levels of trastuzumab combined with anthracyclines for treatment of metastatic breast cancer. Methods: A total of 90 patients with metastatic breast cancer were randomly divided into three groups, including A (N = 32), B (N = 36), and C (N = 22) groups. Group A received treatment with the simultaneous use of anthracyclines and trastuzumab (50 mg/m^2 pirarubicin and 75 mg/m^2 epirubicin for 6 cycles). Group B received sequential therapy with trastuzumab and anthracyclines (60 mg/m^2 pirarubicin and 90 mg/m^2 epirubicin for 21 consecutive days as a chemotherapy cycle; Trastuzumab was given for the first time at the end of one cycle of anthracyclines). Patients were treated continuously for 6 cycles. Group C received 50 mg/m^2 pirarubicin and 75 mg/m^2 epirubicin for 21 consecutive days. This was continued for 6 consecutive cycles. Efficacy levels of treatment in three groups were compared. Health Survey Summary (SF-36) scores were used to assess quality of life levels in the three groups. Echocardiography and enzyme-linked immunosorbent assays (ELISA) were used to detect changes in left ventricular ejection fraction (LVEF) and serum hypersensitive troponin T (hs-cTnT), as well as brain natural peptide amino terminal precursor proteins (NT-proBNP). Progression-free survival times (PFS) and total survival times (OS) were selected for survival analysis. Results: Treatment efficacy levels of group A and group B were better than those of group C ($P < 0.05$). Quality of life levels of group A and group B were also better ($P < 0.05$). There were no significant changes in LVEF of the three groups ($P > 0.05$). Levels of hs-cTnT and NT-proBNP in the serum of the three groups were compared. Group B levels were higher than those in group A and group C ($P < 0.05$). The OS of the three groups was 100%. The PFS of group A and group B was better than that of group C ($P < 0.05$). Conclusion: Synchronized treatment with trastuzumab combined with anthracyclines can significantly improve clinical symptoms, quality of life levels, and prognosis of patients. This method does not increase heart risks. Thus, it is worthy of promotion.

Keywords: Trastuzumab, anthracyclines, metastatic breast cancer, treatment, safety

Introduction

Breast cancer has become one of the most common malignant tumors in women, worldwide. Breast cancer incidence and mortality rates have been consistently high. Data shows that there were more than 250,000 new cases of breast cancer in the United States in 2017, with more than 40,000 people dying from the disease. In recent years, incidence of breast cancer has continued with an upward trend [1, 2]. At present, treatment of breast cancer mainly focuses on improved radical resections and breast conserving surgeries [3]. Although modern medical technology is constantly improving and most patients can achieve better curative effects, there are still many patients at risk of recurrence after surgery [4]. In some underdeveloped areas of the world, many patients are already in advanced stages at the time of diagnosis. Thus, treatment effects are generally poor [5]. Moreover, 15-30% of patients have overexpression of human epidermal growth factor receptor 2 (her-2). Her-2 is a growth factor with tyrosine kinase activity. It can activate multiple signaling pathways, leading to cell proliferation and cancer [6]. Patients with HER-2 positive breast cancer often have worse conditions than ordinary patients. They are prone to recurrence and metastasis, with poor clinical prognosis [7].

Trastuzumab is a novel antibody-drug conjugate. One study found that it can target HER-2

Table 1. Comparison of general information ($\bar{x}$ ± sd) [n (%)]

Clinical factors	Group A (n = 32)	Group B (n = 36)	Group C (n = 22)	F/x^2	P
Age (years)	46.57 ± 6.57	47.32 ± 5.39	45.97 ± 6.13	0.361	0.698
Weight (kg)	62.48 ± 5.38	61.37 ± 6.13	62.83 ± 5.24	0.554	0.577
BMI (kg/m^2)	21.28 ± 2.84	20.48±3.47	21.53 ± 2.64	0.978	0.280
HR (beat/min)	74.60 ± 8.40	76.20±7.80	74.80 ± 8.00	0.387	0.680
SBP (mmHg)	124.60 ± 14.40	128.20 ± 12.60	126.40 ± 14.20	0.589	0.557
DBP (mmHg)	76.20 ± 8.80	78.60 ± 7.40	76.80 ± 7.80	0.817	0.445
Primary tumor size (cm)				0.334	0.846
≤ 5	22 (68.75)	27 (75.00)	16 (72.73)		
> 5	10 (31.25)	9 (25.00)	6 (27.27)		
Tumor staging				1.206	0.877
I	6 (18.75)	9 (25.00)	6 (27.27)		
II	14 (43.75)	15 (41.67)	7 (31.82)		
III	12 (37.50)	12 (33.33)	9 (40.91)		
Tumor types				1.508	0.825
Ductal carcinoma	28 (84.38)	31 (86.11)	20 (90.91)		
Lobular carcinoma	2 (6.25)	2 (5.56)	0 (0.00)		
Other	2 (6.25)	3 (8.33)	2 (9.09)		
Number of axillary lymph node metastases				2.484	0.870
0	12 (37.50)	15 (41.67)	8 (36.36)		
1-3	10 (31.25)	12 (33.33)	6 (27.27)		
4-9	6 (18.75)	3 (8.33)	3 (13.64)		
> 9	4 (12.50)	6 (16.67)	5 (22.73)		
Operation method				0.329	0.849
Improved radical surgery	30 (93.75)	33 (91.67)	21 (95.45)		
Breast conservation surgery	2 (6.25)	3 (8.33)	1 (4.55)		

and express anti-tumor properties, showing good effects on HER-2 positive breast cancer [8]. Combined with other drugs, prognosis and survival rates of patients with HER-2 positive breast cancer undergoing surgical resections can be significantly improved [9]. Anthracyclines are traditional chemotherapy drugs for breast cancer, including epirubicin and doxorubicin. Anthracyclines can act by binding topoisomerase II, inducing cell death, and inhibiting cell DNA and RNA synthesis. Thus, they may inhibit progression of breast cancer [10]. However, both drugs have some degree of cardiotoxicity. Patients may have cardiac adverse events after treatment [8, 10]. However, there are no conclusions concerning the advantages and disadvantages of the combined use of these two drugs in clinical practice. Therefore, the current study focused on evaluation of efficacy and safety levels of different uses of trastuzumab and anthracyclines, aiming to provide clinical reference for treatment of metastatic breast cancer.

Materials and methods

Grouping

A total of 90 patients with metastatic breast cancer were randomly divided into three groups, including A (N = 32), B (N =36), and C (N = 22) groups. Patients in each group received treatment on the same day. Treatment intervention was terminated on the same day after 6 cycles. General clinical data of each group is shown in **Table 1**.

Inclusion criteria: 1) Subjects diagnosed with breast cancer by clinical histopathology; 2) Subjects confirmed as positive her-2 breast cancer by immunohistochemical staining and fluorescence *in situ* hybridization; 3) Ages greater than 18 years old and karst scores [11] greater than 80 points; 4) Patients treated with radical mastectomy or breast conserving surgeries without definite contraindication; and 5) Distant metastasis present.

Table 2. Comparison of treatment efficacy of three groups of patients [n (%)]

Groups	n	CR	PR	SD	PD	DCR
Group A	32	3 (9.38)	14 (43.75)	5 (15.63)	3 (9.38)	29 (90.63)
Group B	36	2 (5.56)	14 (38.89)	13 (36.11)	7 (19.44)	29 (69.44)
Group C	22	0 (0.00)	7 (31.82)	3 (13.64)	12%,# (54.55)	10%,# (45.45)
X^2		2.184	0.781	5.505	15.210	15.210
P		0.336	0.677	0.064	0.001	0.001

Note: % represents compared to Group A, P < 0.05; # represents compared to Group B, P < 0.05.

Exclusion criteria: 1) Preoperative radiotherapy, chemotherapy, or other appropriate treatments; 2) Combined with abnormal heart, brain, liver, and kidney function; 3) Women during pregnancy and lactation; 4) Allergies or contraindications to the drugs used in the experiment; 5) Patients with other systemic malignancies; 6) Patients with typical heart disease, such as unstable angina, and myocardial infarction patients; 7) Mentally abnormal, with vague consciousness or unable to communicate; and 8) Poor obedience to the experimental content.

The current study was approved by the Medical Ethics Committee of Shibei Hospital. All subjects were informed about the experimental content and were willing to cooperate with treatment. Each subject provided informed consent.

Experimental methods

Patients in group A were treated with trastuzumab and anthracyclines simultaneously. Pirarubicin (Shenzhen Wanle Pharmaceutical Co., Ltd., H10930105) has a body surface area of 50 mg/m^2 and pharmorubicin (Shandong New Times Pharmaceutical Co., Ltd., H2012-3260) has a body surface area of 75 mg/m^2. They were used for 21 days as a chemotherapy cycle. At the same time, trastuzumab (Switzerland Roche Pharma, S20160001) was given 8 mg/kg for the first time. Thereafter, it was given at 6 mg/kg each time, once every three weeks. For each cycle, trastuzumab was administered on the same day as the first treatment with anthracyclines, with 6 consecutive cycles.

Patients in group B were treated with trastuzumab and anthracycline sequential therapy. Pirarubicin was given at 60 mg/m^2 and pharmorubicin was given at 90 mg/m^2, with a chemotherapy cycle for 21 consecutive days. Trastuzumab was first administered at the beginning of the next cycle after the end of one cycle of anthracyclines. The rest were treated the same as group B, for a total of 6 cycles.

Patients in group C were treated separately with anthracyclines. Pharmorubicin was given at 50 mg/m^2 and pharmorubicin was given at 75 mg/m^2, with a cycle of chemotherapy for 21 consecutive days and 6 cycles of continuous treatment.

Outcome measures

Primary outcomes: Tumor sizes were measured with breast cancer MRIs before treatment. Efficacy was evaluated after 2 weeks of treatment. Solid Tumor Efficacy Evaluation Criteria (RECIST) [12] were used to assess treatment efficacy. These criteria were divided into complete remission (CR): All target lesions disappeared; Partial remission (PR): Total length and diameter reduction rates of target lesions in patients were more than 30%; Disease stability (SD): Total length and diameter changes of target lesions were between PR and PD; and Disease progression (PD): New target lesions or long diameter summation of target lesions were found in the patients by more than 20%. The effective rate of treatment (DCR) was (CR + PR + SD/total number * 100%).

Secondary outcomes: Three months after the end of chemotherapy, quality of life scores of the three groups of patients, including physical function, mental function, social function, and mental function, were assessed using the Health Survey Summary (SF-36) [13]. The total score of each evaluation was 100. Higher scores indicate better states. Echocardiography was used to monitor left ventricular ejection fraction (LVEF) in the three groups of patients before and after treatment at 3, 6, 9, and 12 months. Early morning venous blood 3 mL was extracted before treatment and after treatment cycles 1, 2, 3, 4, 5, and 6. High-speed centrifugation and supernatant were also extracted. Enzyme-linked immunosorbent assays (ELISA)

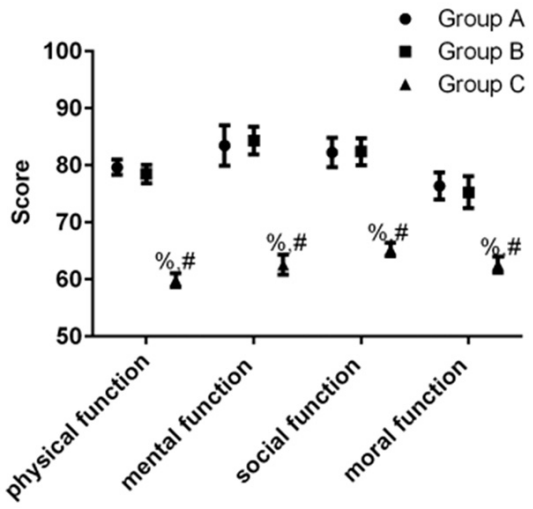

Figure 1. Comparison of living quality between the three groups. Scores of somatic function, psychological function, social function, and mental function of patients in group A and B were higher than those in group C ($P < 0.05$). There were no significant differences in the scores of somatic function, psychological function, social function, and mental function of patients in groups A and B ($P > 0.05$). Note: % represents compared to Group A, $P < 0.05$; # represents compared to Group B, $P < 0.05$.

was used to detect hypersensitive troponin T (hs-cTnT) and brain natural peptide amino terminal precursor proteins (NT-proBNP) in the serum. Detailed steps of the experiment were strictly conducted according to kit specificatiosn. The hs-cTnT kit was purchased from Shanghai Lianmai Bioengineering Co., Ltd., item number JCSW2869. The NT-proBNP kit was purchased from Shanghai Jinger Biological Engineering Co., Ltd., item number JK-(a)-5326. The three groups of patients were followed up for one year. They were asked whether there was disease progression, recurrence and metastasis, and survival. Observed outcomes included overall survival (OS) and progression-free survival (PFS).

Statistical methods: SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of experimental data. GraphPad Prism7 (Beijing Huanzhongruichi Technology CO., LTD., Beijing, China) was used to map the experimental data. Count data are expressed as percentages. Chi-square tests were used for comparisons between the groups. Measurement data are expressed by (mean ± standard deviation). Repeated measures of variance were used for comparisons of different time periods in the group. One-way analysis of variance, followed by Bonferroni's post-hoc tests, was used for comparisons between multiple groups. Median PFS was analyzed using the Kaplan-Meier method. $P < 0.05$ indicates statistical significance.

Results

Comparison of general information

The average age of patients in group A was (46.57 + 6.57). The average age of patients in group B was (47.32 + 5.39). The average age of patients in group C was (45.97 + 6.13). Ages, weights, heart rates, blood pressure, tumor diameters, tumor stages, and tumor types of the three groups were not statistically significant ($P > 0.05$) (**Table 1**).

Comparison of treatment efficacy

After 6 cycles of treatment, 3 patients in group A achieved CR, 14 patients were PR, 5 patients were SD, and 3 patients were PD. In group B, there were 2 cases of CR, 14 cases of PR, 13 cases of SD, and 7 cases of PD. In group C, there were zero CR cases, 7 PR cases, 3 SD cases, and 12 PD cases. DCRs of the three groups were 90.63%, 80.56%, and 45.45%, respectively. The DCR of group C was lower than that of groups A and B ($P < 0.05$). There were no significant differences in DCRs between groups A and B ($P > 0.05$) (**Table 2**).

Quality of life comparison

SF-36 scores were used to evaluate health statuses of the three groups of patients. Results showed that scores of somatic function, psychological function, social function, and mental function of patients in groups A and B were higher than those in group C ($P < 0.05$). There were no significant differences in scores of body function, psychological function, social function, and mental function between the two groups ($P > 0.05$) (**Figure 1**).

Cardiac function comparison

LVEF scores of the three groups before and 3, 6, 9, and 12 months after treatment showed no significant differences ($P > 0.05$). There were no significant differences between LVEF time points at 6, 9, and 12 months ($P > 0.05$). At the same time points, there were no signifi-

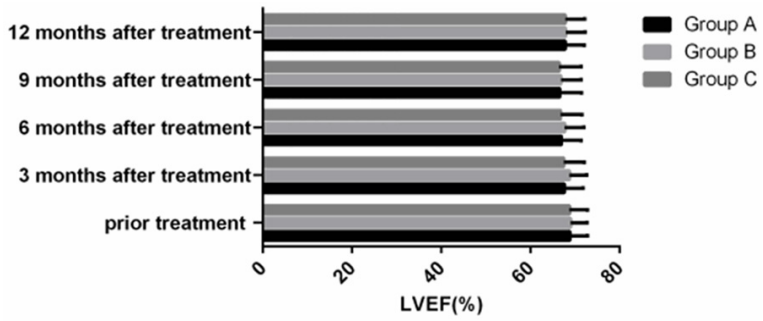

Figure 2. Comparison of LEVF in different periods between the three groups. There were no significant differences in LVEF between the three groups before treatment (P > 0.05). There were no significant differences in LVEF between the three groups before and after treatment at 3, 6, 9, and 12 months (P > 0.05). There were no significant differences in LVEF between the three groups at the same time points (P > 0.05).

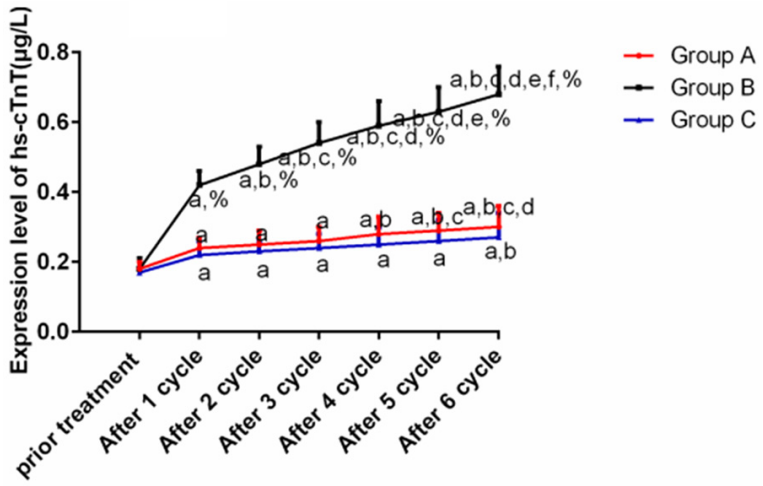

Figure 3. Comparison of hs-cTnT levels in serum before and after treatment for 1, 2, 3, 4, 5, and 6 cycles. There were no significant differences in serum hs-cTnT levels between the three groups before treatment (P > 0.05). After treatment, serum levels of hs-cTnT in each group were higher than those before treatment (P < 0.05). After treatment for 1, 2, 3, 4, 5, and 6 cycles, serum hs-cTnT levels of patients in group B were higher than those in groups A and C (P < 0.05). There were no significant differences in serum hs-cTnT levels between groups A and C (P > 0.05). Note: % represents compared to Group A, P < 0.05; a represents compared to prior treatment, P < 0.05; b represents compared to after treatment 1 cycles, P < 0.05; c represents compared to after treatment 2 cycles, P < 0.05; d represents compared to after treatment 3 cycles, P < 0.05; e represents compared to after treatment 4 cycles, P < 0.05; f represents compared to after treatment 5 cycles, P < 0.05.

cant differences in LVEF between the three groups (P > 0.05) (**Figure 2**).

Comparison of hs-cTnT and NT-proBNP levels in serum before treatment and after 1, 2, 3, 4, 5, and 6 cycles of treatment

ELISA was used to detect levels of hs-cTnT and NT-proBNP in the serum of the three groups before and during treatment. Results showed no significant differences in hs-cTnT and NT-proBNP levels between the three groups before treatment (P > 0.05). Serum levels of hs-cTnT and NT-proBNP in each group of patients were higher than those before treatment (P < 0.05). Levels of hs-cTnT and NT-proBNP in the serum of group B were higher than those in groups A and C after 1, 2, 3, 4, 5, and 6 cycles (P < 0.05). There were no significant differences in serum hs-cTnT and NT-proBNP levels between the two groups (P > 0.05) after 1, 2, 3, 4, 5, and 6 cycles (**Figures 3**, **4**).

Survival analysis

The three groups of patients were followed-up for one year. No patients died in the three groups. OS rate of the three groups was 100.00%. A total of 26 patients had recurrence and metastasis. PFS scores of the three groups were 90.63%, 80.56% and 45.45%, respectively. PFS scores of groups A and B were superior to group C (P < 0.05). There were no significant differences in PFS survival between groups A and B (P > 0.05) (**Figure 5**).

Discussion

With continuous increases in life pressure and bad living habits, incidence rates of breast cancer have also increased [14]. One study found that breast cancer patients tend to have negative emotions, such as anxiety, depression, and despair, after surgery. This seriously affects the quality of life of patients [15]. At present, breast cancer has become an important threat to the health of women. HER-2 positive type is a type with higher prognosis risks. Studies have indicated that, when expression of HER-2 genes on the surface of cancer cells is high, this can trigger the migration

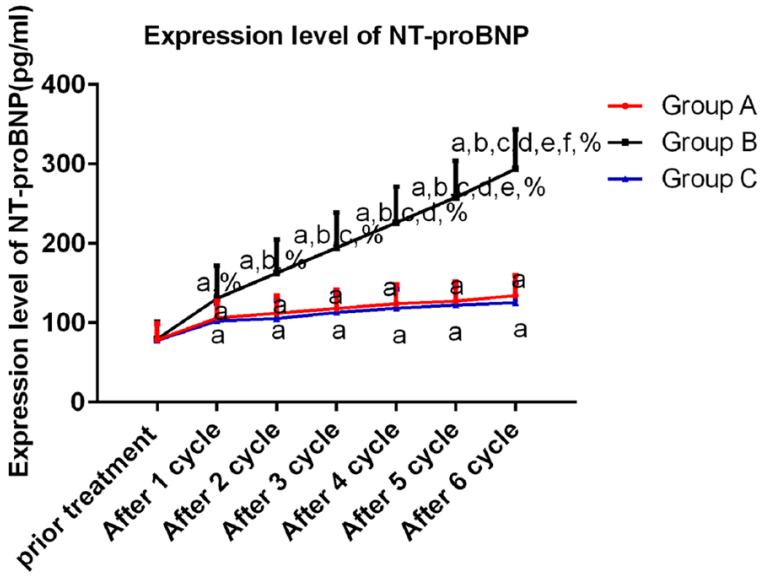

Figure 4. Comparison of NT-proBNP levels in serum before and after treatment for 1, 2, 3, 4, 5, and 6 cycles. There were no significant differences in serum NT-proBNP levels between the three groups before treatment ($P > 0.05$). After treatment, serum levels of NT-proBNP in each group were higher than those before treatment ($P < 0.05$). After treatment for 1, 2, 3, 4, 5, and 6 cycles, serum NT-proBNP levels of patients in group B were higher than those in group A and C ($P < 0.05$). There were no significant differences in serum NT-proBNP levels between groups A and C ($P > 0.05$). Note: % represents compared to Group A, $P < 0.05$; a represents compared to prior treatment, $P < 0.05$; b represents compared to after treatment 1 cycles, $P < 0.05$; c represents compared to after treatment 2 cycles, $P < 0.05$; d represents compared to after treatment 3 cycles, $P < 0.05$; e represents compared to after treatment 4 cycles, $P < 0.05$; f represents compared to after treatment 5 cycles, $P < 0.05$.

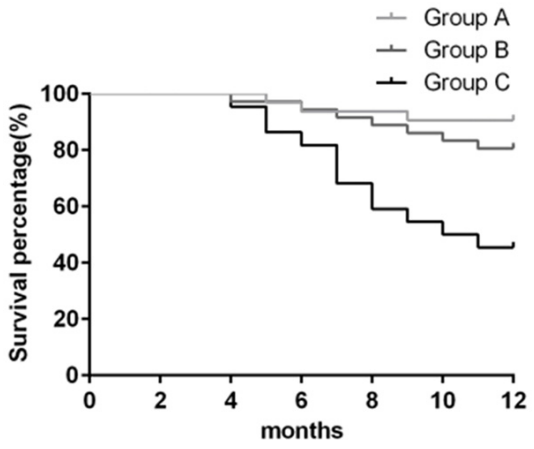

Figure 5. Survival analysis and PFS analyzed in the three groups of patients. A total of 26 patients showed recurrence and metastasis. The PFS of the three groups was 90.63%, 80.56%, and 45.45%. The PFS of groups A and B was superior to that of group C. There were no significant differences in PFS survival between groups A and group B ($P > 0.05$)

of cancer cells in early lesions, as well as the proliferation of advanced primary tumor cells. Data has shown that more than 80% of tumor metastases are from early disseminated cancer cells, indicating a certain correlation between human disseminated cancer cells and positive expression of HER-2 [16].

With the rapid development of modern social science and technology, medical technology is constantly advancing. Currently, treatment of breast cancer is not limited to one or two therapies. Molecular targeted therapy has become the most popular treatment for breast cancer in recent years. Trastuzumab, a targeted drug for HER-2 positive breast cancer, has been approved for treatment of patients with advanced HER-2 positive breast cancer. It can actively exert anti-tumor properties and further improve patient status [17]. However, studies have found that trastuzumab combined with anthracyclines can prolong the survival times of patients with HER-2. Some patients have seen serious cardiac toxicity [18]. Although there are different views on the clinical side effects, there are no definite conclusions. Therefore, the current study focused on the efficacy of trastuzumab combined with anthracyclines in the treatment of metastatic breast cancer, aiming to provide clinical reference for the clinical treatment of patients with metastatic breast cancer.

Present results showed that both group A and group B treated with trastuzumab combined with anthracyclines were better in efficacy and quality of life than group C, which was treated with anthracyclines alone. PFS levels of groups A and B were superior to group C ($P < 0.05$). There were no significant differences in efficacy, quality of life, and PFS between groups A and group B ($P > 0.05$), indicating that the combination of the two drugs can significantly

improve curative effects, quality of life, and prognosis of patients. Current results are in accord with previous studies [19, 20], showing no significant differences in efficacy or survival between synchronous therapy and sequential therapy [21]. However, due to the limitations of experimental conditions in this study, only three groups of patients were followed-up for one year. The current study paid more attention to the disease progression of patients, aiming to observe the control of disease progression via different drug regimens.

Regarding the cardiotoxicity of three different regimens, LVEF levels and serum hs-cTnT and NT-proBNP levels were selected for evaluation. Results showed no significant changes in LVEF in the three groups ($P > 0.05$). Serum levels of hs-cTnTt and NT-proBNP in the three groups were compared. Levels of hs-cTnT and NT-proBNP in group B were higher than those in groups A and C ($P < 0.05$). There were no significant differences in hs-cTnT and NT-proBNP levels between the two groups ($P > 0.05$). Results suggest that trastuzumab combined with anthracyclines is better for cardiotoxicity than trastuzumab combined with anthracyclines in sequential therapy and the use of anthracyclines alone. Of these, LVEF levels did not change significantly. Currently, LVEF is the main indicator used in clinical evaluation of the effects of chemotherapy drugs on the myocardium. However, this method is not very sensitive [22]. Changes in hs-cTnT levels have been found to be independently associated with coronary heart disease, progressive myocardial damage, and severe heart failure [23], having important clinical implications for the detection of complications in an anthracycline-based chemotherapy regimen [22]. In addition, previous studies have found that increased NT-proBNP levels after chemotherapy are significantly correlated with 1-year mortality. Even in the absence of LVEF changes, serum NT-proBNP testing can support early diagnosis of cardiac damage [24]. This is also consistent with present findings. Even if changes before and after the LVEF experiment are not obvious and the changes in serum hs-cTnT and NT-proBNP levels are large, this may indicate that the patient's cardiomyocytes are damaged. However, it may also have something to do with the timing of the experiments. Because of the timeliness of serum biological markers, the time point in the treatment process was chosen for testing. Observing cardiac function after treatment, LVEF is used to detect the time point after treatment. This may be one of the reasons for the difference. On the other hand, previous studies [25] have found that patients receive three to four cycles of trastuzumab after anthracycline-based chemotherapy, compared with 38.5% during trastuzumab treatment. Moreover, 2.7% of patients experienced grade III or IV cardiac adverse events, respectively. Although the study showed that patients with this level of adverse reactions were able to tolerate it, it also showed that the sequential treatment regimen of trastuzumab and anthracyclines was significantly more adverse. Other studies have suggested that the use of trastuzumab and anthracyclines is a safe alternative. After comparing trastuzumab with anthracyclines for synchronous therapy and anthracyclines alone, researchers found a significant increase in total pathologic response rates and no significant increases in cardiac toxicity [26]. This result is consistent with present results, suggesting that trastuzumab and anthracyclines work well in tandem, without causing additional toxic side effects.

There were still some deficiencies to the current study. First, this study only considered short-term efficacy in survival analysis. The follow-up time was not long enough. Follow-ups should be continued to observe the long-term survival of patients. Second, for comparisons of cardiac toxicity, the time chosen among different indicators was not completely consistent. This is used to observe the patient's myocardial tolerance and changes in cardiac function after treatment more realistically. However, the following time points can still be observed or further extended. Comparisons between the treatment process and multiple indicators at multiple time points after treatment may also need further discussion by other scholars. Third, due to limited conditions, the present experiment did not elaborate on how different cardiac toxicity levels were generated among the three groups.

In summary, simultaneous treatment with trastuzumab and anthracyclines can improve clinical efficacy and quality of life levels of patients, to a certain extent. This treatment method does not significantly increase cardiotoxici-

ty, thereby improving the prognosis of patients. Thus, it is worthy of promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Tao Li, Department of General Surgery, Shibei Hospital, No. 4500, Gonghexing Road, Jinan District, Shanghai 200435, China. Tel: +86-13917648223; E-mail: taoli5434664@163.com

References

[1] Torre LA, Siegel RL, Ward E and Jemal A. Global cancer incidence and mortality rates and trends-an update. Cancer Epidemiol Biomarkers Prev 2016; 25: 16-27.

[2] Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[3] Franceschini G, Martin Sanchez A, Di Leone A, Magno S, Moschella F, Accetta C, Masetti R. New trends in breast cancer surgery: a therapeutic approach increasingly efficacy and respectful of the patient. G Chir 2015; 36: 145-52.

[4] Finn DM, Ilfeld BM, Unkart JT, Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, Loland VJ and Wallace MS. Post-mastectomy cancer recurrence with and without a continuous paravertebral block in the immediate postoperative period: a prospective multi-year follow-up pilot study of a randomized, triple-masked, placebo-controlled investigation. J Anesth 2017; 31: 374-379.

[5] Gadgil A, Sauvaget C, Roy N, Muwonge R, Kantharia S, Chakrabarty A, Bantwal K, Haldar I and Sankaranarayanan R. Cancer early detection program based on awareness and clinical breast examination: interim results from an urban community in mumbai, India. Breast 2017; 31: 85-89.

[6] Iqbal N and Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. Mol Biol Int 2014; 2014: 852748-852748.

[7] Perez EA, Romond EH, Suman VJ, Jeong J, Sledge GW, Geyer CE, Martino S, Rastogi P, Gralow JR and Swain SM. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014; 32: 3744-52.

[8] Yeo W, Luk M, Soong IS, Yuen T, Ng T, Mo FK, Chan K, Wong S, Tsang J and Leung C. Efficacy and tolerability of trastuzumab emtansine in advanced human epidermal growth factor receptor 2-positive breast cancer. Hong Kong Med J 2018; 24: 56-62.

[9] Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE, Tanchiu E, Martino S, Paik S and Kaufman PA. Trastuzumab plus adjuvant chemotherapy for operable her2-positive breast cancer. N Engl J Med 2005; 353: 1673-1684.

[10] Zaheed M, Wilcken N, Willson ML, O'Connell DL and Goodwin A. Sequencing of anthracyclines and taxanes in neoadjuvant and adjuvant therapy for early breast cancer. Cochrane Database Syst Rev 2019; 2: CD012873.

[11] Tan J, Tan KA, Zaw AS, Hey D, Kumar A and Kumar N. Evaluation of prognostic factors and a modification to the modified tokuhashi score in patients with spinal metastases from breast cancer. The Spine Journal 2017; 17: S16.

[12] Dirix LY, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, Forero-Torres A, Boccia R, Lippman ME, Somer R, Smakal M, Emens LA, Hrinczenko B, Edenfield W, Gurtler J, von Heydebreck A, Grote HJ, Chin K, Hamilton EP. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN solid tumor study. Breast Cancer Res Treat 2018; 167: 671-686.

[13] Champion VL, Wagner LI, Monahan PO, Daggy JK, Smith L, Cohee AA, Ziner KW, Haase JE, Miller KD and Pradhan KR. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. Cancer 2014; 120: 2237-2246.

[14] Lin X, Chen W, Wei F, Ying M, Wei W and Xie X. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. Sleep Med 2015; 16: 1381-1387.

[15] Gold M, Dunn LB, Phoenix BJ, Paul SM, Hamolsky D, Levine JD and Miaskowski C. Co-occurrence of anxiety and depressive symptoms following breast cancer surgery and its impact on quality of life. Eur J Oncol Nurs 2016; 20: 97-105.

[16] Hosseini H, Obradovic MMS, Hoffmann M, Harper K, Sosa MS, Wernerklein M, Nanduri LK, Werno C, Ehrl C and Maneck M. Early dissemination seeds metastasis in breast cancer. Nature 2016; 540: 552-558.

[17] Gebhart G, Lamberts LE, Wimana Z, Garcia C, Emonts P, Ameye L, Stroobants S, Huizing MT, Aftimos P and Tol J. Molecular imaging as a tool to investigate heterogeneity of advanced HER2-positive breast cancer and to predict patient outcome under trastuzumab emtansine (T-DM1): the ZEPHIR trial. Ann Oncol 2016; 27: 619-24.

[18] Meattini I, Curigliano G, Terziani F, Becherini C, Airoldi M, Allegrini G, Amoroso D, Barni S, Bengala C and Guarneri V. SAFE trial: an ongoing randomized clinical study to assess the role of cardiotoxicity prevention in breast cancer patients treated with anthracyclines with or without trastuzumab. Med Oncol 2017; 34: 75.

[19] Piccartgebhart M, Procter M, Leylandjones B, Goldhirsch A, Untch M, Smith IE, Gianni L, Baselga J, Bell R and Jackisch C. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659-72.

[20] Dall P, Koch T, Gohler T, Selbach J, Ammon A, Eggert J, Gazawi N, Rezek D, Wischnik A and Hielscher C. Trastuzumab in human epidermal growth factor receptor 2-positive early breast cancer: results of a prospective, noninterventional study on routine treatment between 2006 and 2012 in germany. Oncologist 2017; 22: 131-138.

[21] Buzdar AU, Suman VJ, Meric-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, Unzeitig GW, Royce ME and Hunt KK. Disease-free and overall survival among patients with operable HER2-positive breast cancer treated with sequential vs concurrent chemotherapy: the ACOSOG Z1041 (alliance) randomized clinical trial. JAMA Oncol 2018; [Epub ahead of print].

[22] Blaes AH, Rehman A, Vock DM, Luo X, Menge M, Yee D, Missov E and Duprez DA. Utility of high-sensitivity cardiac troponin T in patients receiving anthracycline chemotherapy. Vasc Health Risk Manag 2015; 11: 591-4.

[23] Mcevoy JW, Chen Y, Ndumele CE, Solomon SD, Nambi V, Ballantyne CM, Blumenthal RS, Coresh J and Selvin E. Six-year change in high-sensitivity cardiac troponin t and risk of subsequent coronary heart disease, heart failure, and death. JAMA Cardiol 2016; 1: 519-28.

[24] De Iuliis F, Salerno G, Taglieri L, De Biase L, Lanza R, Cardelli P and Scarpa S. Serum biomarkers evaluation to predict chemotherapy-induced cardiotoxicity in breast cancer patients. Tumour Biol 2016; 37: 3379-87.

[25] Krop IE, Suter TM, Dang CT, Dirix LY, Romieu G, Zamagni C, Citron ML, Campone M, Xu N and Smitt M. Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo) adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. J Clin Oncol 2015; 33: 1136-42.

[26] Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas E, Theriault RL, Pusztai L, Green MC, Arun B and Giordano SH. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005; 23: 3676-85.