ORIGINAL RESEARCH

The Safety of Neoadjuvant Therapy with Polyethylene Glycol Liposome Adriamycin Combined with Docetaxel in Patients with Breast Cancer Complicated by Axillary Lymph Node Metastasis

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ABSTRACT

Objective • To evaluate the safety of the combination of pegylated liposomal doxorubicin and docetaxel in neoadjuvant therapy for breast cancer (BC) with axillary lymph nodes metastasis.

Methods • In this single-arm study, 91 patients with clinical stage IIA–IIIc BC received 6 cycles of pegylated liposomal doxorubicin plus docetaxel as neoadjuvant chemotherapy (NAC). Trastuzumab was allowed in patients with human epidermal growth factor receptor 2-positive tumors. The effects of new anthracycline-polyethylene glycol liposomal doxorubicin on the patients' hearts were studied. The changes in left ventricular ejection fraction (LVEF) before and after treatment were evaluated by echocardiography, and the levels of cardiac-specific biomarker troponin I (cTnI) and N terminal B natriuretic peptide (NT-pro-BNP) were noted before and after treatment.

Result • In our study, 88 patients completed 6 cycles of neoadjuvant chemotherapy. LVEF was within normal range; average LVEF was 67% at baseline, 66% after NAC. The difference was not statistically significant. However, LVEF decreased by more than 10% in 44.4% of patients. There was no significant difference in troponin I or NT-pro-BNP levels before or after treatment. No cardiac events with clinical symptoms were reported.

Conclusion • The combination of polyethylene glycol liposome adriamycin and docetaxel in neoadjuvant chemotherapy in patients with early BC with axillary lymph node metastasis has certain cardiac safety. And in the human epidermal growth factor receptor-2 (HER-2) positive population, polyethylene glycol liposome adriamycin combined with docetaxel and trastuzumab also has certain cardiac safety. (*Altern Ther Health Med.* 2023;29(4):177-183).

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INTRODUCTION

With the development of science and the advent of new therapeutic drugs, the prognosis in patients with cancer has greatly improved. Among these, chemotherapy cannot be downplayed. However, it is well known that chemotherapy is a double-edged sword; it provides patients with anti-tumor treatment effects, but also causes corresponding damage to other important organs of the patient's body. The benefits of anti-tumor therapy may also cause some patients common clinical liver dysfunction, bone marrow suppression and so on. And there are more hidden impacts on patients such as potentially life-threatening cardiac toxicity.[1] Patients may experience adverse cardiovascular (CV) events associated with cancer treatment or potential cardiovascular disease (CVD) exacerbation. CVD is now the second leading cause of long-term morbidity and mortality in cancer survivors.[2-4]

Cardiac dysfunction may be caused by drugs that can cause cardiomyocyte destruction—such as anthracycline—or may be derived from drugs that seem to temporarily affect left ventricular contractility. Moreover, cancer therapy may

be associated with other cardiac events. Routine chemotherapy and targeted therapy are associated with an increased risk for cardiac injury, including left ventricular dysfunction (LVD) and heart failure (HF). There are also some severe treatment-induced effects such as hypertension, vasospasm and thromboembolic ischemia arrhythmias, including prolonged QT intervals, which may, rarely, be life-threatening.[5-6]

In one recent comprehensive review of breast cancer (BC) survivors in the United States, it was noted that the risk for death from CVD in women increased significantly, exceeding their risk for death from the initial cancer itself or recurrent disease.[7-9] The incidence of CV system injury caused by cancer treatment varies greatly depending on the specific cancer treatment used, the duration of treatment and underlying patient concomitant disease. In general, treatment-related cardiac insufficiency in patients with BC is mainly attributed to the use of anthracycline and mediastinal irradiation. One of the more common is the use of anthracycline drugs. Conventional chemotherapy, such as anthracyclines, antimetabolites and cyclophosphamide, can induce permanent cardiomyocyte, leading to acute or chronic LVF.[10,11]

At present, anthracycline is a key component of many cytotoxic programs, which is considered to be the cornerstone of BC treatment. In the current domestic and foreign BC diagnosis and treatment guidelines and various expert consensus, whether in the field of early or advanced BC treatment, we can see a number of anthracycline-containing related treatment recommendations. However, it is well known that although anthracyclines as antitumor agents have improved the prognosis and achieved great success in patients with BC, their use is limited by cardiac toxicity.[12] Particularly when patients with human epidermal growth factor receptor-2 (HER-2) positive BC need to receive targeted therapy with cardiac toxicity, the choice of anthracycline drugs makes clinicians consider the possible cardiac toxicity of anthracycline drugs. Mechanisms of action of anthracycline-induced cardiac injury have been extensively studied and are not fully understood at present.[13]

The cardiotoxic effects of anthracycline have multiple clinical manifestations, possibly ranging from asymptomatic electrocardiogram abnormalities to long-term cardiomyopathy. In patients treated with anthracycline, early identification of cardiac toxicity and measures to reduce cardiac toxicity are extremely important and has become an important field of research in recent years. Pegylated liposomal doxorubicin (PLD) is a representative new formulation of anthracycline doxorubicin, designed to improve the therapeutic efficacy in patients with BC and minimize the adverse events (AEs) associated with conventional anthracycline. The unique delivery of this kind of drug encapsulates doxorubicin in a phospholipid bilayer coated with methoxy polyethylene glycol, which has an important effect on its pharmacokinetics and tissue distribution.[8]

The main purpose of our study was to observe the effect of new anthracycline-polyethylene glycol liposome adriamycin on neoadjuvant chemotherapy, especially on cardiac toxicity. Patients with HER-2 positive BC treated with trastuzumab were included in the study.

MATERIALS AND METHODS

Patient Selection

In this single-arm study, patients with early BC with ipsilateral axillary lymph node metastasis were diagnosed in the Fourth Hospital of Hebei Medical University, Tangshan People's Hospital and Qinhuangdao First Hospital in China from October 2015 to May 2017.

Ethics Approval

This study was approved by the system Ethics Committee of each participating research center and our institutional review board (IRB) also approved a comprehensive ethical review. All patients provided written informed consent before registering for the study. All procedures conducted in this study were in accordance with the ethical standards of the Helsinki Declaration and subsequent amendments.

Inclusion and Exclusion Criteria

Inclusion criteria. Patients were (1) female, age 18 to 70 years; (2) had primary BC (clinical stage IIA -IIIC) positive lymph nodes confirmed by histological examination; had a local measurable mammary gland tumor; (3) planning for neoadjuvant chemotherapy; (4) had a Karnofsky Performance Scale (KPS) score ≥70; (5) had an adequate reserve of bone marrow function: total WBC ≥4.0×109/ L; and platelets≥ 100×10^9/ L, neutrophils ≥2.0×10^9/ L, g /L, ≥ 90 μmol /L, serum creatinine 44-133, normal level of alkaline phosphatase ≤ 2× upper limit of normal, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2× upper limit of normal, bilirubin ≤upper limit of normal; (6) LVEF ≥50%; (7) life expectancy ≥12 months; (8) had a negative pregnancy test (women of childbearing age), and committed to effective contraception during and within 1 year after treatment; (9) signed an informed consent form. If the patient was incompetent for some reason, such as disturbance of consciousness, upper limb paralysis or inability to write, the informed consent of their legally authorized representative was obtained.

Exclusion criteria included patients who (1) had heart disease (New York Heart Association [NYHA]≥II] or severe systemic infections; (2) were allergic, highly sensitive or intolerant to polyethylene glycol liposomal doxorubicin, docetaxel and their excipients; (3) had received radiotherapy or used any test or other chemotherapeutic drugs within 30 days of the first administration; (4) whose participation in the study according to the researchers was not in the patient's best interest (for example, endangered their health) or placed them in any situation that could hinder the evaluation of the program.

At screening, researchers ensured that subjects met all inclusion criteria. If the patient's condition (including laboratory results) changed after screening and before administration of the first dose of the study medications, the patient was withdrawn from the study.

Echocardiography

All study patients underwent echocardiography by chest color Doppler imaging, using 2.5 MHz sensor. Echocardiographic measurements were performed with patients in the left supine position using the standard parasternal long axis and apical view. Record at least 3 consecutive heartbeats were obtained and averaged LVEF is calculated by Simpson's method. Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD), left anterior descending artery (LAD) and right ventricular systolic dysfunction (RVD) values were recorded. Early (E) and late atrial (A) waves were measured from the left ventricular filling records, and the E/A ratio was calculated. Ultrasound doctors collected and analyzed the results.

Blood Index Detection

Peripheral blood was drawn from all research subjects, centrifuged to obtain serum, and stored in a -80°C refrigerator.

Treatment Plan

The patients were given polyethylene glycol liposomal doxorubicin (Shijiazhuang Pharmaceutical Group Oyi Pharmaceutical Co., Ltd.) 30 to 35 mg/m^2 and docetaxel 75 to 80 mg/m^2 via intravenous drip the first day of each cycle (21 days plus 1 cycle), for a total of 6 cycles. Patients with HER-2 positive tumors were given trastuzumab in combination with vein for the first dose of 8 mg /kg, and then maintained at a dose of 6 mg /kg, the first day of each cycle (21 days plus 1 cycle), for a total of 6 cycles. Granulocyte colony stimulating factor (G-CSF) whitening therapy was given after each cycle. After all 6 cycles of neoadjuvant chemotherapy, patients underwent mastectomy or breast conserving surgery, and all patients underwent axillary lymph node dissection.

Results

The expression of estrogen receptor (ER) and progesterone receptor (PgR) was determined via immunohistochemical testing in all tumors, combined with fluorescence *in situ* hybridization (FISH) to detect HER-2 expression. If more than 1% of cancer cells were immunohistochemically ER and PR positive, cancer was classified as ER/PR positive. In a similar fashion, if the immunohistochemical score was 3 or FISH detected gene amplification, patients were classified as having HER-2 positive tumors. Cardiac function assessment was carried out via 2-dimensional echocardiography and estimation of the level of cardiac biomarkers (cTNI、NT-proBNP) prior to the first cycle of chemotherapy (baseline assessment). This was repeated after 6 months. 2D echocardiography was performed by a single operator on the EPIQ 7C cardiovascular system (Philips Research, Cambridge Massachusetts USA). FISH was used to measure NT-proBNP, chemiluminescence was for used cTnI the measurement. Normal: cTnI: 0.0 to 0.02ng/mL; NT-pro-BNP; 0 to 100 pg/mL; Outlier: cTnI: >0.02 ng/mL; NT-pro-BNP cTnI>100 pg/mL. Psychological status: patients' psychological status before and after treatment was assessed using the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS). Each scale contains 20 items (each worth 0 to 4 points), with a critical value of 50. Higher scores indicate more serious patient anxiety/depression.

Observed indicators

The primary outcome measure in this study was the incidence of cardiotoxicity, which was defined as a 10% reduction in LVEF from baseline to 6 months. Although it is clinically difficult to detect the occurrence of cardiotoxicity in the early stage via LVEF measurements, it has been the most common index used clinically to assess cardiac function.[1] Secondary outcome measures were cardiac biomarker cTnI and NT-pro-BNP levels at 6 months and HF or arrhythmia during this period.

Statistical Analysis

IBM™ SPSS.20 software was used for statistical analysis. Measurement data (denoted by [$\bar{x} \pm s$]) and count data (described [%]) were analyzed by independent paired-samples t test and Chi-square test, respectively. $P < .05$ indicated statistical significance.

RESULTS

Patients and Baseline Characteristics

A total of 91 patients were included in this study, with an average age of 50.4 years (29-67 years). All had between clinical stage IIa and IIIc BVn, and were to receive neoadjuvant chemotherapy with polyethylene glycol liposome adriamycin and docetaxel. HER-2 positive patients received trastuzumab targeted therapy at the neoadjuvant stage. Of all patients included in the study, 88 (96.70%) completed all neoadjuvant chemotherapy cycles. A total of 3 patients stopped treatment: 1 had serious adverse events (SAEs), 1 had chemotherapy intolerance and 1 changed chemotherapy regimen due to disease progression. Of the 88 patients, 16 (17.6%) received trastuzumab and 75 (82.4%) received adjuvant treatment. We analyzed PCR-related factors such as ER and PgR status, Ki-67, HER-2 positive status and BC subtype. The result are shown in Table 1.

Ventricular Function

According to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.0, all patients' LVEF was within normal range during neoadjuvant chemotherapy. The average baseline LVEF was 67% (55% to 82%); after neoadjuvant chemotherapy it was 66% (55% to 75%), ie, there was no statistical difference ($P > .05$) (see Table 2 for statistical results). Left ventricular systolic dysfunction, (LVSD): A total of 4 patients (4.4%) showed an LVEF decrease of >10% during treatment. All 4 patients were HER-2 negative and had no symptoms. Compared with the baseline data before chemotherapy, there were no significant changes in cardiac biomarker NT-pro-BNP or cTnI levels after 6 months of treatment ($P > .05$; Table 2).

Table 1. Baseline Demographics and Characteristics of Study Patients (n = 91)

	n	%
Age		
Mean	50.4	
Median (range)	51 (29-67)	
ECOG performance status		
0	75	82.4
1	16	17.6
Clinical stage		
IIa	9	9.9
IIb	36	39.6
IIIa	27	29.7
IIIb	8	8.8
IIIc	11	12.1
Menopausal status		
premenopausal	69	75.8
postmenopausal	22	24.2
Breast cancer subtype (stratification)		
HER-2 (-)	52	57.1
HER-2 (+)	39	42.9
Treatment with trastuzumab		
Yes	16	17.6
No	23	25.3
Estrogen receptor		
Positive	71	78.0
negative	20	22.0
Progesterone Receptor		
positive	29	31.9
negative	62	68.1
Ki-67		
<15%	22	24.2
15%~30%	21	23.1
>30%	48	52.7
Subtype		
Luminal A	13	14.3
Luminal B [Her-2 (-)]	32	35.2
Luminal B [Her-2 (+)]	27	29.7
HER-2 positive (HR-)	12	13.2
Triple negative	7	7.7

Abbreviations: ECOG, Eastern Oncology Cooperative Group.

Table 2. Statistical results

	LVEF	NT-pro-BNP	cTnI
Pre-chemotherapy	66.0 ± 0.60	14.67 ± 8.82	0.012 ± 0.005
Post-chemotherapy	65.9 ± 0.62	15.79 ± 8.44	0.012 ± 0.005
t	1.100	0.870	1.000
P value	.273	.385	1.000

Table 3. Treatment-Related Toxicity (n = 91)

Adverse Events (AEs)	Grade 1-2		Grade 3		Grade 4	
	n	%	n	%	n	%
Hematological toxicity						
Neutropenia	5	5.5%	2	2.2%	-	-
Leukopenia	4	4.4%	1	1.1%	-	-
Anemia	1	1.1%	1	1.1%	-	-
Non-hematological toxixity						
Increased creatinine	3	3.3%	-	-	-	-
ALT increase	8	8.8%	3	3.3%	-	-
AST increase	9	9.9%	-	-	-	-
Nausea	4	4.4%	-	-	-	-
Vomiting	3	3.3%	-	-	-	-
Stomatitis	6	6.6%	3	3.3%	-	-
Hand-foot syndrome	7	7.7%	6	6.6%	1	1.1%
Pneumonia	3	3.3%	2	2.2%	1	1.1%
Fever	4	4.4%	-	-	-	-
Pigmentation of skin	2	2.2%	-	-	-	-
Cough	1	1.1%	-	-	-	-
Hyperglycemia	-	-	1	1.1%	-	-
LVEF decline >10%	4	4.4%	-	-	-	-
Other grade AEs	6	6.6%	-	-	-	-

Table 4. Comparison of SAS and SDS Scores Before and After Treatment

	SAS scores	SDS scores
Pre-chemotherapy	28.3 ± 8.5	27.2 ± 7.1
Post-chemotherapy	13.9 ± 5.1	10.9 ± 5.7
t	13.860	17.080
P value	<.001	<.001

Abbreviations: SAS, Self-rating Anxiety Scale; Self-rating Depression Scale.

Drug Toxicity

As shown in Table 3, hand-foot syndrome (HFS) was the most common adverse event, occurring in 14 (15.4%) stage I-II patients. Typical symptoms were local numbness and desquamated skin; these were effectively controlled after symptomatic treatment and did not affect treatment progress. A total of 9 patients (9.9%) developed stomatitis during neoadjuvant chemotherapy, but had complete recovery after symptomatic treatment. Only 1 patient (1.1%) developed severe renal insufficiency, resulting in discontinuation of neoadjuvant chemotherapy. In addition, neutrophil reduction, leukopenia and skin pigmentation were observed, and ALT and AST were mildly elevated. We closely monitored patients for any changes in central function during neoadjuvant chemotherapy. No significant abnormal changes in cardiac function were found in any patient. According to NCI CTC V4.0, LVEF in all patients was within normal range during neoadjuvant chemotherapy; average LVEF at baseline was 66% (55% to 68%) and it was 65.9% (54% to 67%) after neoadjuvant chemotherapy. Meanwhile, during the study, 4 patients (4.4%) had an LVEF decrease of >10% during treatment. However, none of the patients had symptoms.

Comparison of Psychological Status

In modern clinical treatment, change in patients' psychological status is one of the most important links in clinical medical service. Therefore, it is very important to assess the psychological status of patients during treatment. In this study, we used Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) scores to compare patients' psychological status. As shown in Table 4, the SAS and SDS scores of patients before treatment were 28.3 ± 8.5 and 27.2 ± 7.1, respectively, while the post-treatment scores

were 13.9 ± 5.1 and 10.9 ± 5.7, respectively, significantly lower than before treatment ($P < .05$). This indicates that the adverse psychological state of patients was effectively improved after treatment.

DISCUSSION

BC has become the number 1 malignant tumor worldwide, and the incidence has been increasing every year. With the scientific and technological developments that have taken place, the advent of new drugs and the promotion of standardized diagnosis and treatment of BC, more and more patients with BC can achieve long-term survival. While continuing to pursue improved therapeutic effects, people are paying increasing attention to adverse events and long-term toxicity. Anthracyclines have been used to treat BC for nearly 50 years, and to treat many other different cancers, including lymphoma, leukemia and sarcoma.[15] Anthracyclines, derived from streptomyces, have been the most effective anti-cancer drugs to date.[16] Common anthracyclines include doxorubicin, mitoxetone, abiromycin, doxorubicin and daunorubicin. Anthracyclines have anti-tumor properties that have 4 main mechanisms of action: they disrupt DNA and RNA synthesis via intercalation between base pairs; inhibit topoisomerase II, leading to DNA breakage and prevention of ligase repair[17]; lead to histone expulsion; attenuate DNA repair[18]; and produce iron-mediated free radicals that destroy DNA.[19] Previous research suggested that free radical production induces lipid peroxidation and membrane damage as possible toxic mechanisms. Because of the high affinity of anthracyclines for cardiac phosphoproteins, the heart is particularly vulnerable to this damage.[20] Reduction in the number of cardiomyocytes due to cell and mitochondrial membrane damage is one of the other suggestive mechanisms of doxorubicin-induced cardiotoxicity.[5] Adriamycin-induced HF may occur within hours, weeks or years of exposure, and increases with the cumulative dose of anthracycline: 3% to 5% of patients taking 400 mg/m2, 7% to 26% patients taking 550 mg/m2 and 18% to 48% of patients taking 700 mg/m^2 develop HF.[21-23] Individuals at high risk include patients of extreme age (5 years< or >65 years), who received chest radiation and who have preexisting heart disease or established CV risk factors.[24]

Cardiac toxicity may be acute, early, or delayed, depending on the time of onset. Specifically, acute cardiac toxicity is generally characterized by a transient and rapid decrease in left ventricular systolic force after anthracycline administration. Early onset cardiotoxicity develops during the first year of treatment, while late onset cardiotoxicity develops one year *after* treatment and follows a chronic, progressive course. LVEF is the most common cardiac functional parameter that independently predicts short- and long-term mortality from adverse CV events, including myocardial infarction, ischemic and idiopathic cardiomyopathy and anthracycline-induced cardiomyopathy.[25-29] In our study, we performed careful cardiac monitoring with echocardiography in patients with HER-2 positive disease and found no significant changes in cardiac function. Only 4.4% of patients had a decrease in LVEF of more than 10%, and the lowest LVEF in these patients was >50%. And there were clinical symptoms of the heart.

Furthermore, current studies suggest that LVEF measurement, although convenient, is still a relatively insensitive tool for detecting cardiac toxicity in early stages with some difficulties and limitations. This is largely because the decline in LVEF was not likely to occur until a critical amount of myocardial injury and depletion of cardiac compensatory mechanisms had occurred.[30] Therefore, we selected cTn I and NT-pro-BNP for our observation index.

At the same time, the study confirmed that the likelihood of anthracycline-induced HF doubled with increasing age. Even worse for both doctors and patients, this cardiotoxicity is often irreversible, greatly affecting long-term survival and QoL[40] in patients with cancer. Therefore, oncologists are committed to various studies to avoid or reduce the occurrence of such toxicity. Several currently commonly used cardiac protection strategies in clinical practice, such as limiting the cumulative dose of anthracycline; prolonging the infusion time without reducing the dose; using anthracycline analogs plus drugs, including N-acetylcysteine, tetrazole ring, cyclic ring and captopril. Various angiotensin-converting enzyme (ACE) inhibitors, such as captopril and enalapril, have been used as chemotherapeutic adjuvants to reduce oxidative stress and minimize the production of free radicals, ultimately with the primary aim[31] of reducing cardiac toxicity.

In our study, we assessed the levels of cardiac biomarkers NT-proBNP and CTnI before and 6 months after the onset of treatment, as well as at baseline and 6 months after the onset of chemotherapy and chemotherapy in patients. The results showed that the levels of these 3 markers did not change significantly at 6 months.

HER-2 targeted drugs are a class of drugs that specifically target and inhibit HER-2/neu receptors (also known as ERBB2). Before HER-2 targeted therapy, patients with HER-2 positive BC had a poor prognosis, due to the invasiveness of rapidly growing cancers.

Tratuzumab is a humanized monoclonal antibody. Activation of specific epidermal growth factor can be blocked by HER-2/nerve receptors. inhibition of epidermal growth factor/ HER-2 ligand receptor activity, destruction of intracellular tyrosine kinase phosphorylation, whereas tyrosine kinases are key regulators of cell growth and survival. Administration of trastuzumab with chemotherapy improves theprognosis in patients with metastatic[32] and early operable breast cancer.[33] Although trastuzumab improves response rates in early BC, the risk for cardiac dysfunction is slightly increased; the risk for left ventricular dysfunction is 2.1% after treatment stops, and this risk can be improved.[34] Presumably, the cardiac dysfunction associated with trastuzumab is the result[35] of direct outcomes that inhibit HER-2 in cardiomyocytes. Compared with anthracycline-induced cardiotoxicity, trastuzumab exposure can lead to LVD and HF, which are appear to be essentially reversible.[36]

The highest risk for cardiotoxicity associated with exposure to trastuzumab was in patients aged >50 years, with potential heart disease or hypertension, with a baseline LVEF of 50% to 55% or less and who also received anthracycline therapy. Combined chemotherapy and trastuzumab in neoadjuvant therapy resulted in a large increase in the pathologic complete response (pCR) rate. Although the clinical significance of trastuzumab for asymptomatic left ventricular dysfunction (LVD) is unclear, clinicians have recognized this change and are increasingly paying attention to the hidden cardiotoxicity and will adjust treatment regimens accordingly. However, the simultaneous use of trastuzumab and anthracyclines[37] is associated with a high risk for cardiac toxicity. Although new anti-HER-2 therapy drugs have also been developed in recent years, such as small molecule tyrosine kinase inhibitor lapatinib and our new domestic drug pyrrotinib, because of the short amount of time such drugs have been on the market, evidence-based medical proof in neoadjuvant therapy is not sufficient to completely replace trastuzumab.

Therefore, the strategy of improving cardiac toxicity is more focused on the choice of anthracycline drugs. The use of fewer cardiotoxic anthracyclines minimizes the risk for cardiac adverse events. In the context of anthracycline, there are some oncology-based strategies to reduce the likelihood of treatment-related cardiac toxicity. It has been recommended that oncologists use liposomes to encapsulate doxorubicin in patients considered to exceed the recommended cumulative dose of anthracycline for life. Because of its molecular size, liposome-encapsulated anthracyclines are more preferentially distributed in tumors, because neovascular endothelial development of tumors is incomplete, resulting in stronger permeability. At the same time, it regulates the relative transmission of drugs to other organs, including the heart, and protects normal tissues. A recent analysis of 2 randomized controlled trials that included 521 patients concluded that clinical HF and subclinical cardiac dysfunction were less common in patients treated with liposomal anthracycline than in non-liposomal anthracycline.[38]

PLD and trastuzumab were administered simultaneously in this trial, and the outcome showed that the combined treatment was not significant or safe for cardiac function. In addition, chemotherapy drugs generally have strong toxic and adverse effects that can predispose patients to fear, rebellion and other negative psychology in the treatment process, which is not only not conducive to treatment, but may affect treatment outcomes.[39] In our study, patients' SAS and SDS scores decreased after treatment, indicating that the patients had a better experience with their chemotherapy regimen (polyethylene glycol liposome adriamycin combined with docetaxel). This greatly improved patients' negative psychology and provided a more reliable guarantee of their safety.

Study Limitations

Limitations of this study include a relatively short follow-up of 6 months. In the future, it is necessary to follow these patients regularly evaluate their cardiac function. In addition, the sample size of the study was small.

However, our study showed that the combination of PLD and docetaxel, coupled with trastuzumab in patients who are HER-2 positive, was highly active and provided acceptable safety in these patients with early BC with axillary lymph node metastasis. Moreover, this study suggested that the simultaneous use of PLD and trastuzumab in patients with HER-2 positive BC may provide an effective anthracycline therapy protocol. No known associated cardiotoxicity of conventional anthracycline plus trastuzumab was found in treated patients.

In the future, we also plan to conduct additional studies on more patients with BC receiving such treatment to see if the results can be replicated. At the same time, we have begun research to explore whether some drugs related to heart disease can improve or prevent the cardiac toxicity caused by anthracycline. In addition, more prospective studies are needed to consolidate guidelines for the proper monitoring, prevention and treatment of cancer-related heart disease.

CONCLUSION

The combination of polyethylene glycol liposome adriamycin and docetaxel in neoadjuvant chemotherapy in patients with early BC with axillary lymph node metastasis has certain cardiac safety. And in the HER-2 positive population, polyethylene glycol liposome adriamycin combined with docetaxel and trastuzumab also has certain cardiac safety.

In the future, we also plan to conduct additional studies on more patients with BC receiving such treatment to see if the results can be replicated. At the same time, we have begun some research to explore whether some drugs related to heart disease can improve or prevent the cardiac toxicity caused by anthracycline.

CONFLICT OF INTEREST

None.

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