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Combination of pegylated liposomal doxorubicin and docetaxel as neoadjuvant therapy for breast cancer with axillary lymph node metastasis

Li Wang[1], Yang Hong[2], Jie Ma[3], Meng Han[4], Shuo Zhang[2], Baoen Shan[2] and Yunjiang Liu[2]

Abstract

Objective: To evaluate the efficacy and safety of the combination of pegylated liposomal doxorubicin and docetaxel as neoadjuvant therapy for breast cancer (BC) in patients with axillary lymph node metastasis.

Methods: In this single-arm study, 91 patients with clinical stage IIA–IIIc breast cancer received six cycles of pegylated liposomal doxorubicin plus docetaxel as neoadjuvant chemotherapy (NAC). Trastuzumab was allowed for patients with human epidermal growth factor receptor 2-positive tumors. The primary endpoint was pathologic complete response (pCR) in the breast after surgery. The overall response rate (ORR), Miller–Payne (MP) score of the primary tumors, and incidence of adverse events were also evaluated.

Results: In total, 88 patients completed all cycles of NAC. Fourteen patients (15.4%, 95% confidence interval [CI] = 7.8–22.9) achieved pCR. The ORR was 89% (95% CI = 82.5–95.6), and 72 lesions (79.1%) were rated as MP grade 3 or higher. The left ventricular ejection fraction (LVEF) was within the normal range, although four (4.4%) patients experienced an LVEF decline exceeding 10%. No symptomatic cardiac events were reported.

Conclusion: Preoperative NAC with pegylated liposomal doxorubicin and docetaxel appears effective and safe for treating BC with axillary lymph node metastasis.

[1]Department of Breast Surgery, Xingtai People's Hospital, Xingtai, Hebei, China
[2]Department of Breast Center, Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
[3]Department of Breast Surgery, Tangshan People's Hospital, Tangshan, Hebei, China
[4]Department of Breast Surgery, First Hospital of Qinhuangdao, Qinhuangdao, Hebei, China

Corresponding authors:
Yunjiang Liu and Baoen Shan, Department of Breast Center, the Fourth Hospital of Hebei Medical University, Jiankanglu 12, Shijiazhuang 050011, Hebei, China.
Emails: lyj818326@126.com; baoenshan@hotmail.com

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Introduction

Neoadjuvant chemotherapy (NAC) is of great significance for treating breast cancer (BC) with axillary lymph node metastasis because of its potential to permit surgery for previously inoperable tumors and offer a better chance of breast preservation in patients ineligible for breast-conserving mastectomy.

Anthracyclines combined with taxanes such as docetaxel are among the most active regimens in the treatment of BC, and they have been widely accepted as the standard NAC protocols.[1] Nevertheless, a consensus has not been reached regarding the optimization of these protocols, partly owing to the limited use of anthracyclines because of their potential risk of cumulative cardiac damage. Pegylated liposomal doxorubicin (PLD), a novel dosage form of the representative anthracycline doxorubicin, was developed to improve the therapeutic efficacy and minimize the side effects of conventional anthracyclines. The unique formulation encapsulates doxorubicin within a phospholipid bilayer coated with methoxypolyethylene glycol, which significantly modifies its pharmacokinetics and tissue distribution. Pegylation protects liposomes from detection by the mononuclear phagocyte system, thereby prolonging the circulation time of PLD in the bloodstream.[2] At doses of 10 to 80 mg/m^2, there can be one or two distribution phases: an initial phase with a half-life of 1 to 3 hours and a second phase with a half-life of 30 to 90 hours.[3] PLD can selectively penetrate the endothelial aperture of tumor blood vessels to release doxorubicin at the tumor site, but the drug is rarely release in plasma and healthy tissues. Several studies revealed that the uptake of PLD into the hearts of rodents was lower than that for free doxorubicin, revealing an important advantage of PLD.[3] Clinical studies also revealed that the risk of cardiotoxicity was significantly reduced by PLD. O'Brien et al. conducted a phase III study comparing doxorubicin and PLD as a first-line treatment for 509 patients with metastatic BC. In that study, the overall risk of cardiotoxicity was remarkably higher in the doxorubicin group than in the PLD group (hazard ratio [HR] = 3.16; 95% confidence interval [CI] = 1.58–6.31; $P < 0.001$). In addition, PLD displayed comparable activity as doxorubicin, with overall survival (OS) times of 21 and 22 months, respectively (HR = 0.94, 95% CI = 0.74–1.19).[4]

Because the achievement of pathologic complete response (pCR) may improve survival, this variable can also be used as an indicator for identifying disease-free survival (DFS) and OS after surgery in patients with BC and axillary lymph node metastasis or operable BC.[5–7] Nevertheless, improving pCR using NAC remains a major challenge for clinical because of the limitations of conventional agents, which necessitates additional research on the pathologic responses to newly developed approaches and drugs used for NAC, such as PLD.

Therefore, this study examined the efficacy and safety of PLD for treating patients with BC and axillary lymph node metastasis using pCR as the primary endpoint in addition to other evaluation indicators.

Materials and methods

Patients

Patients diagnosed with BC and axillary lymph node metastasis at the Fourth Hospital of Hebei Medical University, Tangshan People's Hospital, and First Hospital of Qinhuangdao between October 2015 and May 2017 were enrolled in this single-arm study. The inclusion criteria were as follows: (1) women aged 18 to 70 years; (2) primary BC (clinical stage IIa–IIIc and lymph node positivity) confirmed via histological examination with a measurable tumor; (3) scheduled for NAC; (4) Karnofsky (KPS) score $\geq$70; (5) adequate bone marrow functional reserve (total white blood cells $\geq 4.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, neutrophils $\geq 2.0 \times 10^9$/L, hemoglobin $\geq$90 g/L, serum creatinine = 44–133 μmol/L, alkaline phosphatase $\leq 2\times$ upper limit of normal, AST and ALT $\leq 2\times$ upper limit of normal); (6) left ventricular ejection fraction (LVEF) $\geq$50%; (7) expected survival $\geq$12 months; (8) negative pregnancy test result for women of childbearing age and use of contraceptives by both the patient and her spouse during and for 1 year after treatment; and (9) provision of written informed consent. If the subject was not sufficiently competent for reasons such as disturbance of consciousness, paralysis of upper limbs, or inability to write, informed consent was obtained from the legally authorized representative.

The exclusion criteria included cardiac disease (New York Heart Association $\geq$class II) and severe systemic infection. The patients were excluded if they were allergic, highly sensitive, or intolerant to PEG, docetaxel, or its excipients. Patients who had received radiotherapy or used any test drug or other chemotherapy agents within 30 days prior to the first dose of the study drug were also not allowed to register in this study. In addition, if the researchers believed that participating in the trial was not in the best interests of the subjects (e.g., endangering their health) or that the study could place them in any situation that would hamper the evaluation of the protocol, then the subjects were excluded.

At screening, the researchers ensured that subjects met all inclusion criteria. Subjects were removed from the trial if their condition, including the laboratory results, had changed after screening and before administration of the first dose of the study drug.

Treatment plan

The patients received both PLD (Shijiazhuang Pharmaceutical Group Ouyi Pharmaceutical Co., Ltd., Shijiazhuang, China) 30 to 35 mg/m^2 and docetaxel 75 to 80 mg/m^2 intravenously on day 1 of each cycle (21 days) for a total of six cycles. Patients with human epidermal growth factor receptor 2 (HER2)-positive tumors were concurrently treated with intravenous trastuzumab $8 \rightarrow 6$ mg/kg on day 1 of each cycle for six cycles. Granulocyte-colony stimulation factor was administered to these patients after each cycle. Following the completion of NAC, mastectomy or breast-conserving surgery was performed, and all patients underwent axillary lymph node dissection.

Study assessments

All tumors were examined for estrogen receptor (ER), progesterone receptor (PgR), and HER2 expression via immunohistochemistry (IHC) combined with fluorescence in situ hybridization (FISH). Tumors were classified as ER-positive if more than 10% of cancer cells exhibited positive staining on IHC. Likewise, patients were categorized as having HER2-positive tumors if they were scored as 3+ by IHC or

gene amplification (2.0) was identified by FISH.

The tumor assessment was performed via physical examination at baseline and on day 1 of each chemotherapy cycle and by mammography with ultrasound or MRI of the breast at baseline as well as during cycles 2, 4, and 6. RECIST version 1.1 was applied for evaluating the clinical response.

pCR (breast) was defined as the absence of histological evidence of invasive carcinoma in the breast, and pCR (breast + lymph nodes) was defined as the absence of histological evidence of invasive cancer in the breast and axillary lymph nodes. pCR (breast) and pCR (breast + lymph nodes) were evaluated separately. The rate of the conversion to axillary node negativity following NAC was also analyzed.

Adverse events, graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4, were recorded at baseline and after each treatment cycle. Multiple uptake gated acquisition scanning was employed to assess cardiac toxicity at baseline and after every other dose of trastuzumab.

Study endpoints

In the present study, the primary endpoint was the pCR (breast) rate at the time of completion of surgery. The secondary endpoints were pCR (breast + lymph nodes), the overall response rate (ORR, complete response [CR] + partial response [PR]), the rate of grade 4 to 5 responses assessed using the Miller–Payne (MP) grading system, and the incidence of adverse events during NAC.

Statistical analysis

The target enrollment for this phase II trial was calculated using SAS (V9.2, North Carolina State University, Raleigh, NC, USA). It was assumed that the investigational regimen would be of no interest if the pCR rate was $\leq 8\%$ and of interest if the pCR rate was $>8\%$.[6–20] Accordingly, a minimum total sample size of 90 patients was calculated. Assuming a 10% dropout rate, the target enrollment was 100 patients. The hypothesis test was resolved with $\alpha = 0.05$ and power $= 0.80$ using a one-sample hypothesis test for proportion from $\pi = 0.08$ versus the unilateral alternative ($\pi > 0.08$) based on the normal approximation. Statistical description was used as the main method. Demographic characteristics and toxicity rates were presented using frequency tabulations with corresponding percentages. Pathological and clinical response rates (RRs) were described as the number of cases and rate, and presented as point estimates with corresponding exact 95% confidence intervals (CIs).

Ethical approval

This study was approved by the institutional ethics committee of all participating research centers. Our Institutional Review Board also exempted the study from a full board review. All procedures performed in this study were in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Results

Patients and baseline characteristics

Ninety-one patients (mean age, 50.4 years), who primarily had clinical stage IIb and IIIa tumors, were recruited into this study and treated with PLD and docetaxel as NAC. Among the included patients, 88 (96.70%) completed all cycles of NAC (the minimum sample size was not reached, but the purpose of the study could be achieved according to the statisticians). Three patients discontinued treatment

because of serious adverse events (n = 1), intolerance to chemotherapy (n = 1), or disease progression necessitating a change of the chemotherapy regimen (n = 1). Only 16 patients (17.6%) were administered trastuzumab, and 75 patients (82.4%) received adjuvant therapy. The factors related to pCR, including the ER, PgR, and HER2 status; Ki-67; and BC subtype, were also analyzed, as shown in Table 1.

Table 1. Demographics and characteristics of the patients at baseline (n = 91).

	n	%
Age, years		
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)		
HER2−	52	57.1%
HER2+	39	42.9%
Treatment with trastuzumab		
Yes	16	17.6%
No	23	25.3%
ER		
positive	71	78.0%
negative	20	22.0%
PgR		
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 (HER2−)	32	35.2%
Luminal B (HER2+)	27	29.7%
HER2-positive (HR−)	12	13.2%
Triple-negative	7	7.7%

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Assessment of treatment efficacy

The clinical and pathologic assessment is summarized in Table 2. The majority of the patients (89% [81/91], 95% CI = 82.5–95.6) exhibited a clinical CR (16, 17.6%) or partial response (65, 71.4%) before surgery. Eighty-nine patients (97.8%) underwent breast surgery after NAC.

Overall, pCR (breast) was achieved in 14 patients (15.4%, 95% CI = 7.8–22.9) at various clinical stages (IIA, n = 2; IIB, n = 3; IIIA, n = 6; IIIB, n = 2; IIIC, n = 1). In the present study, 20.5% (8/39) of patients with HER2-positive tumors achieved pCR, significantly exceeding the rate of 11.5% (6/52) in the HER2-negative population. Similarly, eight patients had hormone receptor (HR)-positive tumors. Conversion to axillary node negativity was achieved in 26 patients. pCR (breast + lymph nodes) was achieved in 10 patients (11.0%, 95% CI = 4.4–17.5).

Additionally, 16 (17.6%) and 14 tumors (15.4%) were classified as MP grades 4 and 5, respectively. CR was recorded in 16 patients (17.6%), and PR was identified in 65 patients (71.4%), contributing to an ORR of 89%.

Treatment-related toxicity

As presented in Table 3, the most commonly observed side effect was hand-foot syndrome (HFS, 14, 15.4%), which was mostly grade I–II severity and featured the typical symptoms of local numbness and peeling. The symptoms were effectively controlled after symptomatic treatment without disturbing the treatment of malignancy.

Table 2. Assessment of treatment efficacy (n = 91).

	n	%	95% CI
Clinical response (before surgery)			
CR	16	17.6%	
PR	65	71.4%	
SD	9	9.9%	
PD	1	1.1%	
ORR (CR + PR)	81	89%	82.5–95.6
Pathological response			
pCR (breast + lymph nodes)	10	11.0%	4.4–17.5
pCR (breast)	14	15.4%	7.8–22.9
Lymph node negativity	26	28.6%	
MP score			
MP score ≤3	61	67%	
MP score 4	16	17.6%	
MP score 5	14	15.4%	
Surgery	89	97.8%	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; pCR, pathological complete response; MP score, Miller–Payne score; CI, confidence interval.

Nine patients (9.9%) developed stomatitis during NAC and experienced complete recovery following symptomatic treatment. Severe renal dysfunction was only recorded in one patient (1.1%), and this event resulted in the discontinuation of NAC. In addition, conditions such as neutropenia, leukopenia, and skin pigmentation, as well as laboratory changes including ALT and AST elevation, were also observed, but they were mild in severity and controlled after proper clinical management. Substantial attention was paid to the changes of cardiac function during the course of NAC via electrocardiography during each cycle and echocardiography every other cycle, which revealed no significantly abnormal changes in any patients. According to NCI-CTC version 4.0, LVEF was also within the normal range throughout the course of NAC in all subjects. The mean LVEF was 67% (range,

Table 3. Treatment-related toxicity (n = 91).

	Grade 1–2		Grade 3		Grade 4	
AE	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 toxicity						
Increased creatinine	3	3.3%	–	–	–	–
ALT elevation	8	8.8%	3	3.3%	–	–
AST elevation	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%	–	–	–	–

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction.

55%–82%) at baseline and 66% (range, 55%–75%) after NAC. No cases of left ventricular systolic dysfunction were reported. Four patients (4.4%) experienced a >10% decline of LVEF.

Discussion

A number of studies reported clinical RRs of 58% to 91% and pCRs of 3% to 41% after NAC in patients with BC.[8–21,26] Although there is no consensus concerning the optimal protocol for treating BC, it is generally agreed that anthracyclines and taxanes are among the best options. Phase II and III trials have been conducted to examine different combinations of these agents.[8–21,26] The clinical RR of doxorubicin and docetaxel as NAC for BC was 70%.[10] Regarding the use of the combination of epirubicin, cyclophosphamide, and paclitaxel as NAC for patients with stage II–III BC, the ORR and pCR rate were 83.7 and 15.1% respectively. However, the clinical benefits of conventional anthracyclines are limited by their toxicities, especially cardiac toxicity.

PLD has been recognized as an alternative to conventional anthracyclines for BC treatment. However, to the best of our knowledge, only a few studies have tested PLD in combination with other antineoplastics as NAC for BC, with the result revealing an ORR of 62% to 74% and pCR rate of 3% to 16%, PLD was generally well tolerated in subjects, and toxicities were usually mild.[14–17] A recent study demonstrated that PLD plus cyclophosphamide followed by docetaxel is effective and tolerable as NAC in patients with locally advanced BC, with an ORR of 68.75% and pCR rate of 18.75%.[22] Yao et al.[23] found that PLD-based NAC provided comparable efficacy to epirubicin-based treatment in patients with stage II–III locally advanced BC, producing an ORR of 74.1% and pCR rate of 18.5%. A previous study indicated that the combination of PLD and docetaxel is effective and well tolerated in patients with metastatic BC, and we are currently focusing on the use of this regimen as NAC.[24] In this study, the combination of PLD and docetaxel contributed was linked to a clinical ORR of 89% (95% CI = 82.5–95.6) and pCR rate of 15.4% (95% CI = 7.8–22.9). Generally, the efficacy reported in our study was comparable to the findings of other trials related to NAC for BC.[8–25]

Based on the results of a previous BC trial, pCR was reported to be achieved more frequently for HER2-positive and ER-negative tumors than for other subtypes.[25] The finding of a higher pCR in the HER2-positive population was in line with the results of other studies indicating that more patients with HER2-positive tumors achieved pCR after treatment with Herceptin.[8–21,26]

HFS and stomatitis, as the most frequently observed clinical conditions in this study, were mainly in grade I–II in severity and controllable. Most of the other adverse events and laboratory changes were also mild, and patients exhibiting these effects as well as those with relatively more severe events (≥grade 3) experienced a full recovery after appropriate treatment, indicating that this protocol is well tolerated in most patients. Two patients withdrew from the study because of intolerance to chemotherapy or disease progression, and a third patient discontinued treatment because of severe renal dysfunction.

HER2-positive BC is an aggressive disease with a poor prognosis. For patients with HER2-positive lesions an metastasis as well as those with early, operable BC, trastuzumab-containing chemotherapy, which has also been assessed as a neoadjuvant regimen, has a major role in improving outcomes.[21,27,28] Nonetheless, although NAC supplemented with trastuzumab could result in a substantial increase in

the pCR rate, concomitant trastuzumab and anthracycline therapy may result in remarkably increased cardiotoxicity,[29] making this regimen controversial. The use of anthracyclines with lower cardiotoxicity in NAC protocols can minimize the risks of cardiac side effects. Previous research indicated that PLD-based NAC exhibited safety regarding cardiac toxicity,[22,23] and normal cardiac function was observed in patients treated with PLD and trastuzumab.[30] In the current study, patients, especially those with HER2-positive BC, underwent careful cardiac monitoring, and the LVEF was within the normal range, although four patients (4.4%) experienced an LVEF decline exceeding 10%. The results demonstrated PLD provides comparable efficacy and less toxicity, particularly reduced cardiotoxicity, versus conventional anthracyclines, providing evidence for further clinical research and the optimization of neoadjuvant therapy for BC.

One limitation of this study was related to the approach used to evaluate the HER2 and HR status. BC is a heterogeneous disease that should be treated on the basis of the disease status and pathological features. Several studies compared samples from primary tumors with those from corresponding relapsed tumors, revealing discordance in ER, PgR, and HER2 expression.[31–33] The rate of discordance ranged from 10% to 30%, and the changes included both "gains" and "losses" of receptor expression. There is insufficient knowledge concerning the effect of NAC on the expression of molecular markers in BC. Observations of changes in ER and HER2 expression in the current study (data not shown) indicated that the HER2 status should be re-evaluated in surgical tissue specimens after NAC to identify the optimal adjuvant treatment. In addition, this study included a relatively small sample size and a heterogeneous patient population, and thus, the results must be verified in additional studies.

In conclusion, this study confirmed that PLD combined with docetaxel is associated with satisfactory therapeutic effects as NAC for BC, and the side effects of this regimen were mild and controllable in clinical settings. Moreover, for HER2-positive BC, trastuzumab can confer additional protection against cardiotoxicity when used in combination with PLD instead of conventional anthracyclines without compromising therapeutic efficacy. Certainly, clinical trials with larger sample sizes are necessary to further explore therapeutic options and optimize the NAC protocols for patients with BC.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iDs

Baoen Shan https://orcid.org/0000-0003-4775-104X
Yunjiang Liu https://orcid.org/0000-0002-7654-873X

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