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Original Article

Benefits of docetaxel and lobaplatin combined with concurrent chemoradiotherapy for locally advanced breast cancer

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Abstract: Objective: Locally advanced breast cancer (LABC) is best managed with neoadjuvant chemotherapy, followed by surgery and radiotherapy. However, most patients still have inoperable LABC after 4 cycles of adriamycin and cyclophosphamide neoadjuvant chemotherapy. Very few studies have addressed the next step for inoperable cases. This retrospective study analyzed the curative effects and side effects of docetaxel and lobaplatin, combined with concurrent chemoradiation, in patients with LABC by determining objective response rates (ORRs), survival, toxicity profiles, and feasibility of use with neoadjuvant concurrent chemoradiation. Methods: A total of 185 LABC patients, treated at the Department of Breast Surgery, Chongqing University Cancer Hospital, between January 2008 and December 2012, were selected. Patients were randomly divided into two groups. On the first day, the research group was given docetaxel and lobaplatin and patients completed 21 days of synchronous radiotherapy. The control group was given only docetaxel and lobaplatin. The two groups completed four cycles of neoadjuvant chemotherapy. The primary endpoint was patient 5-year progression-free survival (PFS). Patient ORR, 5-year overall survival (OS), and toxic side effects were also assessed. Patient characteristics and toxicity during treatment were recorded to evaluate curative effects and adverse reactions in both groups. Results: Both groups achieved good clinical efficacy after neoadjuvant treatment. However, ORRs, surgical resection rates, tumor cell apoptosis indices, PFS, and OS were significantly higher for the research group than the control group. Additionally, incidence of bone marrow suppression, gastrointestinal tract reaction, cardiac toxicity, and liver damage in the research group was compared with that of the control group. No significant differences were observed. There was more skin dermatitis toxicity in the research group. Conclusion: Present results suggest that the addition of radiation to neoadjuvant chemotherapy is promising because it improves PFS and OS, resulting in overall good outcomes. Docetaxel and lobaplatin, combined with neoadjuvant concurrent chemoradiation, for treatment of LABC can achieve good curative effects with tolerable toxicity. Thus, widespread application should be considered.

Keywords: Docetaxel, lobaplatin, concurrent chemoradiotherapy, locally advanced breast cancer

Introduction

Due to increasing incidence, breast cancer has become a major malignancy in some developed countries [1]. It has been reported that incidence of breast cancer accounts for 7% to 10% of all malignant tumors [2]. With advancements in diagnosis, the proportion of early-stage breast cancer among new cases has increased. However, locally advanced breast cancer (LABC) remains a prominent problem, accounting for 30% to 60% of new diagnoses [3]. LABC refers to T3 or T4 tumors with no distant metastasis and/or breast cancer with N2 or N3 lymph nodes [4]. Neoadjuvant chemotherapy (NAC) is a standard treatment option for LABC. Studies have shown that patients that achieve a complete pathological response (pCR) to NAC have a significantly improved rate of postoperative survival [5]. A previous study found that NAC can help with early eradication of subclinical lesions and improve the prognosis of patients with LABC [6]. NAC has been widely used to reduce tumor volume, to a certain extent, creat-

ing surgical opportunities for patients with LABC and improving treatment effects.

Although the overall survival rate has improved, treatment of LABC remains a concern, especially for LABC cases that remain inoperable after several cycles of NAC. Concurrent chemoradiotherapy (CCRT) is a new model for solid tumor treatment that has been widely used in patients with locally advanced cervical cancer [7] and nasopharyngeal cancer [8, 9], with good efficacy. However, the use of CCRT in neoadjuvant treatment of LABC patients has been rarely reported. Therefore, new and effective methods with tolerable toxicity are necessary for treatment of LABC.

Docetaxel is the most common single drug used for breast cancer chemotherapy. Amat et al. [10] reported that the clinical remission rate of NAC after docetaxel monotherapy for stage II and III breast cancer patients is 68.4%. The pCR rate is 19.8% and the breast-conserving rate is as high as 72.4%. Studies have shown that docetaxel has a significant effect on NAC in patients with LABC, though it is not effective with anthracyclines. The combination of docetaxel and NAC has achieved greater than 40% efficacy [11]. Clinical trials have confirmed that, with NAC, sequential docetaxel in LABC patients can produce better efficacy and increase the rate of pCR after an anthracycline regimen [12]. Lobaplatin shows good antitumor activity and low nephrotoxicity, as well as rates of resistance that do not completely overlap with other platinum therapies [13]. For example, studies have shown that lobaplatin had a synergistic effect on non-small cell lung cancer when combined with anti-tubulin drugs, producing stronger anti-tumor activity than can cisplatin [14]. Therefore, in this study, 97 patients with LABC, undergoing a 4-cycle adriamycin and cyclophosphamide regimen after NAC, were treated with neoadjuvant docetaxel and lobaplatin, combined with CCRT. The aim of this study was to investigate its efficacy and safety.

Methods

Patients and procedures

A total of 201 non-HER-2 LABC patients (stages IIIA-IIIC) were selected. These patients were admitted to the Department of Breast Surgery of Chongqing University Cancer Hospital, from January 2008 to December 2012, and remained inoperable after four cycles of adriamycin and cyclophosphamide NAC. Sixteen patients were excluded because of changes in their disease condition after enrolment. The 185 eligible patients were aged between 18 and 65 years and classified as having LABC, according to the TNM staging method of the American Cancer Joint Committee (AJCC), Seventh Edition [15]. The study was approved by the Ethics Committee of Chongqing Cancer Institute. All patients provided informed consent. All methods were performed in accordance with relevant guidelines and regulations. Patients were randomly divided into two groups: 97 patients in the research group and 88 patients in the control group. Eligible patients met the following criteria: Females; Good general condition (KPS score >80); No history of radiotherapy or biotherapy before treatment; No abnormalities found in routine blood tests or hepatorenal function, electrocardiogram, or echocardiography exams; Chemoradiation tolerance. All patients underwent further staging by computed tomographic scans of the chest, abdomen, and pelvis, as well as bone scans, to exclude detectable distant metastases. Patients with inflammatory breast cancer or severe heart, liver, and kidney damage were excluded. Baseline characteristics of the patients are reported in **Table 1**. There were no significant differences in age, menopausal status, mass location, size, regional lymph node status, clinical stage, pathological type, pathological grade, and molecular classification between the two groups (P>0.05; **Table 1**).

Treatment methods

In all 185 patients, a marker was placed in the center of the tumor before treatment. All patients were treated with docetaxel and lobaplatin NAC: 75 mg/m^2 docetaxel and 30 mg/m^2 lobaplatin were given intravenously on the first day. The effective dose was controlled within 85% to 100% according to toxicities for those receiving chemotherapy. At the same time, patients in the research group received local radiotherapy on the first day of the first cycle. The field was determined with a three-dimensional conformal intensity modulation technique. Irradiation area consisted of the ipsilateral breast and axillary, supraclavicular, and internal mammary lymph node drainage

Table 1. Relationships between clinicopathological factors of the two groups

Factor	n		χ^2 value	*P* value
	Research group (97)	Control group (88)		
Age				
≤35	29 (29.9%)	25 (28.4%)	0.049	0.824
>35	68 (70.1%)	63 (71.6%)		
Menopausal status				
No	72 (74.2%)	66 (75.0%)	0.015	0.904
Yes	25 (25.8%)	22 (25.0%)		
Side				
Right	46 (47.4%)	42 (47.7%)	0.002	0.967
Left	51 (52.6%)	46 (52.3%)		
Tumor diameter				
>5 cm	90 (92.8%)	83 (94.3%)	0.179	0.672
≤5 cm	7 (7.2%)	5 (5.7%)		
Regional lymph nodes				
N0~1	19 (19.6%)	14 (15.9%)	0.426	0.514
N2~3	78 (80.4%)	74 (84.1%)		
Pathological type				
Infiltrating ductal carcinoma	91 (93.8%)	84 (95.5%)	0.243*	0.750*
Infiltrating lobular carcinoma	6 (6.2%)	4 (4.5%)		
Pathological grade				
I~II	27 (27.8%)	25 (28.4%)	0.008	0.931
III	70 (72.2%)	63 (71.6%)		
Molecular type				
Luminal A	17 (17.5%)	15 (17.0%)	0.025	0.988
Luminal B	54 (55.7%)	50 (56.8%)		
Basal pattern	26 (26.8%)	23 (26.2%)		

*Fisher exact test.

regions. The dose inhomogeneity was a maximum of +10% and a minimum of -5% for 2 ccs of volume. The cumulative dose was 42 Gy/21 days, followed by 14 Gy at 2 Gy per fraction to the axilla and originally palpable tumor. Radiation was delivered at one fraction/day for 5 days per week. A skin protection agent was painted on the irradiated area and the skin lesion in the radiotherapy area was recorded. For patients receiving radiation that experienced more than grade 2 radiation reactions, the dose was reduced by 25%. For those experiencing a grade three radiation reaction, the dose was reduced by 50%. Indications of suspended radiation included myelosuppression of the third degree or higher, cardiac toxicity, and skin damage. Patients were withdrawn from the study if radiotherapy had to be delayed for more than 7 days. In this study, each chemotherapy cycle was 21 days. All patients completed 4 cycles of NAC. Routine blood, liver and kidney function, electrocardiogram, left ventricular ejection fraction, myocardial enzyme, and troponin examination results were recorded for each patient in each cycle. Efficacy and toxicity of treatments were evaluated before the next cycle of chemotherapy.

Efficacy and toxicity assessment criteria

Efficacy after treatment was evaluated for primary lesions according to new Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1 [16]. The size of tumor lesions was measured by mammary magnetic resonance imaging to determine the maximum diameter. Complete remission (CR) indicates complete disappearance of tumor lesions. Partial remission (PR) indicates the sum of the maximum diameter of tumor lesions decreased by at least 30%. Stable disease (SD) is defined as a decrease in the sum of the maximum diameter of tumor lesions that did not reach PR or an increase that did not reach progressive disease. Progressive disease (PD) is defined as the sum of the largest diameter of tumor lesions increasing by at least 20% or the appearance of new lesions. The objective response rate (ORRs) was CR+PR. Side effects of chemotherapy toxicity were evaluated according to WHO anti-cancer drug toxicity response classification [17]. Radiotherapy side-effect skin injuries were scored 0-4, according to Radiation Therapy Oncology Group (RTOG) criteria.

Follow-up procedure

After treatment, patients were followed up every 3 months. Patients were regularly followed-up with hospital visits for re-examina-

Table 2. Comparison of DCRs and ORRs after treatment in the two groups of patients (n)

Group	DCRs		*P* value	ORRs		*P* value
	Controlled	Un-controlled		Relieved	Un-relieved	
Research group	92	5	0.633	80	17	0.024
Control group	82	6		60	28	

The DCRs of the research group and the control group were high and there was no significant difference between the two groups (P>0.05). However, the ORRs of the research group after treatment was higher than that of the control group and there was a significant difference between the two groups (P<0.05).

Table 3. Comparison of surgical resection rates after treatment in both groups (n)

Group	Surgical resection	No surgical resection	χ^2 value	*P* value
Research group	88	9	4.624	0.031
Control group	70	18		

tions, as well as via letters and telephone calls. The follow-up period ended December 31, 2017. Three patients were lost to follow-up, including one in the research group and two in the control group. The follow-up rate was 97.6%.

Statistical analysis

Statistical analysis was performed using SAS8.0 software. Descriptive analyses of continuous data, such as tumor cell apoptotic index (AI), are assessed using means and standard deviation. Categorical variables, such as clinicopathologic factors, disease control rates (DCRs), ORRs, surgical resection rates, 5-year progression-free survival (PFS), overall survival (OS), metastatic rates, and toxic events, are described with numbers and percentages. Differences in clinicopathologic factors, DCRs, ORRs, surgical resection rates, PFS, OS, and metastatic rates between the research and control groups were evaluated using χ^2 tests. Comparisons of tumor cell AI were performed using two independent sample t-tests and comparison of tumor cell AI, before and after treatment, was performed using paired t-tests. Toxicity between the groups was compared using Kruskal-Wallis tests. Survival curves were obtained using the Kaplan-Meier method and differences were assessed using the log-rank test. P<0.05 indicates statistical significance.

Results

CCRT improves the ORR of patients with LABC

To determine the DCR and ORR after treatment, 185 patients with LABC were subjected to breast MRIs to evaluate the maximum diameter of tumors before and after 4 cycles of treatment. In the research group, there were 6 cases of CR, 74 of PR, 12 of SD, and 5 of PD. The DCR was 92/97 (94.9%) and the ORR 80/97 (82.5%). In the control group, there were 4 cases of CR, 56 of PR, 22 of SD, and 6 of PD, with a DCR of 82/88 (93.2%) and an ORR 60/88 (68.2%). With neoadjuvant treatment, the DCR was high in both groups. There were no significant differences between the two groups (P>0.05; **Table 2**). However, as a secondary end point of the study, ORRs were higher for the research group, after treatment, than the control group (P<0.05; **Table 2**).

CCRT improves the surgical resection rate of LABC patients

For patients with inoperable LABC, the main purpose of neoadjuvant therapy is to convert the patient to an operable status. The surgical resection rate is an important indicator of the efficacy of neoadjuvant treatment. Eighty-eight patients in the research group underwent breast cancer surgery, with a surgical resection rate of 90.7% (88/97). Nine patients had a wide range of tumors and metastatic flaps could not fill the defect. Seventy-four patients in the control group underwent breast cancer surgery, with a surgical resection rate of 79.5% (70/88). However, 18 cases were not suitable for surgical treatment due to the wide range of tumors. As expected, the surgical resection rate was higher in the research group than control group (P<0.05; **Table 3**).

CCRT increases tumor cell AI in patients with LABC

All patients underwent a gross needle biopsy of the breast mass before and after 4 cycles of treatment. Tumor cell AI was evaluated before and after treatment. Tumor cell AI of patients in the research group treated with CCRT was higher than that of the control group. Tumor cell AI

Table 4. Changes in tumor cell AI (apoptosis index) before and after treatment in the research and control groups (%, ±s)

Group	n	Tumor cell AI	
		Before treatment	After treatment
Research group	97	50.29±2.37	70.21±2.78[a]
Control group	88	50.34±2.10	61.58±2.68[b]
t value		-2.84	-21.46
P value		0.874	<0.001

a, Compared with the research group before treatment, t=-50.64, P<0. 001; b, compared with the control group before treatment, t=-32.36, P<0.001.

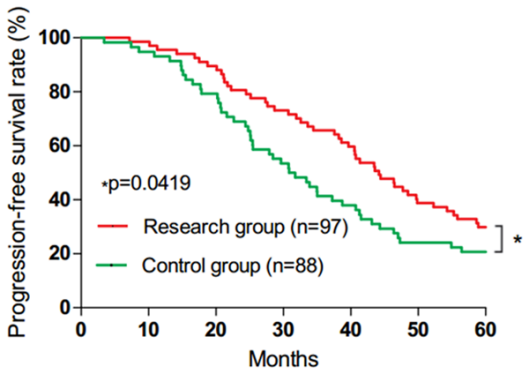

Figure 1. Kaplan-Meier 5-year progression-free survival curves for locally advanced breast cancer patients, according to different treatment programs. There was a significant difference in the progression-free survival rate between the two groups (*P*<0.05).

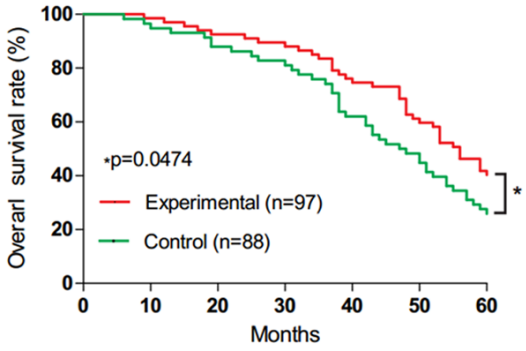

Figure 2. Kaplan-Meier 5-year overall survival curves for locally advanced breast cancer patients, according to different treatment programs. There was a significant difference in the overall survival rate between the two groups (*P*<0.05).

was higher after treatment than before treatment in the research group and control group (P<0.05; **Table 4**).

CCRT improves the clinical efficacy of LABC patients

To determine whether CCRT can yield good clinical effects in LABC patients, Kaplan-Meier survival analysis was employed, using 5-year PFS and OS data for 185 LABC patients. As shown in **Figure 1**, PFS rate in the research group was 53.6% (52/97), much higher than that in the control group (47.7%) (42/88) (P<0.05; **Figure 1**). Five-year OS rate in the research group was 57.7% (56/97), also much higher than that in the control group (51.1%, 45/88) (P<0.05; **Figure 2**). Results also revealed that CCRT patients achieved a great clinical benefit. Present data indicates that CCRT has better long-term clinical efficacy than NAC alone.

Local recurrence and distant metastasis were common in chest walls, bones, liver, lungs, and brains of both groups. In the research group, metastases were observed on the chest wall in 4 cases, bone in 9 cases, liver in 5 cases, lungs in 5 cases, and the brain in 4 cases. In the control group, metastases were observed on the chest wall in 5 cases, bone in 12 cases, liver in 6 cases, lungs in 6 cases, and the brain in 4 cases. The metastatic rate was 27/97 (27.8%) in the research group and 33/88 (37.5%) in the control group, with no significant differences indicated (P>0.05; **Table 5**).

Toxic side effects of CCRT in patients with LABC can be tolerated with good safety

After 4 cycles of neoadjuvant therapy, toxic side effects in the research group were as follows: 63.92% (62/97) had myelosuppression, 60.8% (59/97) had gastrointestinal reactions, 11.3% (11/97) had cardiac toxicity, and 13.4% (13/97) had liver damage. Toxic side effects in the control group included myelosuppression in 62.5% (55/88), gastrointestinal reactions in 59.1% (52/88), cardiac toxicity in 10.0% (8/88), and liver damage in 12.5% (11/88). Neither sepsis nor death occurred in either group. Except for skin lesions, there were no significant differences in toxic side effects between the two groups (P>0.05; **Table 6**).

Discussion

Concurrent neoadjuvant chemoradiotherapy is the standard treatment for locally advanced nasopharyngeal [18, 19], oesophageal [20,

Table 5. Comparison of metastatic rates after treatment in both groups (n)

Group	Metastatic	Non-metastatic	χ^2 value	*P* value
Research group	27	70	1.967	0.161
Control group	33	55		

Table 6. Comparison of toxic side effects in the two patient groups (n)

Toxic side effect	n		Z value	*P* value
	Research group (97)	Control group (88)		
Bone marrow depression				
None	13 (13.4%)	16 (18.1%)	-0.756	0.449
Grade I~II	72 (74.2%)	62 (70.5%)		
Grade III~IV	12 (12.4%)	10 (11.4%)		
Gastrointestinal tract				
None	38 (39.1%)	38 (43.2%)	-0.622	0.533
Grade I~II	47 (48.5%)	41 (46.6%)		
Grade III~IV	12 (12.4%)	9 (10.2%)		
Cardiac toxicity				
None	82 (84.5%)	78 (88.7%)	-0.821	0.410
Grade I~II	13 (13.4%)	9 (10.2%)		
Grade III~IV	2 (2.1%)	1 (1.1%)		
Liver damage				
None	80 (82.5%)	75 (85.3%)	-0.516	0.606
Grade I~II	14 (14.4%)	11 (12.5%)		
Grade III~IV	3 (3.1%)	2 (2.3%)		
Skin damage				
Grade 0	72 (74.2%)	88 (100.0%)	-5.105	<0.001
Grade 1~2	25 (25.8%)	0 (0.0%)		
Grade 3~4	0 (0.0%)	0 (0.0%)		

21], cervical [22], and non-small cell lung [23, 24] cancers. Superior outcomes after CCRT have been demonstrated in these tumor types, as have better local control and improved survival. Surprisingly, only a handful of small studies have addressed the benefits of CCRT for breast cancer. Because of its proven synergistic effects with radiation, CCRT with paclitaxel has been explored in a few previous studies [25] and small studies examining 5-fluorouracil infusion-based chemotherapy for LABC. These reports showed benefits concerning the pCR rate and local control without added toxicity [26]. In contrast, studies of concurrent regimens are uncommon in breast cancer.

Most patients with LABC can undergo surgery after several cycles of NAC. However, the next step of treatment for cases that are still inoperable remains unclear. Radiotherapy is an indispensable part of the LABC treatment plan. Some NAC non-responders might become eligible for surgery through preoperative radiotherapy. Studies have confirmed [27] that a pathologic response to preoperative concurrent paclitaxel radiation translates into superior disease-free survival and OS in patients with LABC. Postoperative radiotherapy, combined with systemic therapy, in LABC patients can significantly increase the local control rate of tumors and prolong OS [28]. Moreover, concurrent treatment was shown to improve local control in lymph node-positive patients [29, 30]. Therefore, it is necessary to explore a safe and effective treatment plan. Consequently, the current study examined the efficacy and safety of CCRT in the neoadjuvant treatment of patients with LABC.

According to present results, the masses before treatment were large and had mostly invaded the skin or the chest wall. Most patients had large axillary nodes and a heavy tumor burden. After CCRT or NAC, the DCR of the patients was high and there were no significant differences between the groups. Although both groups achieved good clinical efficacy, ORRs, surgical resection rates, tumor cell AI, 5-year PFS, and OS were all significantly higher in the research group than the control group. In addition, comparison of local recurrence and distant metastasis rates showed that, despite lower rates in the research group than in the control group, differences were not significant. The reason for this may be that the number of patients enrolled was limited. Therefore, the number of patients should be increased in subsequent studies. Although incidence of myelosuppression was high in both groups, bone marrow suppression was almost normal after symptomatic treatment with

recombinant human granulocyte colony-stimulating factor or recombinant human interleukin-11. Furthermore, there were no significant differences between the two groups in terms of toxic side effects, except for skin lesions. However, local skin lesions caused by radiotherapy in the research group were significantly improved after symptomatic treatment. No patients had to terminate radiotherapy, indicating that CCRT is relatively safe and feasible. The same findings were reported by Beena Kunheri et al. [31].

Results of this study indicate that, for patients with LABC, CCRT prolongs not only PFS but also OS. Overall, the treatment effects of CCRT are better than that of NAC alone. Therefore, combined simultaneous radiotherapy plays an important role in neoadjuvant treatment. Chemotherapy can increase the sensitivity of tumor cells to radiotherapy, which itself enhances the cytotoxicity of chemotherapeutic drugs and the killing effect on tumor cells [32]. The main advantage of CCRT is its ability to increase of the local control rate and reduce the micrometastasis rate by shortening total treatment times, through a combination of two therapeutic effects. CCRT can also reduce drug resistance [33]. Both combinations have a synergistic effect and can improve clinical efficacy in LABC patients. Accordingly, if patients do not receive CCRT treatment, it is very likely that they will suffer from the poor efficacy of single treatment, local recurrence, and systemic disease progression. These effects will result in loss of surgical opportunity and serious risk of mortality.

In summary, although the clinical efficacy of NAC for treatment of LABC is acceptable, clinical efficacy can be further enhanced by combining NAC with simultaneous radiotherapy. Docetaxel with lobaplatin and CCRT has a definite curative effect in the treatment of LABC. Toxic side effects can be tolerated. Indeed, this combination can effectively improve patient quality of life, prolong PFS and OS, and avoid delays in the treatment of chemotherapy-insensitive patients. This combination is worthy of clinical application and in-depth study. However, because of the retrospective nature of our study, present results should be regarded as preliminary. Long-term follow-ups and efficacy evaluations are needed.

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Disclosure of conflict of interest

None.

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