

Efficacy of multimodality therapy for patients with large-sized locally advanced breast cancer - a retrospective analysis of 17 cases

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Summary

The objective of this study was to explore the clinical significance of multimodality therapy for huge-sized locally advanced breast cancer (LABC) in a retrospective analysis of 17 patients with large-sized locally advanced breast cancer. The mean tumor size was 11.5×10.1× cm. Among these 17 patients, three (17.6%) cases developed clinical evidence of distant metastases (liver, lung, bone, etc.), ten cases (58.8%) had skin ulcers, and discharges with a peculiar smell. The patients underwent TEC/AT chemotherapy, interventional therapy, and Ad-p53 gene therapy. All treatments were well-tolerated and 15 (88.2%) cases of the patient underwent standard or modified radical mastectomy successfully. The other two patients, who do not undergo surgical treatment because of metastases and other reasons, were treated with endocrine therapy. Until now, the average survival time has reached 31.5 months. In treating large-sized locally advanced breast cancer, multimodal therapies are able to diminish the burden of the tumor, lower the clinical stage, and increase resection rate of cancer, thus improving survival rates and quality of life for patients.

Key words: LABC; Multimodality therapy; Ad-p53 gene therapy; Interventional therapy.

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer death in women. Early detection and early treatment can significantly reduce the mortality rate of it. However because of educational and economic factors, breast cancer usually will not be detected until it is large. Locally advanced breast cancer (LABC) accounts for 30-60% of newly diagnosed breast cancers in developing countries [1]. LABC is usually complicated with micrometastases, which may develop into new metastases and cause a poor prognosis.

The definition of LABC has not been unified for a long time. The TNM staging system in 2015 NCCN guidelines, defines LABC as Stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), Stage IIIB (T4N0-2M0) [2], but some Stage IIB (T3N0M0) and inflammatory breast cancers have similarities with LABC in terms biological characteristics and clinical behavior, therefore LABC often includes Stage IIB (T3N0M0) and inflammatory breast cancers in some literatures. Currently, the primary treatment for LABC is neoadjuvant chemotherapy (NAC). The advantages of NAC are: 1) reducing the size of the tumor to facilitate further radical surgery, 2) as a drug sensitive test, NAC can be used after the operation, and 3) by eliminating micrometastases, NAC can improve long-term survival in patients. However, because of tumor burden, drug resistance and other factors,

the treatment effect of LABC is usually not as good as expected, and there are still a considerable number of patients with LABC that do not respond to chemotherapy. The tumor may continue to grow despite therapy and the patients will miss the opportunity of treatment.

With the rapid development of medical technology, NAC is no longer the only treatment for breast cancer; the combination of a few comprehensive treatments is used as a clinical treatment, such as transcatheter arterial infusion chemotherapy and embolization, gene therapy, endocrine therapy and radiotherapy, and so on [3-9]. Especially for patients with LABC, multimodality therapy may be more effective. The aim of this study is to evaluate the efficiency of multimodality therapy for patients with large-sized LABC.

Materials and Methods

Patient selection: from 2008 to 2015, 17 patients with LABC were referred to the Department of Breast of People's Liberation Army General Hospital in China. Before treatment, core needle breast biopsies were performed and the results showed invasive ductal carcinoma. All these patients had the same features: 1) locally advanced breast cancer (Stages IIB - IV), 2) no previous treatment history, 3) no history of breast cancer or other cancer, and 4) normal organ function.

Treatment: during the treatment period, patients received intravenous chemotherapy, interventional arterial infusion chemother-

Table 1. — Patient characteristics, treatments, and clinical responses (n = 17).

No.	Age	Tumor size (cm)		Stage	Skin invasion	Metastasis	Intravenous chemotherapy therapy	Ad-p53 therapy	Interventional	Clinical	Surgery response	Overall survival (months)
		Before treatment	After treatment									
1	58	8×7	1.5×1.5	IIIB	Yes	No	TEC*6	No	No	PR (96%)	Yes	>8
2	60	7×6	5×3	IIIB	Yes	No	TEC*4	No	No	PR (65%)	Yes	>6
3	48	9×7	3×3	IIIA	No	No	TEC*3	No	No	PR (86%)	Yes	>6
4	54	9×7	0	IV	Yes	Yes	AT*3	No	No	CR	Yes	22
5	55	7×7	2.1×2.0	IIB	No	No	TEC*4	No	No	PR (91%)	Yes	>51
6	33	9×9	3×3	IIB	No	No	TEC*3	No	No	CR	Yes	>29
7	40	10×10	7×7	IV	No	Yes	TEC*3 (PR-SD)	No	No	PR (51%)	No	>10
8	60	8×8	8×7	IIIA	No	No	TEC*4 (SD)	No	Yes	SD	Yes	>22
9	34	10*9	8×6.5	IIIA	No	No	TEC*3 (PR) -TEC*3 (SD)	No	Yes	PR (43%)	Yes	19
10	42	6×6	4×4	IIIA	No	No	AT (SD)	No	Yes	PR (55%)	Yes	>40
11	61	15×12	7×4	IV	Yes	Yes	TEC*7 (PR) -TEC*1 (SD)	Yes	Yes	PR (84%)	No	>17
12	46	20×18	15×12	IIIC	Yes	No	TEC*2 (PR-SD)	Yes	Yes	PR (50%)	Yes	>29
13	56	20×18	3×3	IIIC	Yes	No	TEC*4 (PR-SD)	Yes	No	PR (97%)	Yes	>48
14	59	20×25	20×23	IIIC	Yes	No	AT, GP (PD)	Yes	Yes	PD	Yes	17
15	43	12×9	5×6	IIIB	Yes	No	TEC*3 (SD)	Yes	Yes	PR (73%)	Yes	>46
16	90	6×5	4×3.5	IIIB	Yes	No	-	Yes	Yes	PR (53%)	Yes	24
17	83	15×15	5×4	IIIB	Yes	No	-	Yes	Yes	PR (91%)	Yes	>88

apy, and Ad-p53 gene injection therapy. At first, all patients with LABC were treated with TEC/AT chemotherapy for three weeks (THP 50 mg/m², EPI 75 mg/m², CTX 600 mg/m², and DXT 75 mg/m²). Then the effectiveness of intravenous chemotherapy was evaluated and patients who were unresponsive and inoperable would be treated with other therapies: Ad-p53 gene therapy combined with intravenous chemotherapy and/or intra-arterial infusion chemotherapy. Interventional arterial infusion chemotherapy was performed via the femoral artery every three weeks. Recombinant human Ad-p53 injection (Ad-p53), was a replication-defective adenoviral vector which was able to restore expression of p53 tumor suppressor gene in tumor cells. rAd-p53 (10¹² VP, viral particles) was diluted with saline and injected into a vein or into tumor.

Evaluation of curative effect: because of the large area of skin ulceration and bleeding in most cases with LABC, conventional imaging techniques such as ultrasound and MRI were not very accurate. Therefore, clinical examination based on a palpable change in tumor size was used for evaluating the response in breast cancer every three weeks. The authors compared response evaluations according to the standard of the Union for International Cancer Control (UICC): complete remission (CR) was defined as complete disappearance of all measurable disease; PR partial remission (PR) was defined as a decrease of more than 50% in tumor size and the absence of new lesions, progressive disease (PD) was defined as an increase of more than 25% in tumor size or appearance of new lesions, and all other outcomes were defined as stable disease (SD).

The study was approved by the Ethics Committee of the PLA Army General Hospital.

Result

From 2008 to 2015, 17 patients with LABC were identified. All the patients were female and the average age at diagnosis was 54 years (range, 33-90 years). The average tumor size was 11.5*10.1cm (range, 6*5-20*25 cm). All

patients were primary diagnosed as locally advanced breast cancer, among which 3 cases (17.6%, 3/17) were diagnosed as having overt metastatic disease. 10 cases (58.8%, 10/17) were noted to have large, ulcerated breast mass with foul-smelling purulent drainage and bleeding. The patients were initially treated with TAC/AT chemotherapy alone or in combination with interventional therapy and/or Ad-p53 gene therapy. All treatments were well tolerated and 15 cases (88.2%, 15/17) underwent standard or modified radical mastectomy successfully. The other 2 patients were not treated with radical mastectomy due to metastases and some other reasons. Among the 17 patients with LABC, 2 cases (11.8%) achieved CR, 13 cases (76.5%) experienced PR. So far the average survival time has reached 31.5 months and we are going to keep following these patients (Table 1).

In the study, eight (47.1%, 8/17) cases were diagnosed with triple-negative breast cancer (TNBC), among which seven cases were treated with intravenous chemotherapy. In the seven cases, four patients were responsive to the therapy (CR and PR, 57.2%, 4/7), and the other three patients (42.8%, 3/7) were resistant to initial chemotherapy and then treated with intravenous chemotherapy combined with Ad-p53 therapy and/or arterial infusion chemotherapy. Among the three cases, two patients achieved PR and one patient showed PD. Clinical evaluation of the comprehensive treatment efficacy in TNBC indicated an overall response rate of 85.7% (6/7). The last patient was a 90-year-old woman who was treated with the combination of arterial infusion chemotherapy and Ad-p53 gene therapy directly and she achieved PR and underwent modified radical mastectomy. The treatment of this patient was well-tolerated and no

stomach problems, such as nausea and vomiting, were observed. The patient died due to cardiovascular disease two years later unexpectedly, without local recurrence or metastases.

Four (23.5%, 4/17) cases were diagnosed with luminal A breast cancer. One case was treated with intravenous chemotherapy and achieved clinical complete response (cCR) and pathologic complete response (pCR). Other two cases were partly responsive to intravenous chemotherapy, but the tumors were still inoperable. Therefore, Ad-p53 and/or interventional therapy were used and the patients achieved PR and underwent surgery. Until now the average survival time has reached 28.5 months with no local recurrence or metastases. The last patient treated with multimodality therapy showed SD. Although she underwent radical mastectomy, a liver metastasis was found later. The authors have been keeping following this patient.

Four (23.5%, 4/17) cases were diagnosed with Luminal B breast cancer. One case treated with intravenous chemotherapy experienced a 96% tumor size reduction and achieved PR. Other two cases were resistant to intravenous chemotherapy, and the tumors were still inoperable. Therefore, Ad-p53 and/or interventional therapy were used and the patients achieved PR (50% and 97% tumor size reduction, respectively). The last patient was an 83-year-old woman with large-sized tumor. Taking in account that her cardiopulmonary compensatory function was weak, she was treated with the combination of arterial infusion chemotherapy and Ad-p53 gene therapy directly. The patient experienced a 91% tumor size reduction and achieved PR without stomach problems, such as nausea and vomiting. Then she underwent radical mastectomy. The disease-free survival time of this patient has reached 88 months.

Only one (5.9%, 1/17) case was diagnosed with HER2-positive advanced breast cancer. Metastases to pericardium and bone were found. The patient was treated with the combination of intravenous chemotherapy and HER2-targeted therapy. The patient experienced a 51% tumor size reduction and achieved PR. Then she was treated with the combination of endocrine therapy (fulvestrant) and HER-2 therapy. The authors have been keeping following this patient, and the progression free survival time has reached ten months.

Discussion

Patients with LABC are at a high risk for systemic disease and local recurrence. They have a five-year survival rate of about 40-75% and a ten-year survival rate of about 30-40% [10]. Notably, LABC constitutes in only 7% of the newly diagnosed breast cancers in Europe and the United States, while in developing countries it constitutes approximately 30-60% of all breast cancers [11]. In some economically under-developed areas, when patients arrive at the hospital, their tumor diameters often are equal to or

greater than 10 cm. These patients with large-sized LABC have a poor prognosis, and the survival rate has not been reported. Ulceration through the skin with exudate and foul smell are characteristics for LABC and bring great suffering to patients, and even life-threatening. In a word, the treatment of LABC is very important and meaningful in China and other developing countries. However, the treatment of patients with large-sized LABC is still difficult. Because LABC has been regarded as a systemic disease, some experts believe that the routine inclusion of breast surgery in a combined modality treatment program for LABC does not appear necessary. In the 13th St Gallen International Breast Cancer Conference, a report showed that surgical resection does not improve survival of patients with LABC. In the present study of 17 patients with LABC, the average survival time has reached 31.5 months and the patients are still being followed. Surgical treatment can significantly reduce psychological stress in patients, enhance their confidence, improve the quality of their life, and improve patient adherence to prescribed medication therapies. Whether overall survival is related to these potential factors still needs to be confirmed. Though surgery is not explicitly reported to be beneficial to survival in patients, it is able to reduce the tumor burden and creates ideal conditions for further treatment.

NAC is now the standard therapy for LABC. Research shows that those who have NAC are more likely to have no residual disease than women who have primary surgery. NAC is able to downstage the tumor for less extensive surgery and patients with LABC, especially T4 tumors can benefit from NAC [12]. It is reasonable to select a regimen that shows a substantial antitumor effect with a high response rate. Numerous studies have demonstrated that the combination of paclitaxel and doxorubicin is extremely active in LABC [13]. In a study on 50 patients with LABC treated by TAC regimen, 19.6% of patients achieved pCR, and at a median follow-up of 41.3 months, almost 80% of patients survived without relapse. Among them, patients with ER/PR-positive had a better response. In another study on 134 patients with LABC, the response to NAC is closely related to molecular subtypes of breast cancer. Luminal A, luminal B (HER2-negative), luminal B (HER2-positive), HER2, and triple negative tumors had 10%, 19%, 42%, 59% and 38% pCR rates, respectively. HER2-positive tumors show a good response to NAC [14]. These results are similar to the present study, but in this study, the patients with luminal A breast cancer treated with intravenous chemotherapy achieved good clinical effects. Whether the response to NAC is related to the tumor burden in large-sized luminal A breast cancer is to be explored.

There are many different types of chemotherapy for LABC. When the first-line treatment does not work, the second-line chemotherapy regimens are usually used. However, switching to another medication may be ineffective and promote tumor progression [15]. A number of clinical



Figure 1. — The effect of the treatment of large advanced breast cancer before and after treatment.

- a) Before chemotherapy.
- b) After four cycles of chemotherapy.
- c) after Ad-p53 therapy combined with chemotherapy.
- d) After radical mastectomy.

studies have indicated that the use of combination therapies results in a greater response rate. For example, Ad-p53 therapy has achieved good results in tumor treatment: in a prospective, open-label, Phase II trial, 13 patients with LABC were treated with intratumoral injection of Ad-p53 combined with chemotherapy. All 12 evaluable patients achieved an objective clinical response and there was no increase in systemic toxicity [16]. It is reported that *in vivo* and *in vitro*, Ad-p53 is able to inhibit the growth of MCF-7 and Ca761 breast cancer cell lines and reverse multidrug resistance of breast cancer cells [9, 17]. In this study, six patients who were resistant to chemotherapy benefited from Ad-p53 gene therapy. The results indicate that Ad-p53 is able to reverse drug resistance effectively (Figure 1). Ad-p53 treatment for breast cancer was able to reduce the risk of ineffective chemotherapy, and the combination therapy did not increase local and systemic adverse reactions. The incorporation of Ad-p53 to combined therapy should be evaluated further in patients with different subtypes of LABC.

Arterial infusion chemotherapy and embolization, as a safe and effective treatment, has been used in the clinic, and has made some achievements in treating LABC [18, 19]. In arterial infusion chemotherapy, the drug is injected through the catheter directly, which is able to decrease the side effects of chemotherapeutic drugs, whereas at the same time achieving a better tumor response through increased drug concentration in the breast. In a study of 53 patients

with LABC, the results show arterial perfusion chemotherapy is able to downstage the tumors and enable successful surgery in a reasonable percentage of patients. In the present study there were two older patients with LABC whose average age was 87-years-old. Taking into account their advancing years, they were treated with the combination of intra-arterial infusion chemotherapy and Ad-p53 gene therapy. The treatment had small side effects. Besides some local pain, no symptoms such as bone marrow suppression, dizziness, fever or discomfort were found. The two patients achieved PR and underwent radical mastectomy. One patient died due to cardiovascular disease two years later. The other patient survived 88 months and is still being monitored. No recurrence or metastases were discovered in the two patients. These results indicated that the combination of intra-arterial infusion chemotherapy and Ad-p53 gene therapy was effective for elderly patients with LABC. In addition, endocrine therapy is used commonly in the treatment of breast cancer and has high safety. Primary endocrine therapy can be used for frail elderly patients with ER/PR-positive breast cancer [20]. Radiotherapy, as a treatment for LABC, also has achieved some good results [4, 21].

As LABC is an extremely complex disease, chemotherapy alone may be ineffective for some patients. A wide range of treatment options, including gene therapy, biological therapy, and interventional therapy are beginning to be used and becoming more and more important in LABC treatment. In this study, multimodal therapies were able to

minish burthen of tumor and lower the clinical stage, and increase resection rate of cancer, thus improving survival rates and quality of life for patients. In addition, multimodal therapies may deserve special attention in the future research.

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