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Original Article

Efficacy of neoadjuvant chemotherapy in breast cancer: arterial infusion chemotherapy vs intravenous chemotherapy

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Abstract: Objective: This study aimed to compare the efficacy of arterial infusion chemotherapy with that of intravenous chemotherapy as neoadjuvant chemotherapy in breast cancer patients. Methods: A total of 92 patients were recruited and received doxorubicin dominant chemotherapy. Patients were randomized into arterial infusion chemotherapy group (n=44; chemoembolization was performed if necessary; group A) and intravenous chemotherapy group (n=48; group V). After chemotherapy, surgical interventions were employed. The adverse effects were evaluated, and the time interval between chemotherapy and surgery was determined. The therapeutic efficacy and long survival rate were compared between them. Results: The remission rate (complete remission and partial remission) in group A (93.18%) was significantly higher than in group V (62.5%). In group V, the incidence of adverse effects (bone marrow suppression, gastrointestinal reactions and alopecia) was significantly higher than in group A. The mean time interval between chemotherapy and surgery in group A was significantly shorter than in group V (25.00±5.34 days vs 56.00±15.65 days; P<0.05). The survival rate within first 5 years was comparable between groups, but the 10-year survival rate in group A was slightly higher than in group V. Conclusion: Arterial infusion chemotherapy may serve as an effective strategy for the neoadjuvant chemotherapy of breast cancer.

Keywords: Breast cancer, neoadjuvant chemotherapy, arterial infusion chemotherapy, intravenous chemotherapy

Introduction

Breast cancer is a common malignancy in women and causes over a half-million deaths each year worldwide [1]. The latest world cancer statistics available from the International Agency for Research on Cancer (IARC) showed that 1,677,000 women were diagnosed with breast cancer and 577,000 women died in 2012. Since 2008, breast cancer incidence has increased by over 20% and breast cancer deaths have risen by 14% [1]. Moreover, most countries with the highest breast cancer mortality rate are low- to middle-income countries (LMICs) and breast cancer in LMICs often presents when locally advanced breast cancer (LABC) [2] that can be easily appreciated at physical exam but is still limited to the breast and draining lymph nodes, without clinical evidence of metastatic spread. Despite being confined to the breast and regional nodes, locally advanced stage often heralds the rapid onset of metastatic disease, explaining high mortality rates.

During the past 60 years, the management of LABC has evolved considerably. Initially patients with LABC were treated with radical mastectomy. Based on the disappointing results of surgery and radiotherapy, and the early promising results of adjuvant chemotherapy in women with axillary node-positive disease, systemic neoadjuvant therapy was subsequently incorporated along with surgery and radiotherapy into the management of patients with LABC.

Neoadjuvant chemotherapy also referred to as preoperative or primary chemotherapy refers to chemotherapy administered before tumor resection [3]. Traditionally, preoperative ("neoadjuvant") systemic therapy has been used to downstage tumors in the hope of making inop-

Table 1. Characteristics of patients with breast cancer at baseline

Group	Age (yr)	Tumor diameter (cm)	TNM stage (n)					Pathological type (n)		
			I	IIa	IIb	IIIa	IIIb	Invasive ductal carcinoma	Invasive lobular carcinoma	Intraductal carcinoma
A (n=44)	43.98±10.9	2.77±1.18	6	20	10	5	3	37	4	3
V (n=48)	46.25±11.2	2.68±0.82	4	25	14	4	1	41	3	4

erable disease operable. In recent years, neoadjuvant therapy has increasingly been used in patients with operable disease [4].

In this study, we compared the efficacy of arterial infusion chemotherapy with that of intravenous chemotherapy in breast cancer patients, and the long term survival rate and adverse effects were evaluated, aiming to find an optimal way by which the neoadjuvant therapy is conducted in breast cancer patients.

Materials and methods

General information

Women who were pathologically diagnosed with breast cancer were recruited between January 2003 and December 2006 from the Second People's Hospital of Shenzhen City. These patients received neoadjuvant chemotherapy. Of these patients, 44 received arterial infusion chemotherapy (A) and 48 underwent intravenous chemotherapy (V). The patients' characteristics were comparable at baseline between two groups (P>0.05) and are shown in **Table 1**. Before therapy, routine blood test, urine and stool analyses, detection of liver and kidney functions, chest X ray, and electrocardiography were conducted to exclude organic lesions and patients had no contradictions to chemotherapy.

Treatment

Group A: Patients lied in a supine position and the right inguina region was sterilized, followed by local anesthesia with 1% lidocaine (10 ml). The right femoral artery was punctured with Seldinger method, and super-selective arteriography was performed at the internal mammary artery, lateral thoracic artery and subclavian artery of the affected breast. The blood supply, solid lesions and lymph node status were evaluated. Chemotherapy with CEF or MEF protocol: Mitomycin (MMC; 10 mg), cyclophosphamide (CTX; 400 mg), epirubicin (EADM; 50 mg) and 5-fluorouracil (5-Fu; 1000 mg) were used for chemotherapy. Arterial infusion chemotherapy was performed via above three arteries. When the affected breast was supplied mainly by the internal mammary artery and the lateral thoracic artery, 50% of chemotherapeutics was infused via major vessel, 30% via subclavian artery and 20% via secondary artery; when the cancer or lymph nodes were not obvious in arteriography, 50% of chemotherapeutics was infused via subclavian artery, 30% via internal mammary artery, and 20% via lateral thoracic artery. When the cancer was very obvious, the major vessel was occluded with 1000-1400 μm gelatin sponge. When infusion was conducted via the subclavian artery, inflatable cuff was used to maintain the pressure at 10-20 mmHg higher than systolic blood pressure, and the cuff was released 30 min later and then maintained for 5 min. When infusion was conducted via the internal mammary artery and the lateral thoracic artery, inflatable cuff was not used. Infusion was performed slowly with a micropump for 2-3 h.

Group V: Anthracyclines (epirubicin) dominant protocol was used. CEF or MEF protocol was used. The chemotherapeutics included MMC (8 mg/m^2), CTX (400-600 mg/m^2), EADM (40 mg/m^2), and 5-Fu (500-750 mg/m^2). Intravenous infusion was conducted once every 3-4 weeks for a total of 1-3 courses.

After chemotherapy, surgical interventions were performed with classical radical mastectomy, modified radical mastectomy or breast-conserving resection.

Angiography

After angiography, the blood supply to the breast cancer was evaluated by at least 2 experienced physicians, and any discrepancy was resolved by discussion.

Determination of therapeutic efficacy

Before and after neoadjuvant chemotherapy, the cancer size was determined by the physi-

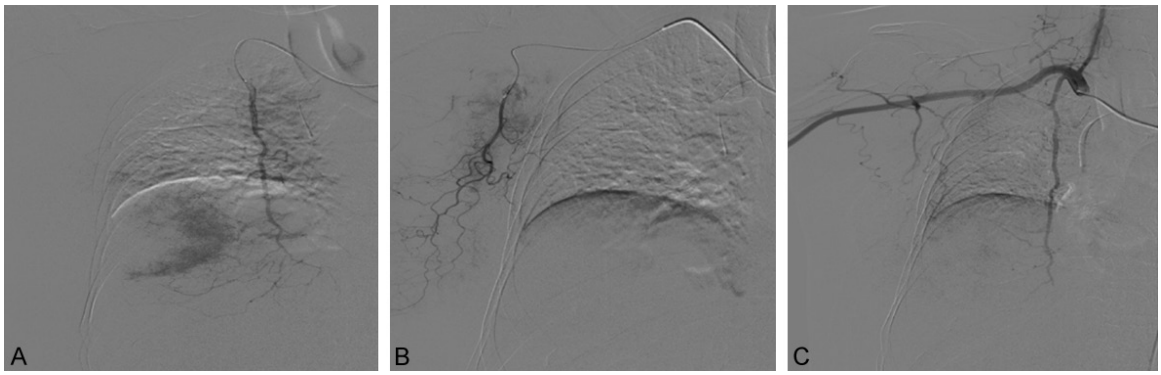

Figure 1. A: Blood vessels in breast cancer and breast cancer in parenchymal phase in angiography of right internal mammary artery; B: Irregular axillary lymph nodes in angiography of right lateral thoracic artery; C: Absence of blood supply to the breast cancer after embolism in angiography of internal mammary artery and lateral thoracic artery.

cians for interventional therapy and surgeons together, and it was measured clinically. According to the Response Evaluation Criteria in Solid Tumors (RECIST1.1), the therapeutic efficacy was classified as complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). The overall efficacy was calculated as follow: Sum of patients with CR and PR/total patients ×100%. The adverse effects of chemotherapy were evaluated according to the classification criteria for acute and subacute adverse effects of anti-tumor drugs. Histological evaluation was conducted as follows: mild pathological change: pathological change was confined to <1/3, a large amount of residual cancer cells was observed, and a variety of lymph nodes were involved; significant pathological change: pathological change was confined to <1/2, residual cancer cells were still observable, and lymph node metastasis was observed; pathological complete remission: there were no invasive lesions in the primary lesions and lymph nodes collected by surgery. The time interval between chemotherapy and surgery referred to the interval from day of initiation of first chemotherapy to the day of surgery.

Follow up

The patients' information was collected by reviewing the medical record and via telephone. The date of the last hospital visit or hospitalization was used for patients lost to follow up. The main end point was the overall survival. Follow up was conducted for 6-130 months in these patients and the last follow up was performed on March 1, 2014.

Statistical analysis

Statistical analysis was performed with SPSS version 19.0. Quantitative data are expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared with t test. Qualitative data are expressed as percentage and compared with chi square test. Survival analysis was conducted with *Kaplan-Meier* method and Log Rank (Mantel-Cox) test. A value of $P<0.05$ was considered statistically significant.

Results

Findings from angiography

Angiography showed the blood vessels enlarged, were irregularly arranged and formed networks. In parenchymal phase, the cancer was not observed and spotty or mass-like. The axillary lymph nodes were significantly enlarged and irregular, and branches of blood vessels were obvious (**Figure 1A** and **1B**). For breast cancer which was obvious in angiography, the major blood vessel was embolism with gelatin sponge after infusion. Re-examination by angiography is shown in **Figure 1C**.

Therapeutic efficacy

According to the RECIST1.1, CR and PR were found in 41 patients in group A with the overall efficacy of 93.81%, which was significantly higher than in group V (62.5%, n=30; P<0.05) (**Table 2**).

Adverse effects

Besides adverse effects shown in **Table 3**, skin flushing was also observed in group A; blisters

Table 2. Therapeutic efficacy in tow groups

Group	Efficacy				Overall efficacy (%)	Difference in cancer diameter (cm)
	CR	PR	SD	PD		
A (n=44)	2	39	3	0	93.18 (41/44)	1.58±0.61
V (n=48)	0	30	18	0	62.50 (30/48)	0.91±0.51

Note: Difference in cancer diameter refers to the difference between cancer sizes before and after chemotherapy; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

or even ulcer were found in several patients in group V, but resolved after symptomatic therapy; light chromatosis was found in several patients in group V. In group V, skin lesions were not observed. In group V, the incidence of bone marrow suppression, gastrointestinal reactions and alopecia was significantly higher than in group A (**Table 3**).

Time interval between chemotherapy and surgery

The mean time interval between chemotherapy and surgery was 25.00±5.34 days in group A, which was significantly shorter than in group V (56.00±15.65 days; $P<0.05$).

Histological examination

In group A, karyopyknosis, nuclear fragmentation, necrosis and infiltration of inflammatory cells as well as cells with abnormal nucleus were observed in sections of 40 patients (40/44; 90.91%). In group V, these findings were observed in 23 patients (23/48; 47.92%). There was significant difference in the proportion of patients with above pathological changes between two groups (**Figure 2**) ($P<0.05$; **Table 4**).

Long term survival

The 1-year, 3-year, 5-year and 10-year survival rate was 97.5%, 85.6%, 82.3% and 78.2%, respectively, in group A and 95.8%, 84.4%, 78.6% and 67.5%, respectively, in group V. Log Rank (Mantel-Cox) test showed the survival rate within first 5 years was comparable between groups, but the 10-year survival rate in group A was slightly higher than in group V (**Figure 3**).

Discussion

Breast cancer is the most commonly diagnosed cancer in women [1]. Surgery followed by adjuvant treatment has been the gold standard for breast cancer treatment for a long time. Unfortunately, many women still experience recurrence of disease, or metastasis of primary tumor after early stage tumor has been treated. More recently, neoadjuvant treatment has been recognized as an important strategy in biomarker and target evaluation [4].

Traditional indications for neoadjuvant therapy in breast cancer include N2 stage-fixed or matted lymph node on ipsilateral side, or clinically apparent ipsilateral internal mammary nodes in the absence of axillary node, making the clinical staging at least stage IIIA or above. Patients with stage IIIB disease with tumors invading the chest wall, skin or both, or with breast cancer of inflammatory nature, would be a good candidate for neoadjuvant therapy [5]. Neoadjuvant therapy should also be considered for women with clinical stage IIA and IIB tumors with a larger tumor who wish to have breast-conserving operations and avoid mastectomy. Not in all, but in many patients, neoadjuvant therapy results in sufficient tumor response to make breast-conserving operations possible. Several studies in the early 2000 s showed that neoadjuvant chemotherapy successfully reduced both locoregional and in breast tumor recurrence even in large T3 and T4 tumors [6, 7]. Neoadjuvant therapy has been evolving rapidly given this benefit [8].

In 1968, Fisher et al [9] proposed the primary lesions of breast cancer were only the focal manifestation of the systematic disease. Neoadjuvant chemotherapy may benefit patients and has been one of standard and classic strategies in the therapy of cancers [10]. The proven benefits of NST justifying its routine clinical use include the following: it improves disease-free survival and overall survival to the same extent as postoperative chemotherapy; it increases breast-conserving surgery (BCS) rates in patients with operable locally advanced breast cancer (clinical stages IIIA except of T3N1M0, IIIB, and IIIC); and it reduces the extent of resection in cancers >2 cm even if a patient is a candidate for BCS. The extent of residual cancer after NST is a powerful prognostic marker [8, 10]. In arterial infusion chemotherapy, chemotherapeutics are infused via the vessels supplying the cancer, which leads to a high concentration of chemotherapeutics

Table 3. Adverse effects in two groups (n; %)

Group	Bone marrow suppression				Gastrointestinal reactions			Alopecia	Peripheral sensory neuropathy	Liver dysfunction
	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III			
A (n=44)	4 (9.09)	1 (2.27)	5 (11.36)	2 (4.54)	10 (22.73)	8 (18.18)	0	12 (27.27)	6 (13.64)	2 (4.5%)
V (n=48)	13 (27.08)	11 (22.92)	3 (6.25)	3 (6.25)	15 (31.25)	22 (45.83)	3 (6.25)	30 (62.50)	5 (10.42)	6 (12.5%)
P	<0.05				<0.05			<0.05	>0.05	>0.05

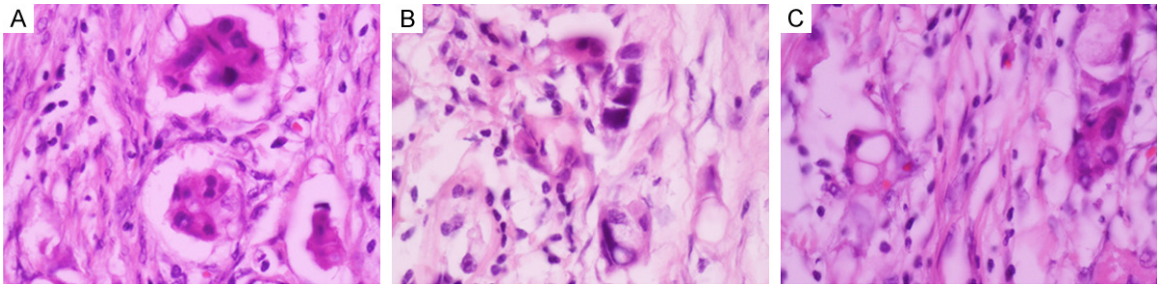

Figure 2. A: Acidophilic change in cytoplasm of breast cancer cells; B: Enlargement and singularity of nucleuses of breast cancer cells; C: Vacuolation of breast cancer cells (HE*400).

Table 4. Histological examination of breast cancer in both groups (n, %)

Group	Significant pathological change	Mild pathological change	Complete pathological remission
A (n=44)	40 (90.91)	4 (9.09)	8 (18.18%)
V (n=48)	23 (47.91)	25 (52.08)	2 (4.17)

at the cancer and adjacent lymph nodes. The drugs that are not metabolized may enter the systemic vein and contact with the cancer again via circulation (second chemotherapy), increasing the therapeutic efficacy [11].

Feldman et al [12] for the first time described the blood supply to the breast cancer by angiography after brachial artery puncture. In recent years, Zhou et al and Zhang et al [13, 14] found that lateral thoracic artery was the major vessel supply the breast cancer, and the blood supplied via the lateral thoracic artery is more than that via the internal mammary artery. The supplied arteries forms a network in breast cancer, and each vessel also has a lot of collateral vessels which connect with each other. Thus, the extent of infusion should be expanded during the arterial infusion chemotherapy, and the chemotherapeutics are infused mainly via the internal mammary artery, lateral thoracic artery and subclavian artery. The dose of chemotherapeutics is determined according to findings from arteriography.

Breast cancer cells are sensitive to chemotherapeutics, especially the anthracyclines and taxanes. CMF protocol has been used as a gold standard in the therapy of breast cancer for more than 30 years [15]. In the present study, anthracycline (epirubicin) dominant protocol was used for chemotherapy (CEF or MEF protocol). Our results showed the overall efficacy was as high as 93.08% in A group, which was significantly higher than in V group. In addition, in our study, more patients in A group developed skin related adverse effects as compared to V group. This may be ascribed to the high concentration of chemotherapeutic in the cancer and surrounding lymph nodes and the contact between drugs and breast cancer is prolonged, leading to endangiitis, vascular thickening and thrombosis as well as skin lesions. These adverse effects resolved after symptomatic therapy.

Liu et al [15] reported that the 5-year survival rate was 93.3% and 56% after arterial infusion chemotherapy and systemic chemotherapy, respectively. Zeng et al reported that the overall effectiveness rate of arterial infusion chemotherapy and embolic therapy was 93.3% for advanced breast cancer, and the 5-year survival rate was as high as 93.3%. In addition, Shimamoto et al and Miura et al [16, 17] proposed that arterial infusion chemotherapy could achieve better efficacy as compared to traditional venous chemotherapy: the short

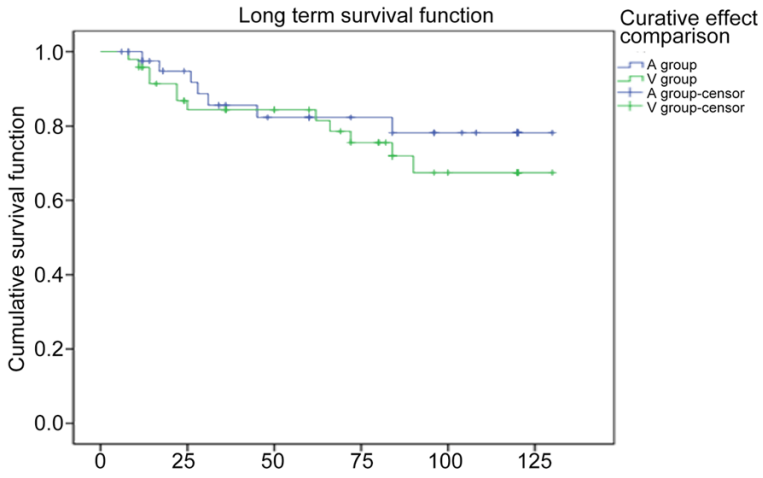

Figure 3. Long term survival rate in two groups.

term effectiveness rate was 20%-30% higher than that of venous chemotherapy; the quality of life was significantly improved and long term survival time was prolonged. These findings were consistent with above mentioned. In the present study, results showed the effectiveness rate was 93.18% in A group, which was similar to previously reported. However, the effectiveness rate in V group was 62.50%, which was lower than previously reported. This might be ascribed to the small course of venous chemotherapy (1-3 courses; 4 weeks in each course). Patients in both groups were followed up for 6-130 months. The survival rate within first 5 years was comparable between two groups, but the 10-year survival rate in A group was higher than in V group.

Our study indicates that arterial infusion chemotherapy is an effective strategy for the neoadjuvant chemotherapy of breast cancer. This neoadjuvant chemotherapy is able to reduce cancer size, which is helpful for the surgical interventions, reduces adverse effects, and shortens the time interval between chemotherapy and surgery. However, arterial infusion chemotherapy fails to significantly improve the long term survival rate in breast cancer patients. This is a retrospective study, and more prospective, randomized and controlled studies are required to confirm our findings.

Disclosure of conflict of interest

None.

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