Short-term Intensive Neoadjuvant Chemotherapy Improving 10-year Survival for Patients with Stage II and Operable Stage III Breast Cancer

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OBJECTIVE To evaluate the 10-year curative effects of short-term intensive neoadjuvant chemotherapy for operable breast cancer.

METHODS A total of 510 patients with stageII and operable stageIII breast cancer were divided into group A (preoperative neoadjuvant chemotherapy 251 cases) and group B (postoperative adjuvant chemotherapy 259 cases). The patients in group A received short-term and intensive neoadjuvant chemotherapy for 4 weeks followed by modified radical mastectomy two weeks after the chemotherapy. The postoperative adjuvant chemotherapy began within two weeks after surgery. The same chemotherapeutic regimen was used for both groups.

RESULTS For stage III in group A the 5-year overall survival rate (OS) and disease-free survival rate (DFS) were 59.2% and 54.9% respectively which were higher than those in group B (28.3% and 20.8% respectively, $P<0.05$). The 10-year OS and DFS were 78.1% and 73.5% respectively for stage II in group A which were higher than those in group B (68.4% and 60.7%, $P<0.05$). The 10-year OS and DFS were 42.3% and 40.4% respectively for stage III in group A which were higher than those in group B (20.4% and 18.4% respectively, $P<0.05$).

CONCLUSION The results showed that intensive neoadjuvant chemotherapy can improve the 10-year survival for patients with stage II and operable stage III breast cancer.

KEYWORS: breast cancer, stage II, III, control study, neoadjuvant chemotherapy, 10-year follow-up.

Breast cancer is a systemic disease, so primary systemic treatment should be given as early as possible. At present, neoadjuvant chemotherapy (also referred to as preoperative or primary chemotherapy) is a routine therapeutic method for patients with inoperable locally advanced breast cancer (LABC) and this approach has been extended to patients with operable breast cancer. The aim of this study was to investigate whether the use of neoadjuvant chemotherapy can improve the long-term survival for patients with stageII and operable stageIII breast cancer by a prospective control study.

MATERIALS AND METHODS

Patient Population and Tumor Characteristics

Between Dec.1986 and Dec. 1990, all 510 female patients with stage II or operable stage III breast cancer diagnosed by fine-needle aspira-

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tion cytology or core needle biopsy were eligible for this study. They were divided into two groups: group A (short-term intensive neoadjuvant chemotherapy), 251 cases and group B (postoperative adjuvant chemotherapy), 259 cases. No distant metastases were found in any patients by systematic examination. Performance status of all patients were Zubrod 0. The two groups were balanced for baseline patient characteristics. There were no significant differences regarding TNM stage, histologic classification of breast cancer, estrogen receptor (ER) and menopausal status between the study groups, being detailed in Table 1.

Treatment

The patients in groupA received short-term intensive neoadjuvant chemotherapy of cyclophosphamide methotrexate and 5Fu (CMF) or 5Fu, adramycin and cyclophosphamide(FAC) once a week for 4 weeks followed by surgery (modified radical mastectomy) two weeks after neoadjuvant chemotherapy. Within 2 weeks postoperatively, chemotherapy was initiated with CMF or FAC regimen for the two group of patients. The protocol for chemotherapy is detailed in Table 2.

Table 1.Characteristics of patients enrolled in group A and B

	Group A	Group B
No. of patients	251	259
Age	23-66	24-68
Stage		
IIA	75	89
IIB	105	117
IIIA	43	30
IIIB	28	23
Histology of breast cancer		
Non-special infiltrating	246	253
Special infiltrating	5	6
Menopausal status		
Premenopausal	184	188
Postmenopausal	67	71
No. of ER status	246	215
ER (+)	145(59.0%)	114(53.0%)
ER (-)	101	101

For all patients in group A and B, the entire chemotherapy of CMF or FAC was designed for 6 cycles, every 2 times being calculated as one cycle in the neoadjuvant chemotherapeutic scheme. The patients receiving the FAC regimen in groups A and B were 21.8% and 20.8%, respectively. There were 176 patients (70.1%) in group A and 173 (66.8%) in group B completing chemotherapy of 6 cycles, the other patients finished 3-5 cycles of chemotherapy.

In group A 18.2% of the patients and in group B 14.0% of the patients were given postoperative adjuvant radiotherapy. Tmoxifen was given to 16.6% of patients in group A and 18.3% of patients in group B for 3-5 years . All patients were followed-up for at least 10 years.

RESULTS

Clinical response to neoadjuvant chemotherapy

In group A, the overall clinical response rates [overall response (OR)=complete response (CR) + partial response (PR)] was 68.9%. The CR and PR were 9.6% and 59.3%, respectively. No progress cases were seen. The OR of patients with a tumor size $\leqslant$4cm was 71.0%,which was higher than that (46.0%) of patients with a tumor size>4cm (P<0.05). Also, the 10-year overall survival (OS) of patients with OR in group A achieved 80.0%, which was much higher than that for patients with MR(minor response) and SD(stable disease)(46.5%, P<0.01). No correlation was found between response and histology, ER status of the tumor or menopausal status of the patients. No obvious toxicity and side effects were seen during the short-term intensive neoadjuvant chemotherapy. All patients underwent their operation on schedule and their wound healing was not affected.

5-year OS and DFS

The 5-year OS and DFS for patients with stage III in group A were 59.2% and 54.9% respectively, which were much higher than those in group B (28.3% and 20.8% respectively, P<0.05). There was no significant difference of OS and DFS at 5-year for patients with stage II between groupA and groupB (Table 3).

10-year OS and DFS

OS and DFS at 10-year for patients with stage II and I-II in group A were higher than those of group B, as detailed in Table 3.

Comparison in group A with group B between OS and T、N status

5-year and 10-year OS of the patients with T_3、T_4 and the number of positive-nodes $\geqslant$4 in group A were higher than those of group B (P<0.05), detailed in Table 4.

The OS of the patients was not related to the ER of the tumor or menopausal status of the patients.

DISCUSSION

The failure of the treatment in the majority of patients with breast cancer is due to the inability to control the disseminated disease. Even patients with node-negative early breast cancer have a relapse or metastases in about 30% within 10 years after treatment[1], thus indicating the potential biologic behavior of metastases via blood circulation from the breast cancer in an early stage. Most patients with breast cancer have subclinical micrometastases at the time of diagnosis, so, it is reasonable to apply systemic treatment as the first step in therapeutic strategy for these patients. Based on this consideration, neoadjuvant chemotherapy was used for locally advanced breast cancer(LABC) with satisfactory results [2]. Thereafter, the preoperative neoadjuvant chemotherapy was adopted for treating operable stageII and III breast cancer and a control study was conducted with postoperative adjuvant chemotherapy. Our results from the present study after a 10-year follow-up showed that short-term intensive neoadjuvant chemotherapy can improve the long-term survival for patients with stageII and operable stageIII breast cancer.

The present study showed that 5-year and 10-year survival of the neoadjuvant chemotherapy group was higher than that of the postoperative adjuvant chemotherapy group, particularly in patients with T_3、T_4 and more than three involved axillary nodes versus one to three involved nodes or no nodes. It is also showed that the 10-year OS of patients with OR in group A achieved 80.0%, which was markedly higher than that for the patients with MR and SD (46.5%), suggesting that the better response of the primary tumor to neoadjuvant chemotherapy may have achieved long-term survival, and a potential cure. The success of neoadjuvant chemotherapy for breast cancer is due to systemic treatment as the first therapeutic modality to control the pre-existing subclinical micrometastases. Besides being taken as a standard therapeutic modality for patients with LABC, patients with any high risk factor of relapse or metastatic operable breast cancer can also be treated with neoadjuvant chemotherapy as early as possible to increase the chance for a cure.

The OS of neoadjuvant chemotherapy group patients was higher than that of the postoperative adjuvant chemotherapy group, even though both chemotherapeutic regimens included the same agents, dosages and treatment cycles. In case of treating patients with a standard chemotherapeutic cycle, cancer

Table 2. Protocol of pre- and postoperative chemotherapy

Protocol	Dosage	Preoperative-	Postoperative-
CMF			
Cyclophosphamide(C)	500mg/m^2,iv	Weekly×4	Days1,8
Methotrexate(M)	40mg/ m^2,iv		every 28 day for one cycle
5-Fu(F)	500mg/m^2,iv rip		
FAC			
5-Fu(F)	500mg/m^2,iv rip	1st and 3rd week with FAC	Day1 with FAC, Day8 with F
Adramycin(A)	40mg/ m^2,iv	2nd and 4th week with FC	every 21days for one cycle
Cyclophosphamide(C)	500mg/m^2,iv		

Table 3. OS and DFS at 5-year and 10-year in groupsTable bothgroups No(percent)

Stage	GroupA		GroupB		*P* value
	OS	DFS	OS	DFS	
5-year					
II	147/180(81.7)	142/180(78.9)	169/206(82.0)	160/206(77.7)	
III	42/71(59.2)	39/71(54.9)	15/53(28.3)	11/53(20.8)	*P*<0.05
IIIA	26/43(60.5)	24/43(55.8)	9/30(30.0)	7/30(23.3)	*P*<0.05
IIIB	16/28(57.1)	15/28(53.6)	6/23(26.1)	4/23(17.4)	*P*<0.05
10-year					
II	118/151(78.1)	111/151(73.5)	134/196(68.4)	119/196(60.7)	*P*<0.05
III	22/52(42.3)	21/52(40.4)	10/49(20.4)	9/49(18.4)	*P*<0.05

Table 4. Relationship between OS and TN status in A and B (percent)

	GroupA	GroupB	*P* value
5-year			
T_1	2/2(100.0)	42/47(89.4)	*P*<0.05
T_2	142/179(79.3)	132/178(74.2)	*P*<0.05
T_3	33/48(68.8)	8/21(38.1)	
T_4	12/22(54.5)	2/13(15.4)	
N(-)	83/102(81.4)	95/116(81.9)	
N(+)	106/149(71.1)	89/143(62.2)	
1-3	67/84(79.8)	57/69(82.6)	
≥4	39/65(60.0)	32/74(43.2)	*P*<0.05
10-year			
T_1	2/2(100.0)	35/47(74.5)	
T_2	107/149(71.8)	104/164(63.4)	
T_3	25/40(62.5)	4/21(19.0)	*P*<0.05
T_4	6/12(50.0)	1/13(7.7)	*P*<0.05
N(-)	82/102(80.4)	89/116(76.7)	
N(+)	58/101(57.4)	55/129(42.6)	*P*<0.05
1-3	36/60(60.0)	40/74(54.1)	
≥4	22/41(53.7)	15/55(27.0)	P<0.01

cells might have more time to recover and grow from each prior to chemotherapy cycle, because dose-response relationships of chemotherapeutic agents may not be linear. Therefore, while high doses of chemotherapeutic agents may not always produce a better efficacy in terms of cell kill, on the contrary, if an effective and lower drug dose would be given more often (intensive chemotherapy), thereby increasing the dosage, more sensitive cancer cells might be eliminated and cytotoxicities of the drug reduced[3-7].

Neoadjuvant chemotherapy has the potential to downstage a tumor by decreasing the size and extent of the tumor mass, thus converting an inoperable tumor into a resectable one, and also may shrink a large primary tumor sufficiently to allow breast-conserving surgery feasible rather than radical mastectomy[8,9].

Postoperative adjuvant chemotherapy was given blindly, as we have no way to monitor its effects. Neoadjuvant chemotherapy allows the primary tumor response to serve as an in vivo chemosensitivity test and may help in the design of subsequent systemic treatment [10-12]. Earlier chemotherapy administration also may have the advantage of a lesser likelihood of drug-resistant lines being present.

Our results and current data [12-16] indicate that a good response of the primary tumor to neoadjuvant chemotherapy may be used as a surrogate indicator for the beneficial effect of neoadjuvant chemotherapy on survival. Therefore future research should be concentrated on neoadjuvant chemotherapy acting as an in vivo chemosensitivity test, providing an opportunity to assess and monitor biologic markers that may predict a response or no-response to a particular chemotherapy regimen. On the basis of the biologic characteristics of a tumor and differences in the response to neoadjuvant chemotherapy, this method of therapy should be regarded as a tool that can be used to individualize treatment for patients with breast cancer.

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