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Neoadjuvant chemotherapy with infusional 5-fluorouracil, adriamycin and cyclophosphamide (iFAC) in locally advanced breast cancer: an early response predicts good prognosis

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Background: The aim of this study was to evaluate the efficacy and safety of neoadjuvant chemotherapy with infusional 5-fluorouracil (5-FU), adriamycin and cyclophosphamide (iFAC) in locally advanced breast cancer (LABC).

Patients and methods: Eighty-two LABC patients were treated with neoadjuvant iFAC chemotherapy including infusional 5-FU (1000 mg/m^2, continuous intravenous infusion, days 1–3), adriamycin (40 mg/m^2, intravenous bolus, day 1) and cyclophosphamide (600 mg/m^2, intravenous bolus, day 1) every 3 weeks until maximum tumor response. Patients subsequently received surgery, adjuvant chemotherapy, radiotherapy and hormonal therapy as appropriate.

Results: Downstaging occurred in 71 of the 82 patients (86.6%). Seventy-two patients (67 patients with downstaging and five patients without downstaging) were resectable (resectability rate, 87.8%). The clinical response rate was 84.2%, with a complete response (CR) rate of 17.1% and a pathological CR rate of 7.8%. During 891 cycles of chemotherapy, the most common grade 3/4 hematological toxicity was leukopenia (36.0%). There were no treatment-related deaths. The median follow-up period was 51 months, with a median overall survival (OS) of 66 months, and a 5 year OS rate of 50.9% for all patients. The 5 year OS and disease-free survival (DFS) rates of the 64 patients who underwent surgery were 55.8% and 44.7%, respectively.

Conclusions: Neoadjuvant chemotherapy with iFAC had a comparable response rate and DFS to the conventional bolus FAC regimen, with an acceptable toxicity in LABC using the AJCC 2002 staging system. An early response to neoadjuvant iFAC was a favorable prognostic factor.

Key words: adriamycin, cyclophosphamide, infusional 5-fluorouracil, locally advanced breast cancer, neoadjuvant chemotherapy

Introduction

Achieving local and distant disease control in locally advanced breast cancer (LABC) remains a challenge despite the decreasing incidence of this cancer. Controversy still exists in the very definition of LABC. Most reports include inoperable stage IIIB in LABC, while others have included either operable stage III or stage IIIC with a positive supraclavicular node [1].

Neoadjuvant chemotherapy followed by locoregional therapy is a standard treatment in LABC. The 5 year overall survival rate has improved from 10–20% with local therapy alone to 30–60% with the multidisciplinary approach [2]. The most effective regimens usually contain adriamycin. Generally, three to four treatment cycles have been reported to induce the clinical response rate of 50–90% and a pathological complete response (pCR) rate <20% [3, 4]. A combined i.v. bolus 5-fluorouracil (5-FU), adriamycin and cyclophosphamide (FAC) regimen has been investigated in a neoadjuvant setting [5] because it was previously reported to induce a good tumor response in metastatic breast cancer [6, 7]. More recently, a bolus FAC regimen has been widely used as neoadjuvant chemotherapy in LABC [5, 8, 9].

The duration of 5-FU exposure is an important determinant of cytotoxicity, yet this agent has a short plasma half-life of approximately 11 min [10]. It was hypothesized that continuous i.v. infusion of 5-FU would overcome this limitation, and the prediction was validated by the observation of improved *in vitro* sensitivity to prolonged low-dose 5-FU exposure versus short high-dose exposure [11]. However, only a few studies have evaluated infusional FAC (iFAC) in the neoadjuvant setting of LABC.

The present study was designed to evaluate the efficacy and safety of an iFAC regimen as neoadjuvant chemotherapy in

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LABC, and to identify the predictive and prognostic factors for response and survival with this regimen. The primary endpoint of this study was response rate and the secondary endpoints were downstaging rate, disease-free survival, overall survival, toxicity and dose intensity.

Patients and methods

Eligibility criteria

LABC was defined as follows for this study: tumor ≥5cm with metastasis to the ipsilateral axillary nodes; tumor with direct extension to the chest wall or skin; tumor with metastasis to the ipsilateral fixed axillary/ipsilateral internal mammary/ipsilateral supraclavicular nodes. Patients with LABC and inflammatory breast cancer (IBC) were eligible for this study. Other eligibility criteria included age ≤70 years, histologically proven infiltrating ductual or lobular carcinoma, Eastern Oncology Cooperative Group (ECOG) performance status ≤2, adequate bone marrow (neutrophils $\geq 2 \times 10^3/\mu l$, platelets $\geq 100 \times 10^3/\mu l$, Hb ≥10.0 g/dl), renal (serum creatinine ≤1.5 times upper normal limit) and liver function [serum bilirubin ≤1.5 times upper normal limit, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤1.5 times upper normal limit], and no previous chemotherapy, radiotherapy or hormone therapy. Patients with other malignancies or bilateral breast cancers were excluded from this study. Eighty-two patients were enrolled between June 1991 and June 2001. As the staging system for breast cancer was changed during the enrollment period, patients were restaged using the American Joint Cancer Committee (AJCC) staging system revised in 2002 [12].

Treatment scheme

The iFAC regimen was administered according to the following schedule: 5-FU 1000 mg/m^2 24 h continuous infusion on days 1–3, adriamycin 40 mg/m^2 i.v. bolus injection on day 1 and cyclophosphamide 600 mg/m^2 i.v. bolus on day 1. The treatment was repeated every 3 weeks. When the tumor response reached a maximum, as determined by there being no change in the tumor size for two consecutive treatment cycles, the resectability was assessed by an oncological surgeon. Criteria of resectability were determined as follows: no distant metastasis, no extensive involvement of the skin, no change of the inflammatory cancer and no fixation of axillary nodes to one another or to other structures. After surgery, adjuvant chemotherapy with iFAC was followed until a maximum of 12 cycles including neoadjuvant chemotherapy. Radiotherapy was performed with a dose of 50.4 Gy over 5.5 weeks. The irradiated volume included the chest wall, ipsilateral internal mammary node and ipsilateral supraclavicular node areas.

If the tumor was unresectable after iFAC, chemotherapy was continued with a salvage regimen. Hormonal treatment was added in those patients who were hormonal receptor positive or in a postmenopausal state. The treatment scheme is summarized in Figure 1.

Response and toxicity evaluation

Tumor measurements were performed by physical examination, mammography and/or ultrasonography and chest CT at the baseline and after every third cycle, or whenever needed. The clinical response was defined according to the World Health Organization (WHO) criteria [13]. An early response was defined as a maximum clinical response within three cycles of iFAC chemotherapy, and a late response was defined as a maximum clinical response occurring after three cycles. The late and no response groups were gathered into a single 'late/no response group'. After surgery, the residual disease was dichotomized into microscopic residual disease (microRD, breast tumor ≤1 cm and negative axillary node) and macroscopic residual disease (macroRD, breast tumor >1 cm or positive axillary node). pCR and microRD were included together in the good pathological response group.

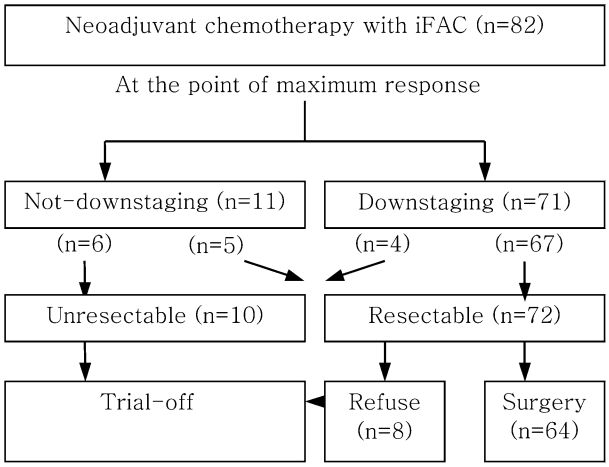

Figure 1. Treatment scheme and results.

Toxicity was graded using the WHO criteria [13]. Granulocyte colony-stimulating factor (G-CSF) was administered in cases of grade 3/4 neutropenia, and the subsequent cycle was delayed until complete recovery. The dose administered was reduced by 25% if a grade 3/4 non-hematological toxicity occurred or was sustained for >2 weeks.

Follow-up evaluation after completion of anticancer treatment

The patients were evaluated every 6 months after completion of treatment. If possible, all suspected recurrences were confirmed by biopsy during the follow-up period. Typical nodules in the liver or the lung, indicated by imaging studies, or lytic areas on the bone indicated by radioisotope bone scan and plain radiographs, were accepted as recurrence without histological confirmation. Locoregional recurrence was defined as recurrence in the chest wall, breast, axillary node or ipsilateral supraclavicular node areas. Disease-free survival (DFS) was defined as the time from curative surgery to cancer recurrence, occurrence of a secondary primary cancer or death without evidence of recurrence. Overall survival (OS) was defined as the time from neoadjuvant chemotherapy to death from all causes.

Statistical methods

All statistical calculations were carried out using SPSS Windows version 11.0 (SPSS Inc., USA). All *P*-values were two-sided and the α-value was set at 0.05. Survival was calculated using the Kaplan–Meier method. A log-rank test was used to compare survival between groups. Prognostic variables were submitted to multivariate analysis using Cox's proportional hazard regression model. Predictive factors for responsiveness were analyzed using a χ^2 test/Fisher's exact test and a logistic regression.

Results

Characteristics of eligible patients

Between June 1991 and June 2001, 82 LABC patients were enrolled in this study. The median follow-up period was 51 months (range 7–122 months) by 31 December 2003. The median age was 47 years (range 29–70 years). All tumors except two infiltrating lobular carcinomas were infiltrating ductal

carcinomas. The ECOG performance status was between 0 and 1 in all patients. Twenty patients (24.4%) had IBC, and 42, 30 and 10 patients were in clinical stages IIIA, IIIB and IIIC, respectively, based on the AJCC 2002 staging system. Detailed patient characteristics are summarized in Table 1.

Treatment results

As shown in the gray shaded region of Table 2, downstaging was observed in 86.6% of patients (71/82). Four of the 71 downstaged patients were still unresectable because of an increased axillary node size (one patient), new breast lesions (two patients) or an unchanged fixed axillary node (one patient). In contrast, five of 11 patients without downstaging became resectable owing to decreased breast tumor size. As a result, 72 patients (67 patients with and five patients without downstaging) were respectable (resectability rate, 87.8%).

Eight of the 72 resectable patients refused surgery. All consenting patients underwent a modified radical mastectomy with an axillary lymph node dissection. The distribution of the pathological stages is summarized in Table 2. After adjuvant chemotherapy, 50.0% of the patients (32/64) received radiotherapy at a median dose of 50.4 Gy (range 48.6–75.6 Gy).

Ten unresectable patients received salvage chemotherapy with a platinum- or taxane-based regimen with or without radiation. Five of the 10 unresectable patients underwent surgery after salvage treatment. Figure 1 provides an overview of the treatment results.

Clinical and pathological response to iFAC chemotherapy

Clinical response was evaluated in breast tumors (82 patients), axillary nodes (69 patients) and supraclavicular nodes (10 patients). The clinical response rates were 84.4% for breast tumor (cCR, 25.6%; cPR, 58.8%), 82.8% for axillary nodes (cCR, 55.7%; cPR, 27.1%) and 100% for supraclavicular nodes (cCR, 100%). The overall response rate (ORR) was 84.2% (cCR, 17.1%; cPR, 67.1%). The pCR rates were 10.9% for breast tumor and 26.6% for axillary nodes. Five patients (7.8%, 5/64) achieved a pCR in both breast tumor and axillary nodes, and seven (10.9%) of the 64 patients who underwent surgery achieved a good pathological response (Table 3).

A discrepancy was noted between cCR and pCR in that only four of the 14 cCR patients had pCR. Of the remaining 10 patients, three had a residual breast tumor without axillary lymph node involvement, two had axillary lymph node involvement without a residual tumor in the breast and five had both a residual tumor in the breast and axillary lymph nodes. In contrast, four of five pCR patients were assessed as having a cCR and the remaining patient was assessed as having a cPR.

Recurrence pattern and disease-free survival

At a median follow-up duration of 51 months (range 7–122 months), 35 (54.7%) of the 64 operated patients experienced recurrence. The most common locoregional and distant recurrence sites were the chest wall and the bone, respectively. The

Table 1. Patient characteristics

	Number	Percentage
Total number of patients	82	
Median age (range) (years)	47 (29–70)	
Initial clinical stage		
IIIA	42	51.3
T1N2M0	1	
T2N2M0	11	
T3N1M0	21	
T3N2M0	9	
IIIB	30	36.5
T4N0M0	14	
T4N1M0	10	
T4N2M0	6	
IIIC	10	12.2
T2N3M0	5	
T2N3M0	5	
Inflammatory breast cancer	20	24.4
Median initial tumor size (range) (cm)	7 (1.5–18)	
Pathology		
Infiltrating ductal carcinoma	80	97.5
Infiltrating lobular carcinoma	2	2.5
Estrogen/progesterone receptor		
Positive/positive	17	52.4
Positive/negative	3	7.1
Negative/positive	0	0
Negative/negative	22	40.5
Unknown	40	–
Menopause state		
Premenopause	44	53.7
Postmenopause	38	46.3

Table 2. Downstaging clinical stage after neoadjuvant chemotherapy

Initial stage	No. of patients	Clinical stage after neoadjuvant chemotherapy					
		0	I	IIA	IIB	IIIA	IIIB
IIIA	42	8	3	18	7	6	0
IIIB	30	3	1	14	7	0	5
IIIC	10	3	1	4	0	2	0
		Pathological stage after surgery					
		0	I	IIA	IIB	IIIA	IIIB
IIIA	32	2	2	12	8	7	1
IIIB	25	2	0	7	7	6	3
IIIC	7	3	0	3	0	7	0

The numbers in the shaded region represent the downstaged patients.

Table 3. Response rate to neoadjuvant iFAC chemotherapy

	Clinical response (n = 82)		Pathological response (n = 64)	
		Number (%)		Number (%)
Primary tumor		n = 82		n = 64
	CR	21 (25.6)	pCR	7 (10.9)
	PR	49 (58.8)	No pCR	57 (89.1)
	SD	6 (7.3)		–
	PD	6 (7.3)		–
AXLN		n = 69		n = 64
	CR	41 (59.4)	pCR	17 (26.6)
	PR	18 (26.1)	No pCR	47 (73.4)
	SD	8 (11.6)		–
	PD	2 (2.9)		–
SCL		(n = 10)		
	CR	10 (100)		–
Total response[a]				
	CR	14 (17.1)	pCR	5 (7.8)
	PR	55 (67.1)	microRD	2 (3.1)
	SD	6 (7.3)	macroRD	57 (89.1)
	PD	7 (8.5)		–

AXLN, axillary lymph node; SCL, supraclavicular node; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathological complete response; micro/macroRD, micro/macro residual disease.

[a]Total response was assessed by the summation of responses in primary tumor, AXLN and SCL based on the WHO response criteria.

locoregional, distant and combined recurrences occurred in 10 (15.6%), 17 (26.6%) and eight (12.5%) patients, respectively. Six of the 10 patients with locoregional recurrence showed a subsequent systemic recurrence, whereas a delayed locoregional recurrence was observed in only one of 17 initial systemic recurrences. The median DFS duration of the 64 operated patients was 45 months [95% confidence interval (CI) 17–73]. The 5 year locoregional recurrence-free survival (LRFS), the 5 year distant recurrence-free survival (DRFS) and the 5 year DFS rates were 68.5%, 51.3% and 44.7%, respectively.

Overall survival

At a median follow-up duration of 51 months (range 7–122 months), 41 (50%) of the 82 patients had died. Forty patients died from disease progression and one died from acute myocardial infarction. The median OS duration of the patients was 66 months (95% CI 43–89), and their 5 and 10 year OS rates were 50.9% and 37.4%, respectively (Figure 2). The median OS duration of the 64 operated patients was 89 months (95% CI 43–129), and their 5 and 10 year OS rates were 57.7% and 44.1%, respectively (Figure 2).

Toxicity profile

The dominating toxicity was myelosuppression. Of a total of 891 cycles, grade 3/4 leukopenia occurred in 36.0%, anemia in 0.8% and thrombocytopenia in 0.5%. Other serious toxicities included one episode of pneumonia with septic shock and three cases of congestive heart failure (CHF). However, there were no treatment-related deaths. The three CHFs occurred after completion of iFAC chemotherapy, and all three patients received cumulative doxorubicin doses of 480 mg/m^2. Heart failure developed at 2 months (two patients) and 46 months (one patient) after completion of iFAC. Oral mucositis and diarrhea were mild.

Dose intensity

The median duration of the neoadjuvant chemotherapy was 10 weeks (range 7–23 weeks) with a median number of three cycles (range two to six). For neoadjuvant chemotherapy, the relative dose intensities (RDIs) were 1.0 (range 0.5–1.0), 1.0 (range 0.6–1.0) and 1.0 (range 0.5–1.0) for 5-FU, adriamycin and cyclophosphamide, respectively. For adjuvant chemotherapy, the RDIs were 0.9 (range 0.6–1.0), 0.9 (range 0.4–1.0) and 0.9 (range 0.4–1.0) for 5-FU, adriamycin and cyclophosphamide, respectively. The RDIs of the combined iFAC regimen in the neoadjuvant and adjuvant settings were 0.98 (range 0.58–1.00) and 0.91 (range 0.91–1.00), respectively.

Prognostic factors for recurrence and survival

Initial tumor size, IBC, initial clinical stage/response and pathological stage/response were evaluated as prognosticators. Table 4 summarizes the significant factors by univariate analysis. Multivariate analysis identified the following independent favorable prognostic factors (Table 4): clinical response for DRFS [hazard ratio (HR) = 3.6, P = 0.03] and OS (HR = 3.7, P = 0.04); early response for LRFS (HR = 4.1, P = 0.002), DRFS (HR = 3.1, P = 0.004), DFS (HR = 3.2, P = 0.01) and OS (HR = 3.6, P = 0.002).

An early response was observed in 51 of the 69 responders (73.9%). The early response subgroup represented prolonged LRFS ($P < 0.000$), DRFS (P = 0.002), DFS ($P < 0.000$) and OS ($P < 0.000$) compared with the late response subgroup (Figure 3).

Predictive factors for early response

In the whole group, early and late/no responses were observed in 51 (62.2%) and 31 (37.8%) patients, respectively. The following variables were evaluated as predictive factors for early response: initial tumor size, IBC and initial stage. The initial tumor size and the initial N stage were significant predictors by univariate analysis (Table 5). Only a small initial tumor size (≤10 cm in long dimension) was a significant favorable predictor for early response according to multivariate analysis (HR = 0.14, P = 0.001).

Discussion

Continuous venous infusion increases dose intensity and prolongs exposure of cancer cells to an active drug [10]. An initial investigation of continuous infusion of 5-FU in colorectal cancer

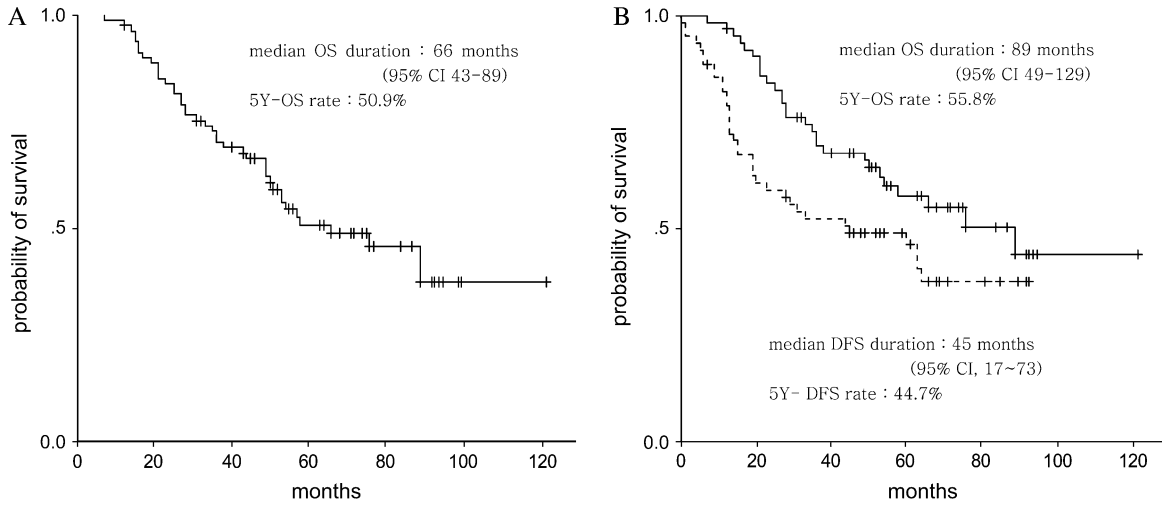

Figure 2. Survivals of (**A**) all 82 patients and (**B**) 64 operated patients. DFS, disease-free survival; OS, overall survival.

Table 4. Multivariate analysis of prognostic factors using Cox's proportional hazard model

Variables	LRFS		DRFS		DFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Initial tumor size (≤10 cm vs >10 cm)	0.7 (0.2–2.1)	0.56	–	–	1.6 (0.7–3.9)	0.26	–	–
Clinical response (CR/PR vs SD/PD)	3.4 (1.0–12.1)	0.06	3.6 (1.1–11.8)	0.03	2.6 (0.8–9.0)	0.12	3.7 (1.1–12.4)	0.04
Early responsiveness (ER vs LR/NR)	4.1 (1.7–10.3)	0.002	3.1 (1.4–6.7)	0.004	3.2 (1.4–7.3)	0.01	3.6 (1.6–8.3)	0.002
Pathological T stage (T1–T2 vs T3–T4)	–	–	–	–	–	–	1.5 (0.7–3.4)	0.33
Pathological N stage (N0 vs N1–N3)	1.3 (0.5–3.6)	0.63	–	–	2.0 (0.8–5.4)	0.15	–	–

LRFS, locoregional recurrence-free survival; DRFS, distant recurrence-free survival; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ER, early response; LR, late response; NR, no response.

demonstrated a high response and less bone marrow toxicity than administration of bolus 5-FU because of the different mode of action [14]. In a prior modified FAM (5-FU, adriamycin, mitomycin-C) trial in advanced gastric cancer at our institute, a trend of prolonged progression-free survival was observed for continuous infusion of 5-FU compared with bolus injection [15]. Later, a similar investigation in metastatic breast cancer resulted in a high response rate of 75% [16].

A bolus FAC regimen is one of the most commonly used treatments in LABC, with a reported clinical response of 72–88% and a pCR of 8–9% [5, 8, 9]. Even with a larger tumor size and a more advanced stage according to the AJCC 2002 staging system, the response rate and DFS of this trial with iFAC were similar to those of the M. D. Anderson Cancer Center clinical trial with a bolus FAC regimen [5]. Another bolus FAC trial in LABC reported a 5 year OS rate of 46% [9]. The 5 year OS rates of stage IIIA (47%) and IIIB (44%) reported by the National Cancer Institute [17] were similar to our 5 year OS rates for stage IIIA (57.6%), IIIB (44.8%) and IIIC (47.9%) patients.

A high pCR of 16% was induced by MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) with a 5 year DFS of 51%. However, because of myelosuppression and diarrhea, only 31% of the patients in that trial were able to complete the intended six cycles of adjuvant MVAC chemotherapy [18]. CVAP (cyclophosphamide, vincristine, doxorubicin, prednisolone) also induced a high pCR of 16% but the long-term survival results are awaited [19]. Recently, sequential docetaxel after anthracycline-based neoadjuvant chemotherapy was found to enhance the clinical response and pathological complete response rates significantly in two randomized phase III trials [19, 20]. However, it should be noted that the initial use of taxanes in LABC faces limitations such as loss of potential second-line drugs in the anthracycline-resistant cases. No data are yet available regarding the long-term survival of this treatment.

The randomized phase III Trial of Preoperative Infusional Chemotherapy (TOPIC1) [21] revealed that neoadjuvant continuous infusional 5-FU-based chemotherapy (5-FU, cisplatin, epirubicin) was no more effective than conventional bolus AC (adriamycin, cyclophosphamide) for early breast cancer. In TOPIC1, the inconvenience of continuous infusional 5-FU could not be justified by a non-significant increase in survival. Our trial is different from TOPIC1 in that infusional 5-FU-based chemotherapy was given to inoperable LABC patients. Infusional 5-FU-based chemotherapy might be overtreatment in cases of operable early breast cancer, and be needed instead for more

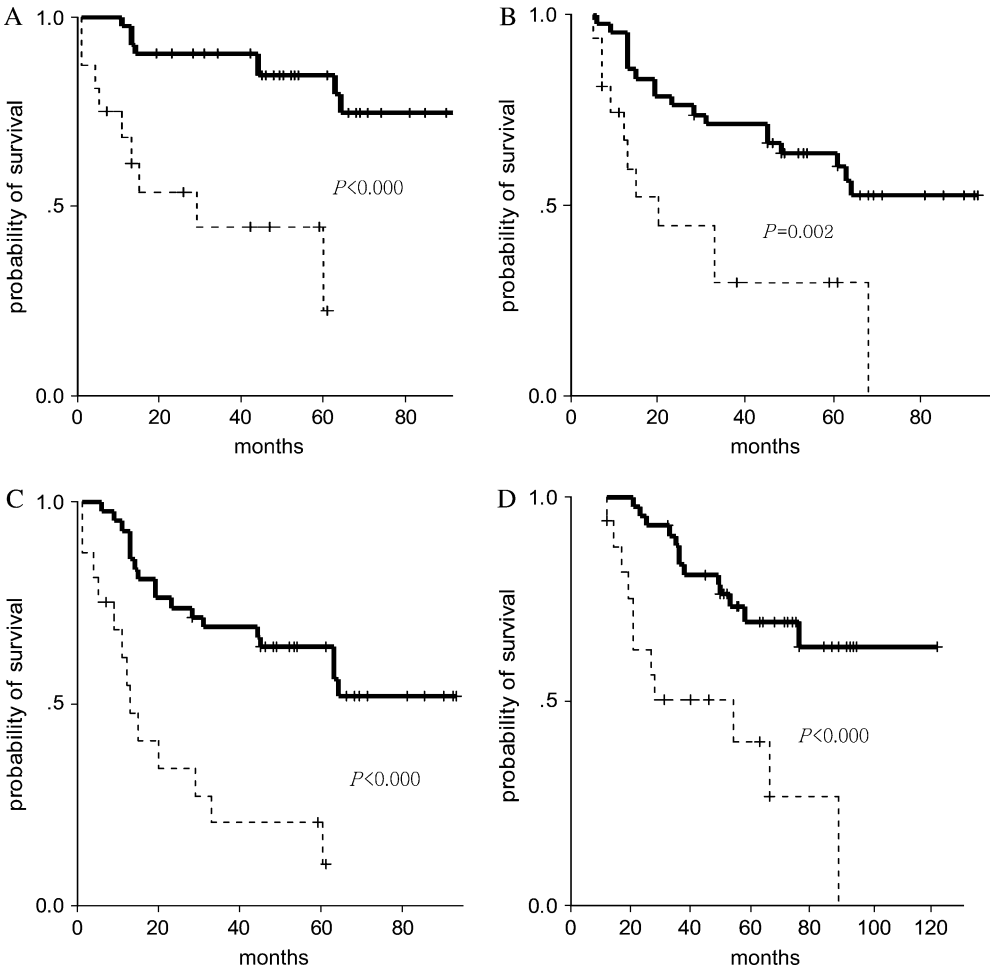

Figure 3. Comparison of survival between early (n = 43; solid curve) and late (n = 17; broken curve) response groups of resected patients: (**A**) locoregional recurrence-free survival; (**B**) distant recurrence-free survival; (**C**) disease-free survival; (**D**) overall survival.

advanced breast cancers, such as inoperable LABC, as reported previously in an advanced and locally advanced breast cancer trial [22].

The toxicities of iFAC chemotherapy were generally mild and acceptable. The major toxicity was bone marrow suppression, which was manageable with G-CSF. Continuous infusion of 5-FU in the iFAC regimen did not cause severe oral mucositis or diarrhea. Hand–foot syndrome was not observed. The occurrence of CHF (3.7%) was lower than in the bolus FAC trial (9.1%) [5]. Continuous infusion of 5-FU showed no evidence of enhancing anthracycline-induced CHF.

Most studies have used a fixed number of neoadjuvant chemotherapy cycles, usually three or four [5, 23]. However, in the present study patients received treatment until the maximum clinical response was achieved, regardless of the number of cycles. The former strategy has the advantage that definitive local therapy is not unnecessarily delayed, although it also presents the disadvantage of missing an opportunity for optimal resection due to insufficient response. Our strategy might improve the response with the potential risk of development of resistant clones.

The clinical benefits of neoadjuvant chemotherapy include downstaging, induction of resectability and breast conservation. In the present study, downstaging and resectability rates were high, but breast conservation was not performed. Hortobagyi and colleagues reported that 23% of patients with stage IIB or III tumors were potential candidates for breast conservation [24]. The breasts of our patients were too small compared with the breast tumor mass to conserve, and the patients did not want to conserve the breast. This cultural trend explains the limited use of breast conservation surgery in Korea.

The limitation of this study was that the tumor measurements were made using classical methods, i.e. physical examination, mammography and/or ultrasonography and chest CT. A discrepancy was noted between cCR and pCR that was attributable to overestimation of the residual tumor from chemotherapy-induced fibrosis or difficulty in detecting microscopic residual tumor by the classical evaluation methods. MRI and positron emission tomography would be expected to increase the accuracy of the tumor response estimate [25, 26].

A pCR is known to represent the best outcome [27, 28]. The good pathological response group in the present study (five pCRs and two microRDs) also showed a trend toward better DFS. As reported in many other studies [5, 29], our investigation found that the clinical response was a favorable prognostic

Table 5. Univariate analysis of predictors for early response

	Early response (n = 51) [number (%)]	Late/no response (n = 31) [number (%)]	P-value
Initial tumor size			
≤10 cm	48 (94.1)	20 (64.5)	0.001
>10 cm	3 (5.9)	11 (35.5)	
IBC			
Non-IBC	42 (82.4)	20 (64.5)	0.068
IBC	9 (17.6)	11 (35.5)	
Clinical T stage			
T1–T2	10 (19.6)	7 (22.6)	0.747
T3–T4	41 (80.4)	24 (77.4)	
Clinical N stage			
N0	5 (9.8)	9 (29.0)	0.025
N1–N3	46 (90.2)	22 (71.0)	
Clinical stage			
IIIA	27 (52.9)	12 (38.7)	0.435
IIIB	18 (35.3)	15 (48.4)	
IIIC	6 (11.8)	4 (12.9)	

IBC, inflammatory breast cancer.

factor. The early response subgroup had a more favorable prognosis than the late response subgroup. This suggests that prolonged preoperative chemotherapy with the same regimen has less benefit in iFAC chemotherapy for late responders, i.e. patients with poor response after three cycles of iFAC should receive chemotherapy with an alternative regimen. Two possible explanations for better outcome in the early response subgroup are as follows: early local therapy may alter the disease course, or an early response to iFAC may represent a biologically predetermined good prognosis. In the results of the National Surgical Adjuvant Breast and Bowel Project B-18, which compared pre- and postoperative chemotherapy in operable cancer, early surgery did not alter the disease course [30]. This finding seems to favor the second suggested explanation above. In the analysis of predictive factors, early responsiveness inversely correlated with initial tumor size. Thus tumor size can be considered to be an important parameter in selecting patients for neoadjuvant iFAC in LABC. Attempts are under way to identify the molecular predictors for early response in our patients by microarray-based comparative genomic hybridization.

In conclusion, neoadjuvant chemotherapy with iFAC had a comparable response rate and DFS to the conventional bolus FAC regimen, with an acceptable toxicity in LABC using the AJCC 2002 staging system. An early response to neoadjuvant iFAC was a favorable prognostic factor.

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