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A randomized trial of adriamycin, cyclophosphamide, ftorafur (ACF) and adriamycin, cyclophosphamide, ftorafur, methotrexate (ACFM) in patients with advanced breast cancer

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Summary. *A prospective randomized trial was conducted comparing the clinical response of 60 patients with advanced breast cancer to a combination of adriamycin, cyclophosphamide, and oral ftorafur (ACF), or to a combination of ACF plus methotrexate (ACFM). The response rate was 12 of 28 (43%) in ACF and 18 of 30 (60%) in ACFM. Responses were seen more frequently in patients in whom fewer than two organs were involved, and responses at dominant metastatic sites were equal for the two arms. The response duration was 21+ (3.5–49.5+) months with ACF, as against 6.9 (1.9–30.8+) months with ACFM ($P < 0.05$). The median survival time from start of therapy was 20.8+ months for ACF, while that for ACFM was 13+ months (statistically not significant). The major toxicities were hair loss, GI toxicity, and leukopenia. The response rate with ACFM was higher than that with ACF, but the addition of methotrexate to ACF did not increase the complete response rate or prolong response duration.*

Introduction

The 5-year relative survival rates determined for the various TMN stagings of breast cancer in 1979 in Japan were 90.1% for stage I, 79.9% for stage II, and 47.1% for stage III [9]. But the survival rate for stage IV is generally under 15%. Breast cancer is one of the most responsive cancers to chemotherapeutic agents, and various combination chemotherapy regimens have been proposed. Cooper's regimen [3] is a typical and well-known regimen that was frequently used earlier. Adriamycin has since been introduced to combination chemotherapy to avoid cross resistance with alkylating agents and antimetabolites. The efficacy of adriamycin as a single agent is superior to that of cyclophosphamide, methotrexate, and L-PAM to some degree [2]. We have already reported the results obtained with a regimen containing adriamycin, cyclophosphamide, and ftorafur (ACF) [7], and in our experience the main side-effect of this regimen is myelosuppression; it is effective without involving serious cardiac toxicity. In an attempt to obtain a higher response (especially complete response) rate we conducted a randomized trial comparing ACF and ACF plus methotrexate (ACFM).

Patients and methods

Sixty patients with measurable metastatic and primary advanced breast cancer were included in this study, which began on 1 March 1979 and closed on 30 April 1983. All patients had previously received radiotherapy, hormone therapy, and/or chemotherapy. Two patients (in the ACF group) were excluded from the final evaluation because of protocol violation. After randomization patients were considered to be evaluable even if only one cycle of therapy was given. A full blood count, total bilirubin, GOT, GPT, serum creatinine, and ECG were done at the start of treatment and at regular intervals thereafter. The minimum hematogical requirements for inclusion in the study were a WBC count of $\geqq$ 4,000/mm^3 and a platelet count of $\geqq 10 \times 10^4$/mm^3. Each patient had a performance status of $\geqq$ 40%, a total bilirubin $\leqq$ 3 mg/dl, GOT or GPT $<$ 4 times normal, serum creatinine $<$ 1.5 mg/dl, and age $\leqq$ 75 years old. Other eligibility criteria were no previous anthracycline therapy, no significant intrinsic heart disease, and no active second type of tumor.

The ACF combination regimen consisted in adriamycin 40 mg/m^2 IV on day 1, cyclophosphamide 130 mg/m^2 IV per day for 5 days, and ftorafur 600 mg/m^2 PO daily, which was continued until the WBC was lower than 2,000/mm^3 (Table 1). The ACFM combination regimen consisted in the same doses of ACF with methotrexate 10–15 mg/m^2 IV on days 1 and 5 of each cycle in addition. The treatment cycles for each combination was 3 weeks. Randomization of patients was done by the envelope system. Any dose modifications for either schedule in the presence of bone marrow suppression were based on the severity of hematological toxicities. Adriamycin was discontinued when a cumulative dose of 350 mg/m^2 was reached, and all drugs were withdrawn when liver function was disturbed to such an extent that values twice the normal limit values obtained prior to treatment were reached and serum creatinine exceeded 2 mg/dl.

Table 1. Schedule for the two drug regimens

ACF	
Adriamycin	40 mg/m^2 IV day 1
Cyclophosphamide	130 mg/m^2 IV days 1–5
Ftorafur	500 mg/m^2 PO daily[a]
	Repeat every 3 weeks
ACFM	
Adriamycin	40 mg/m^2 IV day 1
Cyclophosphamide	130 mg/m^2 IV days 1–5
Ftorafur	500 mg/m^2 PO daily[a]
Methotrexate	10–15 mg/m^2 IV day 1, 5
	Repeat every 3 weeks

[a] Continued until WBC is lower than 2,000/mm^3

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Table 2. Comparison of patient characteristics in the two groups

	ACF	ACFM
Age[a]	55 (32–69)	49 (31–68)
Menopausal status		
Premenopausal	5	6
Postmenopausal	23	24
Performance status (%)[a]	80 (40–100)	80 (40–100)
Time from operation to first recurrence (months)[a]	24 (4–190)	15.5 (2–117)
Time from relapse to ACF, ACFM (months)[a, b]	3.5 (0.5–126.0)	6.0 (0.5–35.0)
No prior treatment (%)	7 (25)	4 (13)
Prior chemotherapy (%)	17 (61)	16 (53)
Number of organ involved		
1–2 (%)	24 (86)	19 (63)
≧3 (%)	4 (14)	11 (37)
Dominant site of disease		
Visceral (%)	16 (57)	15 (50)
Osseous (%)	5 (18)	2 (7)
Soft tissue (%)	7 (25)	13 (43)

[a] Median (range)
[b] Excludes four inoperable cases, two in each group

Table 3. Comparative response data in the two groups

	ACF	ACFM
No. of patients entered	30	30
No. of patients evaluable	28	30
Complete remissions	4	2
Partial remissions	8 } 12 (43%)	16 } 18 (60%)
No change	14	10
Progressive disease	2	2
Days to response[a]	33 (15–90)	33 (8–70)
No. of courses[a]	22 (1–4)	2 (1–3)
Total dose of adriamycin (mg/m^2)[a]	78 (38–112)	78 (30–120)

[a] Median (range)

Table 4. Comparison of response rate by prognostic factors in the two groups

	ACF[a]	ACFM[a]
Number of organs involved		
1–2	10/28 (36)	14/30 (47)
≧3	2/28 (7)	4/30 (13)
Dominant site of disease		
Visceral	6/16 (38)	7/15 (47)
Osseous	1/5 (20)	1/2 (50)
Soft tissue	5/7 (71)	10/13 (77)
Menopausal status		
Premenopausal	2/5 (40)	6/6 (100)
Postmenopausal	10/23 (44)	12/24 (50)

[a] Number of responders/number treated (%)

Objective regressions were assessed according to the UCII response criteria [4], which can be outlined as follows: Complete response (CR), disappearance of all known disease; partial response (PR), ≧ 50% decrease in measurable lesions in the absence of growing tumor at other sites; no change (NC), unchanged lesion (i.e., < 50% decrease or < 25% increase in the size of measurable lesions); progressive disease (PD), progression of some or all lesions and/or appearance of new lesions.

The response duration was determined from the initiation of chemotherapy and survival time was measured from the institution of chemotherapy to death or to the last follow-up examination for patients still alive (30 April 1983). The survival rate was calculated by the Kaplan-Meier method and the generalized Wilcoxon test was used to test the differences between the groups in duration of response to treatment and survival. The Chi-square test was used to assess the comparability of the groups of prognostic factors and to compare remission rates.

Results

In all, 28 patients were randomized to receive ACF and 30 to receive ACFM. Pretreatment patient characteristics, i.e., age, menopausal status, performance status (Karnofsky), time from operation to first recurrence, time from relapse to ACF or ACFM, and prior treatment were similar for the two arms (Table 2). Previous chemotherapy received consisted in adjuvant chemotherapy with ftorafur, L-PAM, or oral cyclophosphamide for 1–10 months, and the proportion of patients who had received prior chemotherapy was 61% (17 of 28) in the ACF group and 53% (16 of 30) in the ACFM group (statistically not significant). The two arms were compared by the distribution of the numbers of organ involved and the dominant site. In the ACF arm 86% (24 of 28) had fewer than two organs involved and in the ACFM arm, 63% (19 of 30). In the ACFM arm, the distribution of dominant site was 57% (16 of 28) visceral, 18% (5 of 28) osseous and 25% (7 of 28) for soft-tissues involvement. In the ACFM arm, 50% (15 of 30) had the dominant metastatic site in visceral, 7% (2 of 30) in osseous, and 43% (13 of 30) in soft tissue.

Antitumor effect

The response rates in the two arms are shown in Table 3. Complete plus partial responses were achieved by 12 of 28 patients (43%) with ACF, as against 18 of 30 (60%) with ACFM (P = 0.14). Days to response, number of treatment

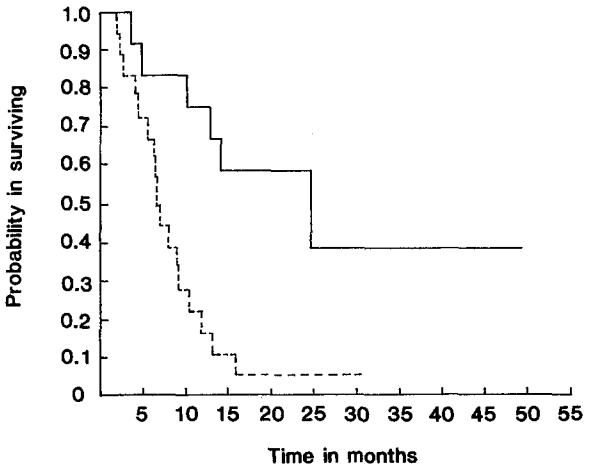

Fig. 1. Duration of response (months) for patients receiving adriamycin, cyclophosphamide, ftorafur (ACF) (———), or ACF plus methotrexate (ACFM) (– – –)

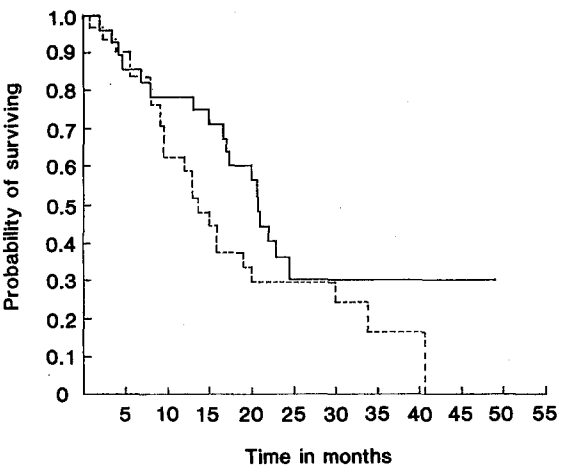

Fig. 2. Survival time from start of therapy (months) for patients receiving adriamycin, cyclophosphamide, ftorafur (ACF) (———) or ACF plus methotrexate (ACFM) (– – –)

Table 5. Comparative data on response duration and survival time in the two groups

	ACF		ACFM	
Response duration (months)[a]	21+	(3.5–49.5+)	6.9	(1.9–30.8+)
Survival time (months)[a]				
All	20.8+	(2–49.5+)	13+	(0.7–40.7)
Responders	23+	(7–49.5+)	14.4	(2.3–36+)
Nonresponders	16.3+	(2–37+)	9.8+	(0.7–40.7)

[a] Median (range)

Table 6. Nonhematological toxicity of ACF and ACFM

	ACF		ACFM	
Hair loss	28/28	(100)	30/30	(100)
Nausea	23	(82)	27	(90)
Vomiting	16	(57)	20	(67)
Anorexia	21	(75)	21	(70)
Stomatitis	6	(21)	4	(13)
Diarrhea	5	(18)	3	(10)
Pigmentation	6	(21)	8	(27)
Liver toxicity	3	(11)	5	(17)

( ): Percentage

Table 7. Hematological toxicity of ACF and ACFM

	ACF		ACFM	
Leukopenia ($< 3{,}000/mm^3$)	28/28	(100%)	28/30	(93%)
$2{,}000 \leqq$ WBC $< 3{,}000$	10	(36%)	8	(26%)
$1{,}000 \leqq$ $< 2{,}000$	15	(53%)	14	(47%)
$< 1{,}000$	3	(11%)	6	(20%)
Thrombocytopenia ($< 100 \times 10^3/mm^3$)	6/28	(21%)	16/30	(53%)[a]
$60 \times 10^3 \leqq$ platelet $< 100 \times 10^3$	3	(11%)	11	(37%)
$30 \times 10^3 \leqq$ $< 60 \times 10^3$	1	(3%)	3	(10%)
$< 30 \times 10^3$	2	(7%)	2	(6%)
Anemia (Decrease of 2 g/dl or more of Hb)	9/28	(32%)	15/30	(50%)
$2 \leqq$ Decrease of Hb < 3	6	(21%)	8	(27%)
$3 \leqq$	3	(11%)	7	(23%)

[a] Statistically significant, $P < 0.05$

courses, and total dose of adriamycin before response were quite similar in the two arms. Response frequency by prognostic factors was also analyzed (Table 4). Responses were seen more frequently in patients in whom fewer than two organs were involved and in patients with metastases in soft tissues. With regards to menopausal status, in the ACF group the response rate was similar for pre- and postmenopausal status, but in the ACFM group the response rate of premenopausal patients was six of six (100%), while that of postmenopausal patients was 12 of 24 (50%) (statistically not significant).

The duration of response was significantly longer with ACF than with ACFM ($P < 0.05$), with a median of 21+ months for ACF and 6.9 months for ACFM (Table 5 and Fig. 1). The median survival time from start of therapy for ACF was 20.8+ months, while that for ACFM was 13+ months (statistically not significant) (Table 5 and Fig. 2). In both arms, the median survival time of responders was longer

than that of nonresponders, and in the ACF arm the survival of responders was significantly longer than that of nonresponders ($P < 0.05$).

Toxicity

The toxicity of the two arms is shown in Tables 6 and 7. Alopecia was observed in all patients treated with either combination. A moderate degree of nausea and vomiting occurred in a high percentage of patients. Anorexia, stomatitis, diarrhea, and pigmentation were observed equally often in the two arms. Cardiac symptoms, viz. palpitations or anginal attacks were seen after administration of adriamycin in one case in each of the two arms, but these symptoms were reversible. Hematological toxicity seen within three courses was similar in the two arms. Of the patients in the ACF group 64% developed leukopenia with less than 2,000/mm^3, which occurred in 67% of patients in the ACFM group. Thrombocytopenia ($P < 0.05$) and anemia were less severe in ACF than in ACFM. But these hematological toxicities were reversible, and no serious liver and renal damages was seen in either arm.

Discussion

Combination chemotherapy with adriamycin, cyclophosphamide, and 5-fluorouracil (5-FU) produces a consistently high objective response rate in patients with metastatic breast cancer. This FAC regimen was used in studies conducted by Young et al. [12] and Bull et al. [1], and the response rate was 82%. The other two studies were carried out by the group at the MD Anderson Hospital and the Southeastern Cancer Study Group (SEG). The response rate at the MD Anderson Hospital was 73% [5] and that recorded by SEG [10] was 64%. These studies led to FAC being considered as a standard combination chemotherapy for advanced breast cancer. In our study we used oral ftorafur instead of 5-FU, for the following reasons: first the oral form of ftorafur was first developed and studied in Japan: secondly, the response rate reported was 39% (17 of 44), which was judged to reflect comparable efficacy to 5-FU [8]; and finally, the oral form was thought to be more convenient for outpatient use. In terms of the efficacy of oral ftorafur, Hortobaggi et al. [6] have studied the combination of AC plus ftorafur plus BCG against metastatic breast cancer and also suggested that the objective response to ftorafur and 5-FU was substantially equal.

In our earlier study [7] the response rate of ACF was 51% (CR 2%, PR 49%) and an increase in the response rate, and especially in the complete remission rate and prolongation of survival time was expected with the ACFM regimen. Methotrexate is known to be an effective drug with moderate hematological toxicity, and the single-agent efficacy reported for it is 34% [2]. In our randomized study of ACF vs ACFM the response rate with ACFM was 60%, as against 43% with ACF, but the difference is not statistically significant and it was considered that the higher response rate with ACFM might be due to the higher proportion and metastases in soft tissues in the ACFM group. There was also no significant difference in clinical response by number of organs involved or dominant sites of involvement in both arms, and nonhematological and hematological toxicities, except for thrombocytopenia, were not significantly different in the two arms. SWOG conducted a three-arm prospective randomized study comparing adriamycin plus 5-FU (AF), adriamycin and 5-FU plus cyclophosphamide (AFC), and AFC plus methotrexate (ACFM) [11]. The response rates in the three arms were 42% for AF, 43% for AFC, and 49% for ACFM. The remission duration and the median survival time were the same in all three arms, but the ACFM regimen was proposed as a standard therapy for advanced breast cancer because it had the highest response rate of the three arms without additional toxicity. Our own study and this report have suggested that the addition of methotrexate of ACF does not result in a higher response rate than is obtained with ACF.

In our study, however, the median remission duration with ACF was 21+ months, as against 6.9 months with ACFM, and the difference is statistically significant ($P < 0.05$). We considered this signficance could result from the difference in the number of CR cases in the two arms: in the ACF group there were four CR cases which maintained long response duration, i.e. 18+, 24+, 24+, 49.5+, while in contrast in the ACFM group only two patients entered CR, with remission durations of 6.7 and 12 months. With regard to survival time in the two arms, we considered that since 14% of patients in the ACF group had advanced disease involving more than three organs, and 37% of patients in the ACFM group, this was why the survival time was longer in the ACF than in the ACFM group.

In conclusion, the addition of methotrexate to ACF did not the increase the response rate or prolong remission duration and survival time. ACF is a standard chemotherapy combination for advanced breast cancer, but it is impossible to add other effective agents, i.e., mitomycin C and vindesine, to ACF because of the significant myelotoxicity of these drugs. We are now conducting a trial with chemoendocrine therapy, ACF plus tamoxifen, instead of ACFM, in an attempt to find an effective treatment for advanced breast cancer.

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