

Feasibility of Adjuvant Chemotherapy for Breast Cancer Patients

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To evaluate the feasibility of adjuvant chemotherapy, we analyzed the toxicities of chemotherapy for primary breast cancer in Japanese women. Since the opening of the National Cancer Center Hospital East, 180 female breast cancer patients have received adjuvant chemotherapy or chemo-hormonal therapy following surgical treatment between June 1992 and December 1995. On the basis of informed consent about prognosis and adjuvant therapy, most patients decided to choose the type of cytotoxic chemotherapy themselves. Adjuvant chemotherapy consisted of oral fluoropyrimidine compounds (OFP), cyclophosphamide + adriamycin \pm 5-fluorouracil [CA(F)] or cyclophosphamide + methotrexate + 5-fluorouracil (CMF). Toxicity was determined using the Toxicity Grading Criteria of the Japan Clinical Oncology Group (JCOG). Sixty-six patients received OFP, 59 CA(F) and the rest 55 CMF. The toxicity grading of leukocytes and neutrophils was significantly higher in patients treated with CA(F) or CMF than in those treated with OFP. Similar results were also seen relating to the toxicity of nausea/vomiting and alopecia. There was no statistical difference in the toxicity grading of hemoglobin, glutamic oxaloacetic transaminase/glutamic pyruvic transaminase (GOT/GPT) and stomatitis/gastritis between the three groups of patients. Interestingly, the number of patients that were forced to discontinue chemotherapy was higher in those receiving OFP than in those receiving CA(F) or CMF. Cytotoxic chemotherapy of CA(F) or CMF results in greater toxicity than OFP, but is tolerated and feasible in the adjuvant setting used in Japanese breast cancer patients from the viewpoint of toxicities by anticancer chemotherapy.

Key words: adjuvant chemotherapy – breast cancer – feasibility – toxicity

INTRODUCTION

Recent meta-analyses of randomized trials have clearly demonstrated that adjuvant chemotherapy in operable breast cancer patients could improve disease-free survival and overall survival (1). In Western countries, combination chemotherapy of cyclophosphamide + adriamycin + 5-fluorouracil (CAF) and cyclophosphamide + methotrexate + 5-fluorouracil (CMF) have been established as the standard adjuvant therapies in patients with node-positive breast cancer and with node-negative high-risk breast cancer (2). Although oral fluoropyrimidine compounds (OFP) are widely used in adjuvant therapy for primary breast cancer in Japan, the survival benefits of OFP-based chemotherapy

remain to be determined. At the Division of Breast Surgery in the National Cancer Center Hospital East (NCCHE), 180 female breast cancer patients have received adjuvant chemotherapy or chemo-hormonal therapy following surgical treatment between June 1992 and December 1995. Most patients decided to choose the type of cytotoxic chemotherapy, because of the lack of clear evidence for the superiority of any one adjuvant chemotherapy regimen in Japan. In this work, the toxicities associated with cytotoxic chemotherapy in these non-randomized patients were analyzed and evaluated to determine the feasibility of adjuvant chemotherapy.

PATIENTS AND METHODS

From the opening of the NCCHE in June 1992 until December 1995, 429 breast cancer patients had been hospitalized. The toxicities of cytotoxic chemotherapy in female breast cancer patients who had undergone total or partial mastectomy with axillary dissection were examined. Patients with node-negative low-risk breast cancer, male breast cancer, bilateral breast cancer, double primary cancer and metastatic breast cancer and those who entered the randomized clinical trials of the Breast Group of the Japan Clinical Oncology Group (JCOG) (Study Nos 9208,

Received January 13, 1997; accepted May 14, 1997

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Abbreviations: OFP, oral fluoropyrimidine compounds; CA(F), cyclophosphamide + adriamycin \pm 5-fluorouracil; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; JCOG, Japan Clinical Oncology Group; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

9401 and 9404) were excluded from the present study. Two patients receiving primary chemotherapy of CAF were included. Most patients and their families were informed of the prognostic factors in the resected specimens such as histological grade, lympho-vascular invasion and the number of nodal metastases and hormonal features such as menopausal status and hormonal receptor status. They were also informed that there was no further confirmation of randomized clinical trials examining OFP, CA or CAF [CA(F)] and CMF in Japan and that they would suffer from toxicities with orally or intravenously mediated chemotherapy. If the patients were eligible for the JCOG trials, they were informed to be able to choose the randomized trials or non-randomized adjuvant therapy. Finally, they decided whether to receive adjuvant therapy or not. About 40% of all patients chose the type of chemotherapy with or without tamoxifen that they would receive. The treatment schedule is shown in Table 1. The drug and daily dose of OFP and the dose and dose intensity of CA(F) or CMF were decided by physician's discretion. Adjuvant chemotherapy was usually started within 4 weeks after surgery, except for irradiation given prior to chemotherapy. Anti-emetic drugs such as domperidone, granisetron and ondancetron had been used frequently during treatment with CA(F) and CMF for the prophylaxis of nausea/vomiting. Granulocyte colony-stimulating factors had never been administered for the rescue of bone marrow suppression. Assessment of toxicity was recorded every 2 months for patients treated with OFP and every 3 or 4 weeks for patients treated with CA(F) or CMF. The highest grade toxicity recorded during the treatment was analyzed using the

Toxicity Grading Criteria of JCOG (3). The treatment was discontinued in the case of a grade 2 or greater level of toxicity excluding nausea/vomiting and alopecia and then the same treatment without dose modification was continued again if grade 1 toxicity was reached within 4 weeks.

Statistical significance was determined using the chi-squared test.

RESULTS

One hundred eighty female patients received chemotherapy (Table 2). Of the 180 patients, 66 received OFP, 59 received CA or CAF and the remaining 55 received CMF. OFP consisted of 5-fluorouracil, UFT, doxifluridine and carmofur. The patients treated with CA(F) had more advanced disease and more progressive nodal metastases than those treated with OFP or CMF ($p < 0.0001$). Adjuvant radiation therapy following partial mastectomy was performed in 11 patients treated with OFP, 9 patients treated with CA(F) and 9 patients treated with CMF. Since the influence of radiation therapy on toxicity of chemotherapy was clearly undetermined (4), all events are summarized in this paper. Table 3 shows the cumulative dose of cytotoxic agents. Twenty-two patients treated with OFP and 3 patients treated with CA or CMF were still receiving chemotherapy at the time of investigation in July 1996. Patients receiving OFP had a relatively low dose with a mean duration of 13–18 months and patients receiving CA(F) or CMF had an intermediate dose of adriamycin or methotrexate over a mean period of 5 months.

Table 1. Treatment schedule

Chemotherapy	Dose	Duration	No. of patients
Oral fluoropyrimidine compounds			
5-Fluorouracil	150 or 200 mg (daily)	24 months	25
UFT	300 or 400 mg (daily)	24 months	22
Doxifluridine	600 or 800 mg (daily)	24 months	11
Carmofur	300, 400 or 600 mg (daily)	24 months	9
Cyclophosphamide	400 or 500 mg/m ² (i.v.)	every 4 weeks	37
+ Adriamycin	+40 or 50 mg/m ² (i.v.)	×6 cycles	
Cyclophosphamide	500 mg/m ² (i.v.)	every 3 or 4 weeks	22
+ Adriamycin	+40 or 50 mg/m ² (i.v.)	×6 cycles	
+ 5-Fluorouracil	+500 mg/m ² (i.v.)		
Cyclophosphamide	100 mg (p.o.) (days 1–14)	every 4 weeks	6
+ Methotrexate	+30 or 40 mg/m ² (i.v.) (days 1, 8)	×6 cycles	
+ 5-Fluorouracil	+500 mg/m ² (i.v.) (days 1, 8)		
Cyclophosphamide	500 mg/m ² (i.v.)	every 3 weeks	49
+ Methotrexate	+40 or 50 mg/m ² (i.v.)	×6 or 8 cycles	
+ 5-Fluorouracil	+500 mg/m ² (i.v.)		

Statistical significance was determined using the chi-squared test.

Table 2. Patient characteristics

Characteristics	No. of patients receiving adjuvant chemotherapy			P value*
	Oral fluoropyrimidine compounds	CA or CAF	CMF	
All patients	66	59	55	
Age (yr)				
<35	5	2	8	0.303
36–50	32	28	24	
>51	29	29	23	
Stage				
I	10	1	4	<0.0001
IIA, IIB	54	33	44	
IIIA, IIIB	2	25	7	
Nodal status				
0	33	3	29	<0.0001
1–9	32	31	23	
>10	1	25	3	
Chemotherapy				
Alone	24	12	27	0.0054
With tamoxifen	42	47	28	
Operation method				
Total mastectomy	53	47	42	0.856
Partial mastectomy	13	12	13	

*Statistical analysis used by the chi-squared test.

Table 3. Cumulative dose

Chemotherapy	Total dose (mean; median)	Duration (mean) (months)
Oral fluoropyrimidine compounds (g)		
5-Fluorouracil	18–144 (103; 108)	3–24 (18)
UFT	16–264 (135; 156)	1–24 (13)
Doxifluridine	108–552 (319; 324)	6–24 (17)
Carmofur	36–432 (213; 171)	2–24 (15)
CA or CAF		
Adriamycin (mg/m ²)	150–500 (250; 240)	2–8 (5)
CMF		
Methotrexate (mg/m ²)	120–480 (263; 240)	3–6 (5)

Toxicities including hypertension, weight gain/loss, metabolic toxicity, pulmonary toxicity and coagulation were rarely tested for in the outpatient setting. Chemotherapy-induced amenorrhea in premenopausal women was not precisely recorded. These toxicities have been omitted in this paper. Thrombocytopenia ($<10 \times 10^4/\mu\text{l}$) was not observed with any chemotherapy. The toxicity grading of leukocytes and neutrophils was significantly higher in patients treated with CA(F) or CMF than in those treated with OFP ($p < 0.0001$ and $p = 0.0001$, respectively) (Table 4).

Similar results were also seen with nausea/vomiting and alopecia. However, there was no statistical difference in the levels of toxicity of hemoglobin, glutamic oxaloacetic transaminase/glutamic pyruvic transaminase (GOT/GPT) and stomatitis/gastritis between the three groups of patients. In miscellaneous toxicities, constipation was experienced in patients treated with CA(F) and CMF (19 and 7%) (Table 5). The highest grade of any one toxicity was significantly different between the three treatment groups (Table 6, $p < 0.0001$), because greater hematological or gastrointestinal toxicity was caused by CA(F) or CMF. However, the highest grade of any one toxicity was not associated with menopausal status in each of the three treatment groups and not with radiation therapy in all of the patients.

Interestingly, the number of patients who were required to or wished to discontinue chemotherapy was greater in patients treated with OFP than in those treated with CA(F) or CMF (Table 7). With the exception of patients who relapsed during treatment, 9 of the 66 patients treated with OFP (13.6%) were forced to discontinue the treatment, compared with 3 of the 59 patients treated with CA(F) (5.1%) and 1 of the 55 patients treated with CMF (1.8%) ($p = 0.0325$). The mean and median treatment duration in patients treated with OFP, CA(F) and CMF were 6 and 3 months, 5 and 5 months and 3 and 3 months, respectively. The ratios of cumulative dose to scheduled dose of OFP, CA(F) and CMF given these patients were 0.03–0.78, 0.5–0.83 and 0.5, respectively.

Table 4. Comparison of toxicity with oral fluoropyrimidine compounds (OFP) and CA(F) and CMF

Toxicity	JCOG grade										P value*
	0		1		2		3		4		
	n	%	n	%	n	%	n	%	n	%	
Hemoglobin											
OFP	57	86	7	11	2	3	0	0			0.201
CA or CAF	42	71	13	22	4	7	0	0			
CMF	42	76	12	22	1	2	0	0			
Leukocytes											
OFP	43	65	19	29	4	6	0	0	0	0	<0.0001
CA or CAF	15	25	23	39	18	31	3	5	0	0	
CMF	18	33	16	29	21	38	0	0	0	0	
Neutrophils											
OFP	57	86	9	14	0	0	0	0	0	0	0.0001
CA or CAF	31	53	11	19	15	25	2	3	0	0	
CMF	32	58	13	24	10	18	0	0	0	0	
Nausea/vomiting											
OFP	59	89	5	8	2	3	0	0			<0.0001
CA or CAF	13	22	19	32	25	42	2	3			
CMF	20	36	23	42	12	22	0	0			
Stomatitis/gastritis											
OFP	59	89	4	6	2	3	1	2	0	0	0.678
CA or CAF	50	85	8	14	1	2	0	0	0	0	
CMF	49	89	5	9	1	2	0	0	0	0	
GOT/GPT											
OFP	57	86	7	11	1	2	1	2	0	0	0.924
CA or CAF	53	90	5	8	1	2	0	0	0	0	
CMF	49	89	5	9	1	2	0	0	0	0	
Alopecia											
OFP	66	100	0	0	0	0					< 0.0001
CA or CAF	1	2	51	86	7	12					
CMF	51	93	4	7	0	0					

*Statistical analysis used by the chi-squared test.

Two patients treated with CA(F) and one patient treated with CMF refused to continue the treatment. One patient was taken off CA, because of a possible diagnosis of variant angina (grade 2 cardiac ischemia, Table 5). On the other hand, four patients treated with OFP refused chemotherapy for psychological reasons, including one patient with a complaint of grade 1 sensory loss on forearms and one patient with severe epigastric pain without gastrointestinal disorder. One patient could not continue oral chemo-hormonal therapy, because of a transient ischemic attack diagnosed at a local hospital, possibly caused by tamoxifen. Furthermore, four patients discontinued the treatment with OFP, because of a grade 2 or greater level of toxicity: one patient had grade 4 diarrhea and grade 3 stomatitis, one patient had grade 3 liver dysfunction, one patient had grade 3 sensory loss

of smell and one patient had grade 2 refractory cystitis (Table 4 and 5). No difference was observed in the frequency of discontinuance between the four kinds of OFP regimens.

DISCUSSION

In a recent working conference, adjuvant chemotherapy for breast cancer was recognized to have survival benefits (2). In Japan, many kinds of fluoropyrimidine derivatives have been widely used in the adjuvant setting of chemotherapy in breast cancer patients (5). However, there have been no randomized adjuvant trials of primary breast cancer comparing OFP with CA(F) or CMF until recently. There is confusion about the use of cytotoxic chemotherapy for primary breast cancer in Japan (6).

Table 5. Miscellaneous toxicities

Toxicity	JCOG grade (No. of patients)	
	1	2
Infection		
Acute cystitis		
OFP	2	1
CA(F)	1	–
CMF	1	–
Herpes zoster		
CA(F)	–	1
Others		
OFP	2	–
CA(F)	3	–
CMF	1	–
Neurological		
Constipation		
CA(F)	11	–
CMF	4	–
Headache		
CA(F)	2	–
CMF	2	–
Sensory		
OFP	1	1
CMF	1	–
Drug fever		
CA(F)	2	–
Skin		
Edema		
CA(F)	1	–
Skin rash		
OFP	1	1
CA(F)	3	–
CMF	3	–
Diarrhea		
OFP	1 (grade 4)	–
Cardiac		
Ischemia		
CA(F)	–	1

OFP-based chemotherapy is believed to be less toxic. In general, long-term chemotherapy regimens show problems with compliance and early relapse during treatment (7,8). Although four patients treated with OFP (6%) could not complete the treatment for reason of grade 2 or greater toxicity, four patients (6%) refused to continue the treatment for reasons other than toxicity or early relapse. The same tendency on discontinuance of OFP was shown in the treatment of advanced breast cancer patients (9,10). These results suggest that long-term oral chemotherapy may induce psychological problems in OFP-treated patients without severe toxicity.

Table 6. Highest grade toxicity in each patient

Grade	No. of patients (%)		
	Oral fluoropyrimidine compounds	CA or CAF	CMF
0	21 (32)	0 (0)	2 (4)
1	30 (45)	19 (32)	22 (40)
2	13 (20)	33 (56)	31 (56)
3	1 (2)	7 (12)	0 (0)
4	1 (2)	0 (0)	0 (0)
Total	66 (100)	56 (100)	55 (100)

Table 7. Reasons for discontinuance

Reason	No. of patients		
	Oral fluoropyrimidine compounds	CA or CMF	CMF
Grade 2 or greater			
level of toxicity	4	1	0
Patient's refusal	4	2	1
Physician's discretion	1	0	0
Recurrence	5	2	0
Total No.			
except recurrence	9	3	1

In contrast, patients treated with CA(F) or CMF had high incidences of grade 2 or greater toxicity (68 or 56%) (Table 6), but showed better compliance. The reason is that most patients recognized the benefits and toxicities of intravenously mediated chemotherapy before treatment and then chose the type of chemotherapy themselves without physician's discretion. In the adjuvant trials of CA(F) and CMF in Western countries, the incidence of grade 2 or greater toxicity like neutropenia, vomiting and alopecia was reported to range between 30 and 70% (11–13). However, 80% or more patients completed the treatment.

In conclusion, combination chemotherapy of CA(F) or CMF results in greater toxicity than OFP-based chemotherapy, but is well tolerated and feasible in the adjuvant setting in Japanese breast cancer patients from the viewpoint of toxicities by anticancer agents. One of the most important issues of adjuvant chemotherapy for primary breast cancer in Japan is to clarify the benefits for survival of OFP, when compared with standard combination chemotherapy in Western countries. The feasibility of adjuvant chemotherapy will also need to be addressed in randomized clinical trials in the near future.

Acknowledgment

The author is very grateful to Dr Shigeaki Yoshida, Deputy Director, NCCHE, for his advice.

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