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Original Paper

Postoperative Adjuvant Randomised Trial Comparing Chemo-endocrine Therapy, Chemotherapy and Immunotherapy for Patients with Stage II Breast Cancer: 5-year Results from The Nishinihon Cooperative Study Group of Adjuvant Chemo-endocrine Therapy for Breast Cancer (ACETBC) of Japan

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Between 1985 and 1988, the effect of using ftorafur (FT) or PSK (an immunotherapy agent) in combination with the conventional postoperative adjuvant therapy using mitomycin (MMC) plus tamoxifen (TAM) was assessed in stage II, oestrogen receptor-positive (ER+) breast cancer patients. Furthermore, in ER– breast cancer stage II patients, the effects of postoperative adjuvant therapy using MMC plus FT were compared with the effects of postoperative adjuvant therapy using MMC plus PSK. Patients had primary stage II breast cancer and had undergone total mastectomy plus axillary dissection or more radical surgery. On the day of surgery, MMC (13 mg/m^2) was administered intravenously. Then, ER+ patients received one of three regimens of drug therapy, starting 2 weeks after surgery: regimen A (daily oral treatment with 20 mg of TAM), regimen B (daily oral treatment with 20 mg of TAM and 600 mg of FT) or regimen C (daily oral treatment with 20 mg of TAM and 3 g of PSK). ER– patients received either regimen D (daily oral treatment with 600 mg of FT) or regimen E (daily oral treatment with 3 g of PSK), starting 2 weeks after surgery. Of the 540 ER+ patients registered, 525 were evaluated. The 5-year overall survival rate for ER+ patients was higher for patients who received regimen B (94.2%) than for those who received regimen A (86.9%) or regimen C (89.9%) ($P = 0.063$). The 5-year relapse-free survival rate was higher for regimen B (88.9%) than for regimen A (78.6%) and regimen C (77.2%) ($P = 0.010$). Stratified analysis revealed better results with the FT-combined therapy in patients positive for lymph node metastasis and premenopausal patients. These results indicate the effectiveness of using FT in combination with TAM. Of the 376 ER– patients registered, 364 were evaluated. The 5-year overall and relapse-free survival rate for ER– patients did not differ significantly between patients who received regimen D and those who received regimen E.

Key words: breast cancer, adjuvant therapy, randomised controlled trial, tamoxifen, ftorafur, PSK
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INTRODUCTION

In the United States of America and in Europe, multidrug chemotherapy, such as cyclophosphamide, methotrexate and 5-fluorouracil (CMF), has been used as a standard regimen, not only in the treatment of advanced or recurrent cancer, but also as a means of postoperative adjuvant therapy for breast cancer [1]. Alternatively, in Japan, studies of mitomycin (MMC) and cyclophosphamide (CPA) were carried out in the period 1960–1979 [2–4]. Those studies revealed the usefulness of these agents in postoperative adjuvant chemotherapy.

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In the 1970s, ftorafur (FT; Taiho Pharmaceutical Co., Tokyo), a prodrug of 5-fluorouracil (5-FU) which can better utilise the features of the time-dependent drug 5-FU, was developed. Wada and associates reported that chemoendocrine therapy using tamoxifen (TAM) and FT resulted in a higher response rate for advanced or recurrent breast cancer than therapy using TAM or FT alone [5].

PSK is a protein-bound polysaccharide derived from the mycelium of a *Basidiomycetes, Coriolus versicolor* [6], and it has been used as a non-specific biological response modifer (BRM), similar to *Bacillus* Calmette-Guerin (BCG), levamisole and *Corynebacterium*. Fujimoto and colleagues reported that the survival rate of patients given PSK in combination with carboquone therapy was higher than that of patients administered carboquone therapy, but the difference was not significant [7]. Following these findings, we assessed the effect of using FT or PSK in combination with TAM as a postoperative adjuvant treatment for patients with oestrogen receptor-positive (ER+) breast cancer who received MMC on the day of surgery. In addition, we compared the effect of postoperative adjuvant therapy using FT and that using PSK in patients with oestrogen receptor-negative (ER–) breast cancer who received MMC on the day of surgery. In both assessments, the overall survival and relapse-free survival were analysed.

PATIENTS AND METHODS

The patients had primary stage II breast cancer, according to the TNM classification (UICC, 1972), and had undergone total mastectomy plus axillary dissection or more radical surgery. Patients with bilateral breast cancer, patients with non-invasive carcinoma by histological findings, males with breast cancer, patients with inflammatory breast cancer, pregnant or lactating patients, and patients with double cancers were excluded from this trial. Other eligibility criteria included a leucocyte count greater than 3000/μl, a platelet count greater than 100 000/μl, a total protein level greater than 6.0 g/dl, no other medical illness, and informed consent.

The patients were allocated to different regimens (Figure 1) by the sealed-envelope method. On the day of surgery, MMC (13 mg/m^2) was administed intravenously. Then, ER+ patients received one of three regimens of drug therapy, starting 2 weeks after surgery: regimen A (daily oral treatment with 20 mg of TAM), regimen B (daily oral treatment with 20 mg of TAM and 600 mg of FT), or regimen C (daily oral treatment with 20 mg of TAM and 3 g of PSK). ER– patients received one of two regimens of drug therapy, starting 2 weeks after surgery: regimen D (daily oral treatment with 600 mg of FT) or regimen E (daily oral treatment with 3 g of PSK). The treatment period was 2 years for all regimens. Upon detection of recurrence, the therapy was changed to another when the physician in charge regarded such a change as necessary. These studies were carried out at 78 facilities in western Japan from February 1985 to March 1988.

The ER status was determined at the Otsuka Assay Institute (Tokyo) by the dextran-coated charcoal method, with the cut-off level set at 5.0 fmol/mg of protein. Staging and histological classification were performed according to the General Rules for Clinical and Pathological Recording of Breast Cancer by the Japanese Breast Cancer Society [8]. Clinical examinations, including chest radiography, bone radiography or scintigraphy, full blood count and liver function tests, and a physical examination, were performed periodically. The distribution of background variables in each group and the incidence of side-effects were assessed by the chi-square test, the *U*-test and the *H*-test. The postoperative overall survival and relapse-free survival rates were calculated by the Kaplan–Meier method and evaluated by the log-rank test.

RESULTS

Patients' characteristics are shown in Table 1. Of the 540 ER+ patients registered, 525 (97.2%) were evaluated: 15 patients were excluded from the analysis for the following reasons: 2 benign cases, 1 patient with ductal carcinoma *in situ* (DCIS), 1 patient with bilateral breast cancer, 2 patients aged 76 years or older, and 9 patients with protocol violations. There were no significant differences in age, menopausal

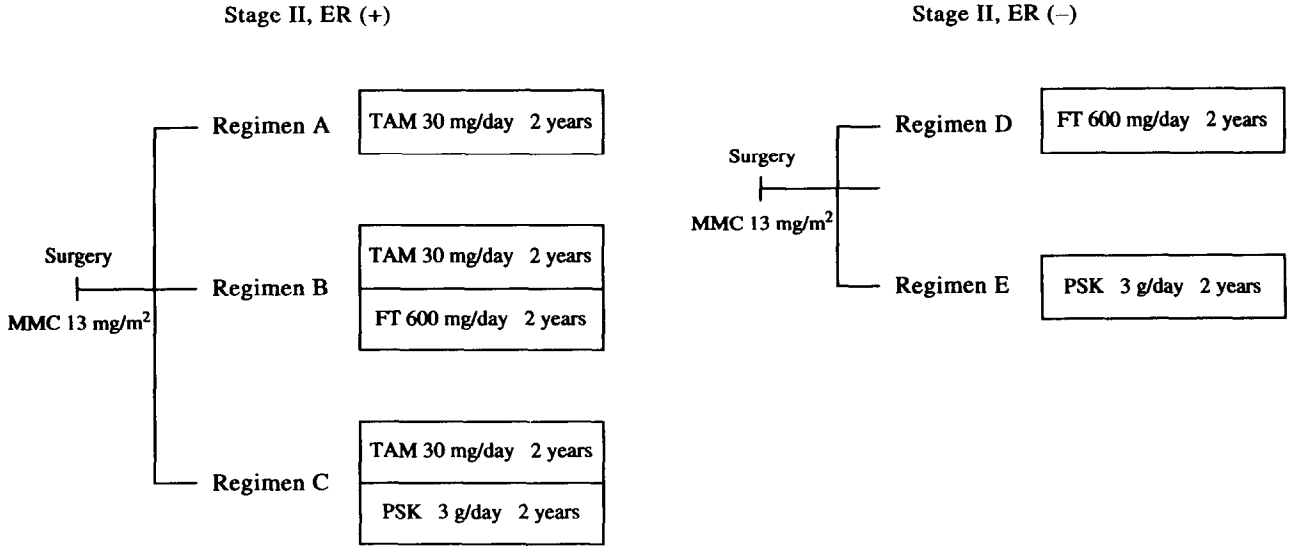

Figure 1. Outline of the protocol. Following intravenous administration of mitomycin C (MMC) (13 mg/m^2) on the day of surgery, tamoxifen (TAM) (20 mg/day) was administered orally in group A, starting 2 weeks after surgery. In group B, both TAM (20 mg/day) and ftorafur (FT) (600 mg/day) were administered orally, concomitantly. In group C, both TAM (20 mg/day) and PSK (3 g/day) were administered orally, concomitantly. FT (600 mg/day) was administered orally to group D, starting 2 weeks after the surgery. PSK (3 g/day) was administered orally to group E.

Table 1. Patients' characteristics

	Stage II, ER (+)			Stage II, ER (–)	
	Regimen A	Regimen B	Regimen C	Regimen D	Regimen E
No. of registered patients	178	182	180	193	183
No. of evaluable patients	175	178	172	185	179
Median age (years) (range)	56 (31–75)	52 (31–73)	52 (28–74)	51 (27–75)	53 (27–75)
Menopausal status					
Premenopausal	67	79	80	80	80
Postmenopausal	108	99	91	104	99
Unknown	0	0	1	1	0
Mastectomy					
Modified	43	33	33	31	38
Standard	107	119	118	120	111
Extended	25	26	21	34	30
Tumour size (cm)					
0–2.0	8*	9	10	9	14
2.1–5.0	167	169	162	176	165
Lymph node metastases					
0	95	110	105	106	98
1–3	46	47	45	56	49
4–10	22	19	18	17	24
≥11	11	2	4	5	8
Unknown	1	0	0	1	0
Histological type					
Papillotubular	37	35	34	37	37
Solid-tubular	67	66	62	85	77
Scirrhous	57	63	56	44	39
Special types	9	9	13	15	19
Unknown	5	5	7	4	7

*Includes 1 case without any palpable tumour.

status, operative procedure, tumour size, number of axillary lymph node metastases or histological type of the tumour among the different groups of patients. Five years after surgery, 93.3% of the patients were followed for overall survival, and 86.5% of the patients were followed for relapse-free survival. The median follow-up time was 6.9 years. Of the 376 ER– patients registered, 364 (96.8%) were evaluated. There were no significant differences in any of the parameters in Table 1 among the different groups of patients. Five years after surgery, 92.9% of the patients were followed for overall survival, and 87.4% of the patients were followed for relapse-free survival. The median follow-up time was 6.8 years.

Five-year overall survival and relapse-free survival

Figure 2 shows the five-year overall survival and relapse-free survival curves for the evaluated ER+ patients. The 5-year overall survival rate was higher for patients who received regimen B (94.2%) than for those who received regimen A (86.9%) or C (89.9%), but this difference only approached significance ($P = 0.063$). The 5-year relapse-free survival rate was significantly higher for patients who received regimen B (88.9%) than for those who received regimens A (78.6%) and C (77.2%) ($P = 0.010$). For ER– patients, the 5-year overall and relapse-free surivival did not differ significantly between patients who received regimen D and those who received regimen E (Figure 3).

Stratified analysis

Stratified analysis was performed by classifying the ER+ patients on the basis of menopausal status, tumour size and the number of axillary lymph node metastases (Table 2). When premenopausal patients were analysed, both the overall survival ($P = 0.021$) and the relapse-free survival rates ($P = 0.021$) were significantly higher with regimen B. In the postmenopausal patients, the rates showed no differences among the different regimens. When patients with a tumour diameter of 2.0 cm or less were analysed, neither the overall survival nor the relapse-free survival rates showed significant differences between the different regimens. In the patients with a tumour size of 2.1–5.0 cm, only the relapse-free survival rate was significantly ($P = 0.0066$) higher with regimen B than the other regimens. In patients without axillary lymph node metastases, the overall survival and relapse-free survival rates did not differ between the different regimens. Patients who received regimen B had a higher relapse-free survival rate than those who received either of the other regimens, when this analysis was confined to patients with one to three lymph node metastases ($P = 0.058$; almost significant) and patients with four or more lymph node metastases ($P = 0.047$; significant).

Number and causes of deaths

Of the ER+ patients, 22 receiving regimen A died, including 19 who died from the cancer (86.4%); 10 patients receiving regimen B died, including 9 who died from the cancer (90.0%); and 17 patients receiving regimen C died, including 14 who died from cancer (82.4%). Of the ER– patients, 28 patients receiving regimen D died, including 24 who died from the cancer (85.7%), and 31 patients receiving regimen E died, including 29 who died from the cancer (93.5%).

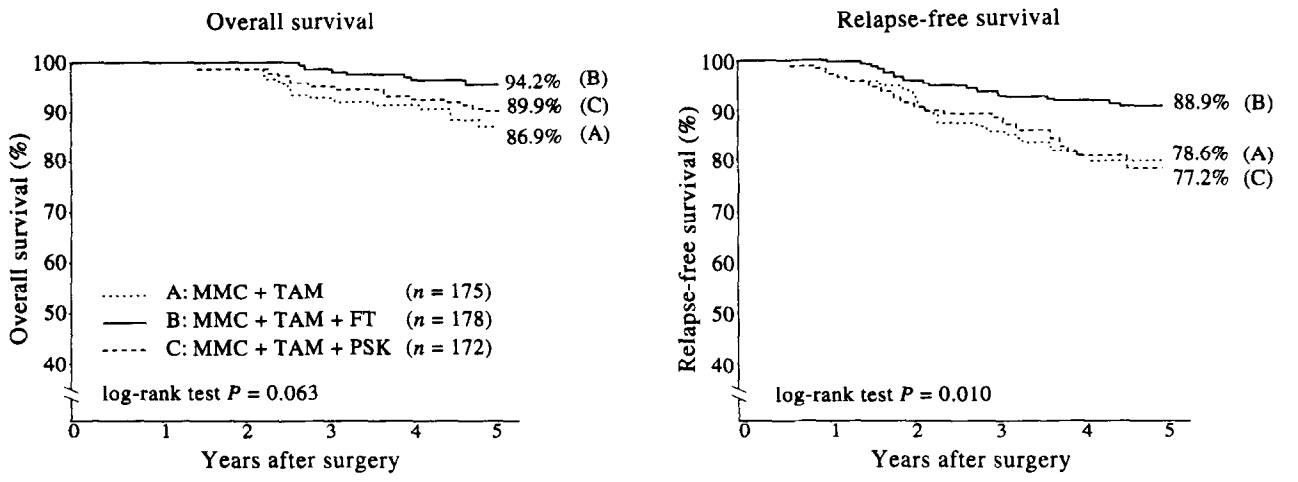

Figure 2. Five-year overall survival and relapse-free survival curves in stage II, ER+ cases. Regimen B tended to be better ($P = 0.063$) with respect to the 5-year overall survival, and was significantly better ($P = 0.010$) with respect to the 5-year relapse-free survival than regimens A and C.

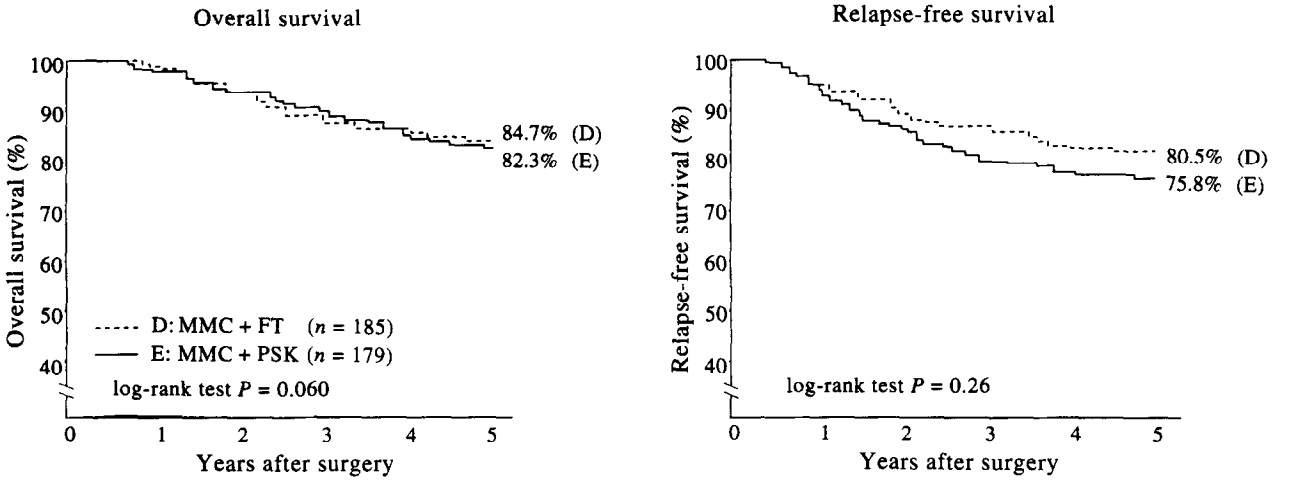

Figure 3. Five-year overall survival and relapse-free survival curves in stage II, ER– cases. No significant differences were observed between the therapeutic regimens in the ER– cases.

Incidence and site of recurrence

Table 3 shows the number of recurrences and their sites. In the ER+ group, recurrence developed in 35 patients receiving regimen A (20.0%), 19 receiving regimen B (10.7%) and 37 receiving regimen C (21.5%). The three most common sites in terms of the frequency of recurrence were bone, lymph nodes and liver in regimen A group; the bone, lung and liver in regimen B group; and the bone, lung and lymph nodes in the regimen C group. The incidences of recurrence in the soft tissue ($P = 0.049$) and bone ($P = 0.096$) were lower for regimen B than for the other regimens. In the ER– group, recurrence developed in 35 patients receiving regimen D (18.9%) and 42 receiving regimen E (23.5%). For both regimens, the three most common sites of first recurrence were bone, lymph nodes and lung.

Administered doses of drugs

Table 4 shows the doses of the four drugs, MMC, TAM, FT and PSK, in each regimen. The mean total dose of MMC was 13.1–13.4 mg in all regimens, and MMC was given above the planned total dose in all regimens. The mean total doses of TAM, FT and PSK were 19.2–20.2, 363–384 and 1910–1950 g in all regimens, respectively. TAM, FT and PSK were given at 89.3–93.9, 84.4–89.3 and 88.8–90.7% of the planned total doses of the drugs, respectively. The total administered doses of the drugs did not differ significantly among the regimens.

Adverse reactions

Table 5 shows the adverse reactions observed and their respective incidences. Leucopenia, anorexia, nausea, vomiting and general fatigue were the major adverse reactions. In the ER+ group, the incidences of pigmentation ($P = 0.077$), anorexia ($P = 0.06$) and nausea/vomiting ($P = 0.079$) were higher for regimen B, which included FT, than for any of the other regimens. In the ER– group, the incidence of leucopenia ($P = 0.055$), pigmentation ($P = 0.046$), anorexia ($P = 0.059$), nausea/vomiting ($P = 0.035$) and general fatigue ($P = 0.077$) were higher for regimen D, which included FT, than for regimen E.

DISCUSSION

Numerous studies have been carried out on chemotherapy and endocrine therapy for use as postoperative adjuvant ther-

Table 2. Five-year results according to menopausal status, tumour size and the number of axillary lymph node metastases

OS and RFS	Regimen A	Regimen B	Regimen C	Log-rank test
Premenopausal				
OS	82.7	96.0	92.1	$P=0.021$
RFS	73.2	90.6	79.1	$P=0.021$
Postmenopausal				
OS	89.4	92.9	87.7	$P=0.46$
RFS	82.0	87.6	75.3	$P=0.11$
Tumour size: 0–2.0 cm				
OS	100	100	100	$P=1.00$
RFS	57.1	75.0	90.0	$P=0.31$
Tumour size: 2.1–5.0 cm				
OS	86.6	94.0	89.3	$P=0.067$
RFS	79.9	89.7	76.9	$P=0.0066$
Node-negative				
OS	94.6	95.3	94.2	$P=0.93$
RFS	90.8	89.6	85.1	$P=0.42$
Node-positive (1–3)				
OS	86.7	97.8	87.9	$P=0.14$
RFS	76.9	93.4	73.8	$P=0.058$
Node-postive (≥4)				
OS	64.4	81.0	72.7	$P=0.42$
RFS	45.2	76.2	45.5	$P=0.047$

OS, overall survival (%); RFS, relapse-free survival (%).

apy for breast cancer. In the United States and Europe, TAM has been used as a standard drug for endocrine therapy, and CMF therapy has been employed as a standard chemotherapy for this purpose. It is generally thought that the prognosis for breast cancer is better for Japanese patients than for Western patients [9]. In Japan, Yoshimoto and associates [2] carried out a prospective randomised trial of postoperative adjuvant chemotherapy using MMC as a single agent for patients with operable breast cancer. Their data indicated that administration of only 0.8 mg/kg of MMC significantly reduced the recurrence rate in premenopausal patients during a 10-year follow-up period after surgery. In general, oral chemotherapeutic agents such as CPA and pyrimidine fluoride, whose side-effects are milder than those of CMF or CAF (cyclophosphamide, doxorubicin, 5-FU) therapy and which have shown relatively high efficacy against advanced or recurrent breast cancer, i.e. a response rate between 20 and 40% [10, 11], have often been used in Japan for postoperative adjuvant therapy [3, 4]. PSK, a biological response modifier, does not have strong direct antitumour action, but it is thought to prolong the survival of patients through its favourable effect on the immune functions. Some investigators reported that PSK prolonged the survival of patients with gastric or colorectal cancer [12, 13].

In the present study, we assessed the effects of FT or PSK in combination with TAM in cases of ER+ breast cancer, for which TAM is a standard postoperative adjuvant therapy according to the existing criteria. For these cases, the overall

Table 3. Frequency and site of recurrence

	Stage II, ER (+)			Stage II, ER (–)	
	Regimen A	Regimen B	Regimen C	Regimen D	Regimen E
No. of evaluable patients	175	178	172	185	179
	(%)	(%)	(%)	(%)	(%)
No. of recurrent patients	35 (20.0)	19 (10.7)	37 (21.5)	35 (18.9)	42 (23.5)
Soft tissue	15 (8.6)	5 (2.8)	14 (8.1)	16 (8.6)	21 (11.7)
Contralateral breast	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Skin	1 (0.6)	2 (1.1)	3 (1.7)	5 (2.7)	10 (5.6)
Subcutaneous layers	3 (1.7)	2 (1.1)	0 (0.0)	2 (1.1)	4 (2.2)
Lymph nodes	12 (6.9)	2 (1.1)	8 (4.7)	13 (7.0)	10 (5.6)
Mediastinum/lung hilus	0 (0.0)	0 (0.0)	3 (1.7)	1 (0.5)	0 (0.0)
Others	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)†	0 (0.0)
Bone	18 (10.3)	9 (5.1)	19 (11.0)	14 (7.6)	16 (8.9)
Viscera	12 (6.9)	8 (4.5)	14 (8.1)	17 (9.2)	22 (12.3)
Lung	5 (2.9)	4 (2.2)	10 (5.8)	7 (3.8)	11 (6.1)
Pleura	2 (1.1)	1 (0.6)	3 (1.7)	5 (2.7)	0 (0.0)
Pericardial fluid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver	6 (3.4)	3 (1.7)	5 (2.9)	6 (3.2)	8 (4.5)
Peritoneal cavity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Brain	1 (0.6)	0 (0.0)	2 (1.2)	4 (2.2)	6 (3.4)
Others	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)‡	0 (0.0)
Others	0 (0.0)	0 (0.0)	1 (0.6)*	0 (0.0)	0 (0.0)

*Unknown; †Right intercostal muscle; ‡Mediastinum/epigastric area.

Table 4. Administered doses of drugs

		Stage II, ER (+)			Stage II, ER (–)	
		Regimen A	Regimen B	Regimen C	Regimen D	Regimen E
Drug	Planned total dose	Administered total dose (mean ± S.D.)			Administered total dose (mean ± S.D.)	
MMC	13 mg/m²*	13.2 ± 1.7 mg (101.5%)†	13.2 ± 1.0 mg (101.5%)	13.3 ± 1.4 mg (102.3%)	13.4 ± 1.4 mg (103.1%)	13.1 ± 1.5 mg (100.8%)
TAM	21.5 g	20.2 ± 6.0 g (93.9%)	20.2 ± 6.2 g (93.9%)	19.2 ± 7.1 g (89.3%)	—	—
FT	430 g	—	384 ± 129 g (89.3%)	—	363 ± 153 g (84.4%)	—
PSK	2150 g	—	—	1950 ± 688 g (90.7%)	—	1910 ± 758 g (88.8%)

*Body surface area was calculated with the Mee–Du Bois formula: $S = W^{0.425} \times H^{0.725} \times 71.84$; †Percentage of administered total dose per planned total dose.

Table 5. Adverse reactions

	Stage II, ER (+)			Stage II, ER (–)	
	Regimen A	Regimen B	Regimen C	Regimen D	Regimen E
No. of evaluable cases	175	178	172	185	179
	(%)	(%)	(%)	(%)	(%)
Leucopenia (<3000/μl)	19 (10.9)	28 (15.7)	29 (16.9)	40 (21.6)	24 (13.4)
Thrombocytopenia (<70 000/μl)	4 (2.3)	5 (2.8)	5 (2.9)	1 (0.5)	2 (1.1)
Elevated LDH (≥600 U)	5 (2.9)	5 (2.8)	10 (5.8)	11 (5.9)	10 (5.6)
Elevated GOT (≥100 U)	11 (6.3)	9 (5.1)	18 (10.5)	11 (5.9)	11 (6.1)
Elevated GPT (≥100 U)	11 (6.3)	12 (6.7)	20 (11.6)	18 (9.7)	11 (6.1)
Pigmentation*	2 (1.1)	9 (5.1)	4 (2.3)	10 (5.4)	2 (1.1)
Anorexia*	17 (9.7)	33 (18.5)	26 (15.1)	47 (25.4)	30 (16.8)
Nausea/vomiting*	9 (5.1)	21 (11.8)	17 (9.9)	30 (16.2)	15 (8.4)
General fatigue*	24 (13.7)	18 (10.1)	25 (14.5)	41 (22.2)	20 (11.2)
Diarrhoea*	1 (0.6)	5 (2.8)	6 (3.5)	7 (3.8)	4 (2.2)

*Judged by the physician in charge.

survival and the relapse-free survival rates were analysed. In ER– patients, we compared the effects of FT with those of PSK. The administration period of TAM, FT and PSK was set at 2 years, based on a report documenting that the recurrence rate was 29.9% within 1 year following surgery, 22.6% between 1 and 2 years following surgery and 16.9% between 2 and 3 years following surgery [14]. According to the current predominant view, it is recommended that TAM be administered for 2 years or more [1]. In the present study, the regimen including FT resulted in a higher overall survival rate and relapse-free survival rate in ER+ patients. Stratified analysis revealed better results with FT-combined therapy in patients positive for lymph node metastasis and premenopausal patients.

Although numerous studies have been published on the effects of TAM in combination with other chemotherapeutic agents, there have been few published reports regarding the effects of using other chemotherapeutic drugs in combination with TAM. As in the present study, Bocardo and colleagues [15] assessed the effects of CMF therapy in combination with TAM in ER+ patients and found this regimen to increase the 5-year relapse-free survival rate ($P = 0.1$). On the basis of the data collected in numerous studies on the effects of TAM therapy after surgery and the effects of TAM in combination with other chemotherapeutic agents, it has been determined that TAM is primarily indicated in postmenopausal patients. For this reason, the subjects of previous studies were often postmenopausal women or women over 50 years of age. Among those studies, those of Goldhirsch and coworkers [16] and Fisher and associates [17] demonstrated positive effects of TAM-combined chemotherapy on the overall survival and relapse-free survival, and the report of Pearson and colleagues [18] indicated a similar positive effect on relapse-free survival. In the present study, the combined use of FT and other drugs had a favourable effect in premenopausal patients. For postmenopausal patients, the 5-year relapse-free survival rate was higher in the FT-combined group (87.6%) than in the TAM alone group (82.0%), but this difference was not statistically significant. These results can be interpreted as indicating that the number of ER+ postmenopausal patients was not large enough to detect the efficacy of the drugs used in combination with TAM, because TAM itself is highly effective in these patients.

According to the treatment recommendation adopted at the 4th International Conference on Adjuvant Therapies for Primary Breast Cancer [1], chemotherapy with or without TAM is recommended for ER+ premenopausal patients, while TAM with or without chemotherapy is recommended for ER+ postmenopausal patients. Our results agree with those recommendations, although the types of chemotherapeutic agents used differ between our study and the treatment recommendations. Furthermore, the FT-combined therapy caused less adverse reactions than did CMF or CAF therapy. This finding may be regarded as an advantage of FT-combined therapy. CPA, used in the CMF regimen, is known to induce amenorrhoea. For this reason, some investigations state that this therapy contributes greatly to improving the prognosis for breast cancer by effecting chemical oophorectomy [19]. However, FT is unlikely to effect chemical oophorectomy, because FT does not induce amenorrhoea, although it disturbs normal menstruation cycles [20]. The use of PSK in combination with TAM had no positive effect. This result may be attributable to the selection of ER+ patients, who are thought to respond well to TAM. However, since the difference in the survival rate between the MMC plus TAM group and the MMC plus TAM plus PSK group was 3.0%, it seems necessary to study further the effects of PSK-combined regimens.

For ER– patients, the results for survival were non-significant, but the MMC plus FT therapy resulted in a 2.4% higher overall survival rate and a 4.7% higher relapse-free survival rate than the MMC plus PSK therapy. According to the EBCTCG report [21], TAM increased the 5-year overall survival rate by 3.6% and the 5-year relapse-free survival rate by 8.3%, while CMF therapy increased the 5-year overall survival rate by 3.3% and the 5-year relapse-free survival rate by 9.2%. The magnitude of the differences in the overall survival and relapse free survival rates between the two regimens compared in the present study was thus approximately half the magnitude reported by the EBCTCG [21]. If this finding is combined with the knowledge that detecting the efficacy of postoperative adjuvant therapy in Japanese patients is difficult because the prognosis for Japanese patients with breast cancer is better than that for Western patients, it seems necessary to study a large number of patients to detect statistically significant differences. Previous reports concerning postoperative adjuvant immunotherapy pertained primarily to BCG, levamisole and *Corynebacterium parvum*. In many studies, the number of patients examined was small. The study conducted by the EBCTCG [21] revealed no evident effects of these agents. Therefore, for this kind of study to be performed more efficiently, it seems necessary to modify the method of patient selection and the drug combination.

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