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ORIGINAL ARTICLE

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A randomized trial comparing ftorafur alone with ftorafur plus tamoxifen in postoperative adjuvant therapy for breast cancer

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Abstract A randomized study was performed in 35 centers in the Kinki area of Japan to determine the effectiveness of ftorafur (FT) plus tamoxifen (TAM) compared with FT monotherapy in postoperative adjuvant therapy for breast cancer. Patients were randomized by the envelope method to receive either FT 600 mg/day or FT 600 mg/day plus TAM 20 mg/day orally for 1 year, starting on day 7 after mastectomy. Between April 1982 and January 1985, 628 patients were assigned to treatment with FT alone and 626 to treatment with FT + TAM. Of these, 571 (90.9%) and 539 (86.1%) patients, respectively, met the eligibility requirements for this study. There were no significant differences in major background factors between the two groups of eligible patients. Five-year survival rates were 91.4% for FT alone and 91.1% for FT + TAM (not significantly different). Five-year disease-free survival rates showed a tendency towards a better prognosis ($P = 0.090$) in the FT + TAM group, with observed rates of 83.0% for FT alone and 86.7% for FT + TAM. Stratified analysis showed that disease-free survival with FT + TAM is better than with FT alone for patients aged 50 years or more ($P = 0.048$) and for patients with from one to three positive nodes ($P = 0.064$).

Key words Tamoxifen · Ftorafur · Adjuvant therapy · Breast cancer

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Introduction

There have been several reports on the results of adjuvant therapy for breast cancer with tamoxifen (TAM) versus surgery alone and chemotherapy + TAM versus chemotherapy alone. In western countries, cyclophosphamide (CPA) methotrexate, plus 5-fluorouracil (CMF) therapy has been the standard chemotherapy regimen. In contrast, in Japan, CPA and oral therapy with fluorinated pyrimidines have most commonly been used as postoperative adjuvant treatments, since these agents have been confirmed to give an appreciable response in advanced or recurrent breast cancer, with very few adverse reactions. Of the oral fluorinated pyri-midines, the response rate to ftorafur (FT) was reported to be 27–42% in advanced or recurrent breast cancer [1, 2, 9, 10, 16]. In the first study by our cooperative group, comparison of postoperative FT versus a 'no treatment' control group showed better disease-free survival in the FT group, although this did not reach statistical significance. It was also reported that when TAM was added to FT, a higher response rate with longer survival was obtained in advanced or recurrent breast cancer [15].

To investigate the efficacy of TAM added to FT, a multicenter cooperative study was conducted, comparing TAM + FT with FT alone for postoperative adjuvant therapy. There was no definite standard for the duration of FT treatment. A report from the Japanese Breast Cancer Society [14] stated that 15.4% of recurrences occurred within 6 months after surgery,

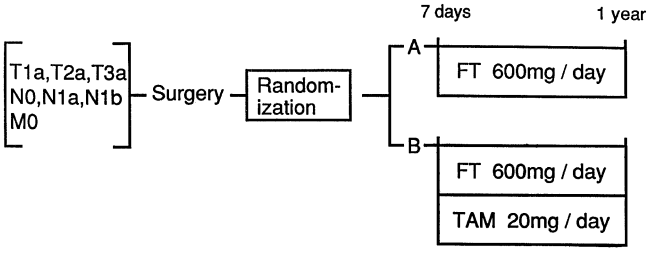

Fig. 1 Outline of the study protocol

21.6% occurred between 6 months and 1 year, 27.1% occurred between 1 and 2 years, and 14.8% occurred between 2 and 3 years, suggesting that it is necessary to continue therapy for at least 1 year. Based on these data, both FT and TAM were administered for 1 year. Stratified analysis by age showed that the addition of TAM improved the 5-year disease-free survival (DFS) rate in patients aged 50 years or more. This is in contrast to western evidence which has shown improvement only in patients aged $\geqslant$ 50 years [6, 8] or in postmenopausal patients [4, 7].

Subjects and methods

An outline of the study protocol is shown in Fig. 1. Eligibility criteria for this study were: age 70 years or less; TNM classification (1972) T1a, T2a, or T3a, N0, N1a, or N1b, and M0; six or less histologically proven axillary lymph node metastases; and completed curative surgery for breast cancer. Patients with inflammatory breast cancer, breast cancer during pregnancy or lactation, or multiple cancers, as well as male patients with breast cancer, were excluded from the study. Using the envelope method, patients were randomized to treatment with FT 600 mg/day (FT alone) or FT 600 mg/day + TAM 20 mg/day (FT + TAM), starting 7 days after mastectomy and continuing for 1 year. If cancer recurred during the study, other forms of therapy were substituted by the attending physician. Estrogen receptors (ER) were assayed using dextran-coated charcoal; ER at 3.1 fmol/mg or higher was considered positive. The major background factors were analyzed using the t test or c^2 test. Survival rates and DFS rates were calculated using Kaplan-Meier's method, and data were then analyzed using the log rank test. A value of $P < 0.05$ was considered statistically significant, and a value of $P < 0.10$ was considered as a tendency towards statistical significance.

Results

Patient characteristics

During the period of 2 years and 10 months between April 1982 and January 1985, 628 patients were assigned to the FT alone group and 626 to the FT + TAM group. Of these, 571 (90.9%) and 539 (86.1%) patients, respectively, were eligible for the study. Of the patients who were not eligible, the most common reason was the presence of seven or more positive nodes, found in 24 FT alone patients (3.8%), and 33 FT + TAM patients (5.3%). The criteria for the eligibility of patients are summarized in Table 1, and major background data for the eligible patients are shown in Table 2. There were no significant differences

Table 1 Eligibility criteria for patients. Figures in parentheses represent percentages. (*FT* ftorafur, *TAM* tamoxifen)

	FT group	FT + TAM group	Total
Number of registrants	628	626	1254
Number of ineligible patients	57 (9)	87 (14)	144 (11)
Ineligible (benign)	1	1	2
Carcinoma in situ	11	16	27
Bilateral breast cancer	2	1	3
Multiple cancer	2	9	11
Non-TNM classified	5	11	16
Over 70 years of age	5	13	18
History of cancer therapy	2	1	3
History of non-therapeutic surgery	2	1	3
Positive nodes $\geqslant$ 7	24	33	57
Tissue findings not available	4	1	5
Number of eligible patients	571	539	1110

Table 2 Characteristics of eligible patients treated with ftorafur (*FT*) alone or in combination with tamoxifen (*FT + TAM*). (*ER* estrogen receptors)

Number of eligible patients	FT 571	FT + TAM 539
Age		
Median	49	48
Range	28–70	27–70
Stage		
I	199	169
II	345	340
IIIa	27	30
Menopausal status		
Post-menopausal	356	311
Pre-menopausal	215	228
Surgical procedures		
Debulking	213	192
Standard	197	189
Extended	161	158
Number of nodes involved		
0	384	365
1–3	162	146
4–6	25	28
Histologic type		
Papilotubular carcinoma	186	175
Medullary tubular carcinoma	246	231
Scirrhous carcinoma	109	96
Special type carcinoma	23	35
Unspecified type	7	2
ER		
+	254	256
−	126	118
Not known	191	165
Total dose given (median)		
FT	213 g	215 g
TAM		7.3 g

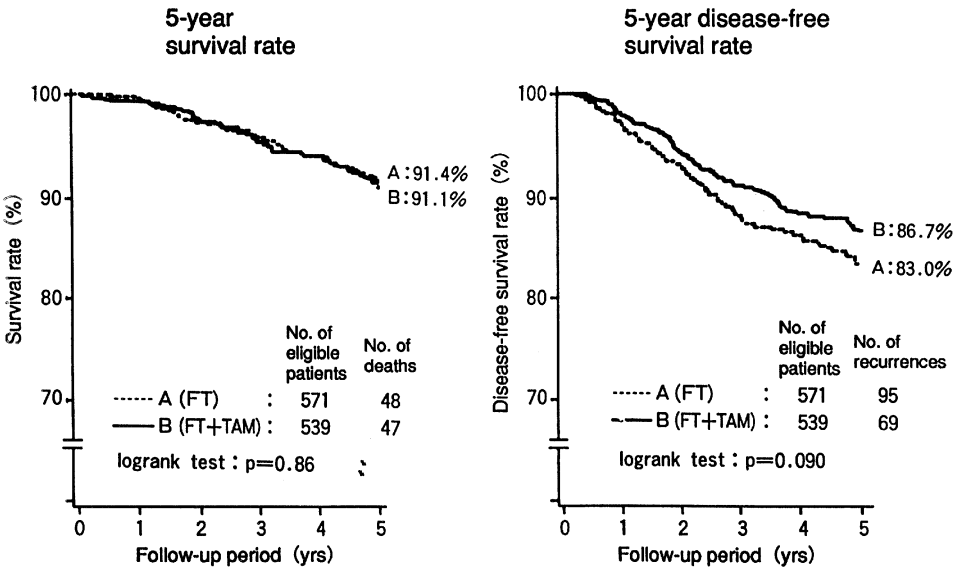

Fig. 2 Five-year results of eligible patients

Table 3 Five-year results by prognostic factors

	Treatment regimen	*n*	Five-year survival rate (%)	Log-rank test (*P*)	Five-year disease-free survival rate (%)	Long-rank test (*P*)
ER(+)	FT	254	91.6	0.85	81.8	0.22
	FT + TAM	256	91.3		85.9	
ER(−)	FT	126	89.3	0.39	75.7	0.11
	FT + TAM	118	85.3		84.2	
0 nodes	FT	384	95.8	0.31	90.1	0.25
	FT + TAM	365	94.1		92.6	
1–3 nodes	FT	162	83.7	0.18	70.7	0.064
	FT + TAM	146	88.8		79.7	
4–6 nodes	FT	25	73.9	0.50	53.2	0.58
	FT + TAM	28	63.9		44.1	
Age $\leq$ 49 years	FT	306	92.6	0.45	83.0	0.62
	FT + TAM	286	91.1		84.8	
Age $\geq$ 50 years	FT	265	90.0	0.63	83.0	0.048
	FT + TAM	253	91.1		88.8	

between the two groups for any of the factors. The median total dose was 213 g for FT in the FT alone group and 215 g for FT and 7.3 g for TAM in the FT + TAM group, showing that nearly 100% of the intended doses were actually given. Survival and recurrence data were updated on 31 December 1990, showing a median observation period of 5.7 years. Data from 95.3% and 90.3% of the patients, respectively, were available for follow-up analysis.

Results after 5 years

The 5-year overall survival (OS) rate was 91.4% for FT alone and 91.1% for FT + TAM, with no significant difference between the two groups. The 5-year DFS rate showed a tendency towards a significantly better prognosis with FT + TAM than with FT alone (Fig. 2): 86.7% versus 83.0% ($P = 0.090$). There were 48 deaths in the FT alone group, and 47 in the FT + TAM group: of these, 41 (85.4%) and 40 (85.1%) deaths, respectively, were related to recurrence. There were 95 recurrences in the FT group and 69 in the FT + TAM group.

It is well established that the response to TAM is positively related to ER status and the patient's age. Furthermore, the extent of nodal involvement is shown to be the most important prognostic indicator. The results were therefore stratified according to these factors, as shown in Table 3. When TAM was included in the treatment regimen, a tendency towards significantly better prognosis ($P = 0.064$) was seen for patients with from one to three nodes, and also for patients aged $\geqslant 50$ years ($P = 0.048$).

Side effects

Major adverse reactions included anorexia (19.8% with FT alone versus 21.7% for FT + TAM), nausea or vomiting (20.5% versus 19.7%), malaise (15.2% versus 13.9%), impaired hepatic function (SGOT $\geqslant$ 100: 11.4% versus 9.3%; SGPT $\geqslant$ 100: 17.5% versus 11.9%), and leukocytopenia (12.1% versus 11.1%). Adverse reactions were less common and were milder than those associated with CMF and other multiple-drug therapies.

Discussion

The results of the Early Breast Cancer Trialists' Collaborative Group [3], which evaluated the effectiveness of postoperative adjuvant therapy for breast cancer, showed that adding TAM to the treatment regimen improved the 5-year survival rate to 77.5% (3.6% higher than the level of 73.9% observed in the control group which did not receive TAM), and also improved the 5-year DFS rate to 67.9% (8.3% higher than the level of 59.6% in the control group). The present study showed 5-year survival rates of 91.1% for patients who received TAM and 91.4% for those who did not, and 5-year DFS rates of 86.7% and 83.0%, respectively. It was thought that the observed difference was modest because about two-thirds of our patients were node-negative and the prognosis was very good, regardless of the addition of TAM to the treatment regimen.

The prognosis tends to be better for Japanese patients with breast cancer than for their western counterparts [12]. The present study included patients who were at a relatively early stage of the disease, and who underwent curative surgery (modified radical mastectomy or more extended procedures). In addition, patients who underwent surgery alone were not used as the control group. These may be among the reasons why the addition of TAM did not show statistically significant benefits with regard to survival. A larger number of study patients and a longer follow-up period may exhibit a difference large enough for statistical significance. Another possible reason was that TAM was administered for the relatively short period of 1 year. The Early Breast Cancer Trialists' Collaborative Group [3] suggested that the longer the period of TAM treatment, the greater the improvement in survival. To address these questions in Japanese patients, the next study to compare 1-year treatment with TAM with 3-year treatment is ongoing.

Stratified analysis of the data with regard to regional lymph nodes, the most important determinant of prognosis in patients with breast cancer, showed that the addition of TAM did not give an additional response in node-negative patients or in patients with from four to six positive nodes. In contrast, the 5-year DFS rate was 70.7% in patients with from one to three positive nodes in the FT alone group, while 79.7% was observed in the FT + TAM group—a marginally significant difference ($P = 0.064$), the reason being that TAM was probably more active in the group with from one to three positive nodes. Our speculation here is that TAM could have induced an additional response in patients with from one to three positive nodes, judging from previous Japanese evidence that postoperative adjuvant therapy with mitomycin C plus CPA [11] or FT [13] improved 5-year DFS rates in patients with one to three positive nodes, compared with surgery alone. Thus, our results suggest that breast cancer in a moderately advanced stage may be more susceptible to adjuvant chemotherapy or adjuvant chemoendocrine therapy.

Stratified analysis by age showed that the addition of TAM improved the 5-year DFS rate in patients aged 50 years or more. Many studies done in western countries have demonstrated that adding TAM to chemotherapy improves 5-year DFS only in patients aged $\geqslant$ 50 years [6, 8] or in postmenopausal patients [4, 7]. These studies have usually employed CMF for baseline chemotherapy, which is different from the therapeutic regimen used in this study. However, a similar tendency was observed in response patterns following the addition of TAM.

Table 4 Guidelines for postoperative adjuvant therapy for breast cancer. (*TAM* tamoxifen, *ER* estrogen receptor, *HR* hormone receptor)

Risk factor	Pre-menopausal		Post-menopausal		Elderly patient (>70 years)	
0 nodes (minimal/low risk)	No treatment versus TAM		No treatment versus TAM		No treatment	
0 nodes (low risk)	TAM		TAM		TAM	
0 nodes (high risk)	ER (+) Chemotherapy ± TAM	ER (−) Chemotherapy	ER (+) TAM ± chemotherapy	ER (−) Chemotherapy ± TAM	TAM (chemotherapy if tolerated)	
Nodes present	HR (+) Chemotherapy ± TAM	HR (−) Chemotherapy	HR (+) TAM ± chemotherapy	HR (−) Chemotherapy ± TAM	HR (−) TAM	HR (−) Chemo therapy

Table 5 Participating medical centers

Osaka Prefecture
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Second Depatment of Surgery, Osaka City University Medical School
Department of Oncologic Surgery, The Research Institute for Microbial Diseases, Osaka University
Department of Surgery, The Center for Adult Disease, Osaka
Department of Surgery, Osaka National Hospital
First Department of Surgery, Osaka University Medical School
First Department of Surgery, Kinki University School of Medicine
Department of Surgery, Osaka Medical College
Osaka Koseinenkin Hospital
Tazuke Kofukai Kitano Hospital
Osaka Red Cross Hospital
Toyonaka Municipal Hospital
Sakai Municipal Hospital
Mino Municipal Hospital
Osaka Police Hospital
First Department of Surgery, Osaka Prefectural Hospital
Osaka Rosai Hospital
Higashi-Osaka Central Hospital
Nihon-Seimei Saiseikai Nissei Hospital
Department of Surgery, Kansai Meical University
Ikuwa-kai Kinen Hospital
Hyogo Prefecture
First Department of Surgery, Kobe University School of Medicine
Hyogo Prefectural Medical Center for Adults
Konan Hospital
Nishinomiya Municipal Central Hospital
First Department of Surgery, Hyogo College of Medicine
Second Department of Surgery, Hyogo College of Medicine
Hyogo Prefectural Nishinomiya Hospital
Hyogo Prefectural Amagasaki Hospital
Kawasaki Hospital
Himeji National Hospital
Okayama Prefecture
Kawasaki Medical School
Oomoto Hospital
Kyoto Prefecture
Kodama Breast Clinic

The present study showed that TAM produced additional responses to FT in breast cancer patients aged $\geqslant 50$ years and in those with from one to three positive nodes. The guidelines for adjuvant therapy which were proposed at the 4th International Conference on Adjuvant Therapy of Primary Breast Cancer in St. Gallen, Switzerland, in February 1992 [5] are shown in Table 4. If the patients with from one to three positive nodes in our study are considered comparable to the node-negative high-risk patients in these guidelines, our data seem to support this recommendation. The number of patients included in the present study was limited, and was not sufficiently large for adequate stratified analysis. Meta-analysis of data for large groups of patients is strongly recommended.

The medical centers which participated in the present research program are shown in Table 5. The authors would like to express their appreciation for the long-term cooperation of these centers.

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