Dose-escalation phase I study in metastatic breast cancer patients with combination of paclitaxel and tegafur·uracil

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Abstract. The study present the results of the dose-setting study of concomitant weekly administration of paclitaxel and tegafur·uracil (UFT) for metastatic breast cancer. Eligible patients who entered the study underwent two or more courses of weekly paclitaxel + UFT therapy as the protocol therapy. The initial dose (level 1) was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day. At level 2, paclitaxel remained the same, but UFT was increased to 600 mg/day. At level 3, only paclitaxel was increased to 90 mg/m^2. Twelve patients were enrolled in this study between September 2000 and September 2002. Three patients were assigned to level 1. Grade 3 liver dysfunction (increased aspartate aminotransferase and alanine aminotransferase) was noted in one patient and grade 4 neutropenia was noted in one patient, showing that dose-limiting toxicity was detected in 2/3 patients. In accordance with the protocol, UFT was fixed at 400 mg/day and paclitaxel was decreased to 60 mg/m^2 at level -1, and then increased to 70 mg/m^2 at level 0. The overall effective rate after completion of two courses was 33% (3/9) including one case of complete response and two cases of partial responses. The remaining patients presented with stable diseases and no patient had progressive disease. In this study, weekly paclitaxel with concomitant UFT was administered. The recommended doses of paclitaxel and UFT were determined to be 70 mg/m^2 and 400 mg/day, respectively. As the toxicity profile shows, the highest toxicity level of this regimen was neutropenia and liver dysfunction, and dose-limiting toxicity was neutropenia.

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Introduction

An anthracycline-containing regimen represents the first-line palliative chemotherapy (1-3). However, it is necessary to develop non-anthracycline combination regimens to provide salvage therapy in metastatic breast cancer patients who have relapsed during or after anthracycline-containing combinations. Although new salvage chemotherapy using (or in combination with) novel anticancer drugs has been studied (4-6), survival benefits and higher response rates are often countered by increased toxicity and complexity of regimen. An effective combination chemotherapy regimen that is both simple and has lesser toxicity would be valuable.

Paclitaxel is highly effective for both breast cancer without previous treatment (7) and breast cancer previously treated with anthracycline (8). Findings in a Japanese late phase II study showed the effective rate in metastatic breast cancer patients to be 33.7% (21/62) (9). Clinical evaluation of weekly regimens was frequently performed. Higher effects with mild adverse events compared to those of the approved dosage/application method, comprising an every-three-week regimen, have also been reported (10). These regimens can be administered on an outpatient basis, which is an advantage.

5-Fluorouracil is used in combination with anthracycline anticancer drugs and cyclophosphamide for the treatment of breast cancer and is administered by bolus injection in many cases. However, continuous intravenous infusion is the best administration method because the effect of 5-fluorouracil is time-dependent and increases with the duration of exposure of tumor cells (11). Several reports have shown that continuous intravenous infusion was effective for colon carcinoma.

Thus, we paid attention to tegafur·uracil (UFT) because its oral administration obtains area under the curve comparable to that obtained by continuous intravenous infusion of 5-fluorouracil. UFT is an anticancer drug developed in Japan and consists

of the masked compound of 5-fluorouracil (tegafur) and uracil. UFT inhibits the rate-limiting decomposition enzymes of 5-fluorouracil that is dihydropyrimidine dehydrogenase (DPD). UFT has tegafur and uracil at a molar ratio of 1:4. The effects of UFT alone on local progressive and metastatic breast cancer were reported to be 32 (12) and 39% (13), respectively.

This study presents the results of the dose-setting study of concomitant weekly administration of paclitaxel and UFT for metastatic breast cancer.

Patients and methods

The eligibility criterion of this study was the presence of a measurable or evaluable lesion. Other criteria included: a two-week or longer drug withdrawal after previous therapy, adequate bone marrow function, liver function and renal function, 75-year-old or younger age, an expected survival of 3 months or longer, performance status 0-2 and the absence of active double cancer. Informed consent was obtained in writing from the patients enrolled in the study.

Eligible patients who entered the study underwent 2 or more courses of weekly paclitaxel + UFT therapy as the protocol therapy. One course of this regimen took 4 weeks. Paclitaxel was infused intravenously for 60 min on days 1, 8 and 15, and UFT was orally administered daily for 21 days, followed by drug withdrawal for 1 week. As premedication for hypersensitive reactions, dexamethasone 20 mg d.i.v., diphenhydramine 500 mg p.o. and ranitidine 50 mg i.v. were administered 30 min before paclitaxel administration.

The dose escalation schedule was set as: the initial dose (level 1) was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day. At level 2, paclitaxel remained the same, but UFT was increased to 600 mg/day. At level 3, only paclitaxel was increased to 90 mg/m^2. When the initial dose was determined to be the maximum tolerated dose (MTD), level 0 and level -1 were set as follows: at level 0 and level -1, the dose of UFT was fixed at 400 mg/day and paclitaxel was changed to 70 mg/m^2 at level 0 and 60 mg/m^2 at level -1 (Table I). Dose-limiting toxicity (DLT) was defined in accordance with the National Cancer Institute Common Toxicity Criteria. The criteria were: grade 4 thrombocytopenia, grade 3 pyrexial neutropenia (≥38˚C), grade 4 neutropenia that persists for ≥4 days, grade 3-4 peripheral neuropathy and grade 3-4 non-hematological toxicity (excluding depilation, nausea and vomiting). One dose level was assigned to a cohort of 3 patients and when no DLT was noted, the study proceeded to the next dose level. When DLT was noted in 1/3, 3 additional patients were assigned to the same level. When DLT was noted in ≥2 patients at the same dose level, the dose was determined to be MTD. A one-level lower dose than MTD was selected as the recommended dose (RD) for the phase II study.

Table I. Dose escalation scheme.

Dose level	Paclitaxel (mg/m^2)	UFT (mg/body)
-1	60	400
0	70	400
1	80	400
2	80	600
3	90	600

Table II. Patient characteristics.

Characteristics	No. of patients	%
No. of patients entered	12	
Age, year		
Median	53	
Range	40-73	
Performance status		
0	10	83.3
1	2	16.7
2	0	0.0
Menopausal status		
Pre-	3	25.0
Post-	9	75.0
No. of metastatic sites involved		
1	8	66.7
2	4	33.3
Hormone receptor status		
Estrogen or progesterone		
Positive receptor	7	58.3
Negative receptor	5	41.7
Unknown	0	0.0
Prior chemotherapy		
Prior adjuvant chemotherapy	9	75.0
Prior chemotherapy for metastatic disease	8	66.7
Prior anthracycline	10	83.3
Prior taxane	4	33.3

Table III. Toxicity according to dosing level.

Level	PTX/UFT	No. of patients	DLT	No. of patients with DLT
-1	60/400	5	-	0
0	70/400	4	-	0
1	80/400	3	Liver dysfunction, neutropenia	2

PTX, paclitaxel; DLT, dose-limiting toxicity; UFT, uracil and tegafur.

Table IV. Toxicity profiles.

	Grade									
	0		1		2		3		4	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%
Leukocytopenia	7	64	1	9	1	9	2	18	-	
Neutropenia	7	64	1	9	1	9	-		2	18
Thrombocytopenia	11	100	-		-		-		-	
Fever	11	100	-		-		-		-	
Diarrhea	11	100	-		-		-		-	
Alopecia	-		7	64	4	36	-		-	
Neurosensory	6	55	5	45	-		-		-	
Skin	11	100	-		-		-		-	
Stomatitis	10	91	1	9	-		-		-	
Arthralgia	10	91	1	9	-		-		-	
Myalgia	11	100	-		-		-		-	
Liver dysfunction	10	91	-		-		-		1	9
Hypersensitivity reaction	10	91	-		1	9	-		-	
Fatigue	9	82	2	18	-		-		-	
Appetite loss	9	82	2	18	-		-		-	
Nausea	9	82	2	18	-		-		-	
Headache	9	82	2	18	-		-		-	
Flushing	8	73	3	27	-		-		-	

Results

Twelve patients were enrolled in this study between September 2000 and September 2002. The median age of the patients was 52.8 years of age (42-67 years) and the performance status (ECOG) was 0 in the 12 patients (Table II). Eleven patients had metastatic breast cancer and 1 patient had local progressive breast cancer. Patients with metastatic breast cancer had previously undergone chemotherapy and 6 of them were on chemotherapy including anthracycline.

Three patients were assigned to level 1. Grade 3 liver dysfunction (increased apartate aminotransferase and alanine aminotransferase) was noted in 1 patient and grade 4 neutropenia was noted in 1 patient, showing that DLT was detected in 2/3 patients. In accordance with the protocol, UFT was fixed at 400 mg/day and paclitaxel was decreased to 60 mg/m^2 at level -1 and then increased to 70 mg/m^2 at level 0.

Five patients were assigned to level -1, and 2 of the patients were handled as dropouts. One dropout developed grade 3 neutropenia in the first course and postponed administration of the drugs. Recovery, however, was delayed and the protocol therapy was discontinued. The safety evaluation committee advised the addition of 1 patient to confirm safety and 1 patient was thus added. However, the fourth patient was also judged as a dropout, since hypersensitive reaction developed immediately after initial administration of paclitaxel. Thus, 5 patients were enrolled. No DLT was noted in 3 patients judged evaluable and the study proceeded to the next step. At level 0 no DLT was noted in any patient. One patient was judged to be a dropout due to grade 4 neutropenia. However, persistence of neutropenia for 4 days or longer could not be confirmed (Table III). Based on these findings, MTD in this protocol was paclitaxel, 80 mg/m^2 and UFT, 400 mg/day; RD was paclitaxel, 70 mg/m^2 and UFT, 400 mg/day.

Table V. Overall tumor response.

Tumor response	Dose level		
	-1 (n=3)	0 (n=3)	1 (n=3)
CR	0	0	0
PR	0	2	1
SD	3	1	2
PD	0	0	0
CR+PR	0	2 (66.7%)	1 (33.3%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table IV shows the frequency of the main adverse events. DLT was neutropenia, but was complicated in 1 patient at level 1 and liver dysfunction occurred in 1 patient at level 1. The incidence of grade 3-4 neutropenia was 18%.

Non-hematological drug-related toxicities were rarely severe and remained easily manageable except liver dysfunction, noted in 1 patient at level 1. Toxicities included alopecia (overall incidence 100%), neuropathy neurosensory (45%), stomatitis (9%), arthralgia (9%), fatigue (18%), appetite loss (18%), nausea (18%), headache (18%) and flushing (27%).

The overall effective rate after completion of 2 courses was 33% (3/9) including three cases of partial responses. The remaining patients presented with stable diseases (SD) and no patient had progressive disease. At dose levels, the effective rate at level 0, which was RD, was 66.7% (2/3) and continuity was also high (Table V). In continuous administration, partial responses were confirmed in some patients after 7 courses and complete response was confirmed in the remaining patients after 4 courses. Regarding the regional effects, the effect was noted in the liver, cervical lymph nodes and local skin.

Discussion

Our starting hypothesis is that administrating paclitaxel on a weekly basis not only improves the tolerability but in combination with oral UFT may also improve the anticancer effect. The results of our phase I trial, show both of these aspects. At the phase II recommended dose, the regimen was well tolerated and was associated with promising anticancer activity (14).

As chemotherapy for progressive/recurrent breast cancer, the current first choice is combination chemotherapy using multiple drugs, including anthracycline anticancer drugs. After taxan anticancer drugs were introduced, the efficacy of taxans for patients who became resistant to anthracyclines has been reported. Comparative studies, as well as studies on the combination of these anticancer drugs are underway.

Furthermore, weekly administration of paclitaxel in comparison with the standard every-three-week administration was recently investigated. Seidman *et al* performed a phase II clinical study of the weekly administration of paclitaxel in anthracycline-resistant breast cancer patients and obtained a high effective rate of 53% (10). Weekly administration was also reported in Japan, where adverse events (peripheral neuropathy and inhibition of the bone marrow) were milder and the effect was higher than those with every-three-week administration (15). According to Kimura *et al*, when 80 mg/m^2 paclitaxel was administered for 3 weeks followed by one-week withdrawal, a high effective rate of 71.4% was obtained (16).

5-Fluorouracil is included in combination regimens with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), as well as cyclophosphamide, epirubicin and 5-fluorouracil (CEF), and is administered intravenously. In contrast, oral 5-fluorouracil anticancer drugs are frequently administered in Japan. UFT is an oral anticancer drug consisting of tegafur and uracil. UFT inhibits the rate-limiting decomposition enzyme DPD, and is called dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine (DIF). The effective rate of UFT was found to be 32% (16/50) in a Japanese phase II study (10).

Basic investigations of the combination of paclitaxel and UFT using a lung-metastasized breast cancer model have been reported. The concomitant administration of the two drugs inhibited cancer growth without increasing toxicity. Thus, the duration of growth inhibition by paclitaxel alone was short (7-14 days) and re-growth occurred during the administration period, while the combination with UFT inhibited cancer growth for an extensive period of time. Repeated administration of paclitaxel has been reported to induce MDR and resistance, but 5-fluorouracil does not cross-react with MDR. Thus, the combination of paclitaxel and 5-fluorouracil is a useful one. In addition, DPD activity is higher in metastatic than in primary lesions, suggesting that a DIF UFT is an appropriate 5-fluorouracil anticancer drug in combination with paclitaxel.

In this study, weekly paclitaxel with concomitant UFT was administered. The recommended doses of paclitaxel and UFT were determined to be 70 mg/m^2 and 400 mg/day, respectively. As the toxicity profile shows, the major toxicity of this regimen was neutropenia and liver dysfunction, and DLT was neutropenia. Although hypersensitive reaction was noted after the initial administration of paclitaxel in 1 patient, no peripheral nerve toxicity attributable to paclitaxel occurred. This was a phase I study that aimed to determine the recommended dose. However, the number of patients enrolled was small and the effective rate at RD was 66.7% (2/3), suggesting the usefulness of this regimen.

Based on the results of this study, a phase II study is being performed at the recommended dose determined in the phase I study in patients previously treated with anthracycline. Results of this phase II study are anticipated.

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