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Report on nationwide pooled data and cohort investigation in UFT phase II study

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Summary. UFT is a compound in which futraful (FT) and uracil are combined at a ratio of 1:4. UFT was given orally at a daily dose of 300–600 mg in a phase II study. Pooled data on a UFT phase II study of 438 evaluable patients, at 104 institutions revealed a response in carcinoma of the stomach (27.7%), pancreas (25.0%), gallbladder and bile duct (25.0%), liver (19.2%), colon and rectum (25.0%), breast (32.0%), and lung (7.0%). The mainly gastrointestinal toxicity resulted in anorexia (24.3%), nausea and vomiting (12.5%), and diarrhea (11.8%). On the other hand, hematological toxicity was rare and mild. To analyze the life-prolonging effect of the therapy, a cohort study was carried out in 438 cases collected in the UFT phase II study 5 years after the commencement of the therapy. The 50% survival time for 185 patients with gastric cancer was 185 days. The corresponding times in 54 patients with colorectal cancer and 49 with breast cancer were 227 and 505 days, respectively. A historical comparative study of UFT and FT, which was administered in the same institutions for equal evaluation, revealed that UFT had a significantly better effect than FT without more pronounced side effects with the equivalent dose schedule. In conclusion, UFT can be considered a useful agent against cancers over a broad spectrum, especially in gastrointestinal cancer.

Introduction

UFT is a new compound combining FT and uracil at a ratio of 1:4. Developed by Fujii et al. and based on the biochemical modulation of FT by uracil [1–4, 7, 26, 27], this compound causes an elevation of the 5-fluorouracil (5-FU) concentration in tumor tissue compared with blood or normal tissue, along with enhancement of the antitumor activity of FT.

The UFT phase II study was carried out at 104 institutions from April 1979 to September 1980, and the data of 665 cases were pooled. Detailed data from the study have already been reported elsewhere by the institutions concerned [5, 9, 11, 13, 15, 17–20, 24, 25, 28, 30, 31, 33–36]. This report presents the results of the nationwide pooled data relating to the phase II study and a historically controlled study of UFT and FT in Japan, in an attempt to analyze the therapeutic effect of UFT. A cohort investigation of survival time conducted in the study patients more than 5 years after the commencement of the therapy is also reported.

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Materials and methods

In all, 665 patients were given UFT orally at a daily dose of 300–600 mg as the FT quantitiy (dosage of UFT is described by the dosage of FT contained in UFT) two or three times a day for more than 4 weeks. A total of 438 cases and 551 cases were evaluable for efficacy and side effect in the phase II study, respectively. No specific treatment was prescribed after termination of the UFT phase II study. In the cohort study, the outcome as of July 1985 of the 438 evaluable patients in the UFT phase II study was investigated. The survival rate was calculated by the Kaplan-Meier method.

Results

Clinical efficacy

Responses were achieved in carcinoma of the stomach (27.7%), pancreas (25.0%), gallbladder and bile duct (25.0%), liver (19.2%), colon and rectum (25.0%), breast (32.0%) and lung (7.0%). In addition, though the numbers of cases were limited, responses were achieved in carcinoma of the head and neck, thyroid, esophagus, kidney and prostate (Table 1).

Side effects

There were complaints or recognition of subjective or objective side effects in 41.4% of the 551 evaluable cases. Hematological toxicity was noted in only 6.9% of the patients. Gastrointestinal toxicity resulted in anorexia (24.3%), nausea and vomiting (12.5%), and diarrhea (11.1%). Skin symptoms were pigmentation (5.1%) and drug eruption (2.0%). Neurological toxicity was seen in only 1.8%. Hematological toxicity (Table 2) resulted in leukocytopenia with $<3000/mm^3$ (4.0%), anemia with RBC $<300\times10^4/mm^3$ (2.5%), and thrombocytopenia with $<7\times10^4/mm^3$ (2.2%).

Period and cumulative dose of UFT until response and its duration

Of 110 responders, the response was observed within 4 weeks in 89%. The average time to response and cumulative dose of UFT to response were 6.7 weeks and 21.7 g in gastric cancer, 5.3 weeks and 20.6 g in breast cancer, and 7.6 weeks and 29.0 g in cancer in other sites. The duration

Table 1. Pooled data on efficacy of UFT in the phase II studies

Response / Tumor	Eligible cases	Evaluable cases	Direct response					Response rate
			CR	PR	NC	(MR)	PD	CR + PR (%)
Head and neck	17	12	1	2	5		4	25.0
Thyroid	12	10		5	5			50.0
Esophagus	7	2		1			1	50.0
Stomach	286	188	3	49	96	(12)	40	27.7
Pancreas	20	16		4	8		4	25.0
Gallbladder and bile duct	17	12		3	9			25.0
Liver	45	26		5	17		4	19.2
Colon and rectum	80	56		14	30	(5)	12	25.0
Breast	78	50	1	15	28	(1)	6	32.0
Lung	57	43		3	29	(2)	11	7.0
Kidney	7	4		1	2	(2)	1	25.0
Prostate	3	1		1				100.0
Others	36	18		2	10	(2)	6	11.1
Total	665	438	5	105	239	(24)	89	25.1

Table 2. Side effects of UFT

Evaluable cases	551
Patients with subjective and objective side effects	41.4%
Patients with hematological side effects	6.9%

Toxicity	Cases (%)
Gl toxicity	
Anorexia	134 (24.3)
Nausea and Vomiting	69 (12.5)
Diarrhea	61 (11.1)
Epigastric pain	7 (1.3)
Stomatitis	29 (5.3)
Other GI toxicity	11 (2.0)
Skin toxicity	
Pigmentation	28 (5.1)
Eruption	11 (2.0)
Other skin signs	3 (0.5)
Neurologic signs	10 (1.8)
Bleeding	2 (0.4)
Malaise	31 (5.6)
Others	8 (1.5)
Leukocytopenia	22 (4.0)
Erythrocytopenia	14 (2.5)
Thrombocytopenia	12 (2.2)
Hepatic dysfunction	3 (0.6)

of the response was 41.3 weeks in gastric cancer with CR (complete remission) and 11.4 weeks with PR (partial remission). In breast cancer, the duration of CR and PR was 10 weeks and 9.2 weeks, respectively. The overall duration of CR and PR was 38.3 weeks and 11.8 weeks, respectively.

Relationship between prior chemotherapy and response

The response rate in patients who had not received any prior chemotherapy was 27.3% (65/238), as against 22.9% (45/200) in those who had. When prior chemotherapy was divided according as whether fluorinated pyrimidines were or were not included, the response rate to UFT was 24.4% (39/160) and 15.0% (6/40), respectively.

Clinical efficiacy by histopathological type of tumor

In the largest subgroup, 367 patients with adenocarcinoma, the response rate was 26.7%, including CR in 1.0%. In 30 patients with squamous cell carcinoma the response rate was 13.3%, including 1 CR. In addition, in 25 cases with hepatocellular carcinoma, response was achieved in 16.0%.

Survival time

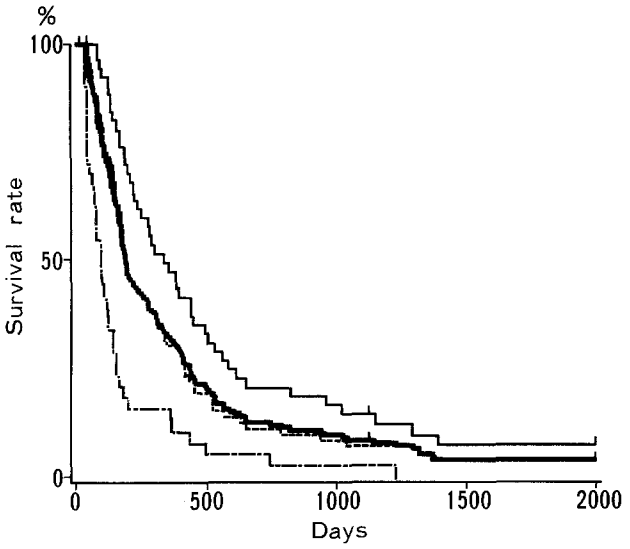
Of the 438 evaluable patients, 424 were to included in the cohort study, since in 14 patients follow-up proved impossible for various reasons. Except for gastric cancer, colorectal cancer and breast cancer, statistical analysis was not possible because of inadequate numbers.

In 185 gastric cancer patients, the 50% survival time was 185 days; in the responders (CR + PR) in this group it was 336 days, in patients with MR (minimal response) and NC (no change), 183 days, and in those with PD (progressive diseases), 97 days (Fig. 1). When these patients were divided by the histopathological type of gastric cancer, the 50% survival time was 182 days in the 51 patients with differentiated carcinoma (papillary adenocarcinoma, tubular adenocarcinoma, well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma). It was also 182 days in the 41 patients with undifferentiated carcinoma (undifferentiated adenocarcinoma, mucinous adenocarcinoma and signet-ring, scirrhous, and undifferentiated carcinoma). The 50% survival time in responders was 383 days for differentiated types (17 cases) and 581 days in for undifferentiated types (11 cases).

In 54 patients with colorectal cancer the overall 50% survival time was 227 days; distributed by response it was 339 days (CR + PR), 230 days (MR + NC), and 158 days (PD) (Fig. 2). In 49 patients with breast cancer the overall 50% survival was 505 days: CR and PR, 484 days; MR and PR, 565 days; and PD, 264 days (Fig. 3).

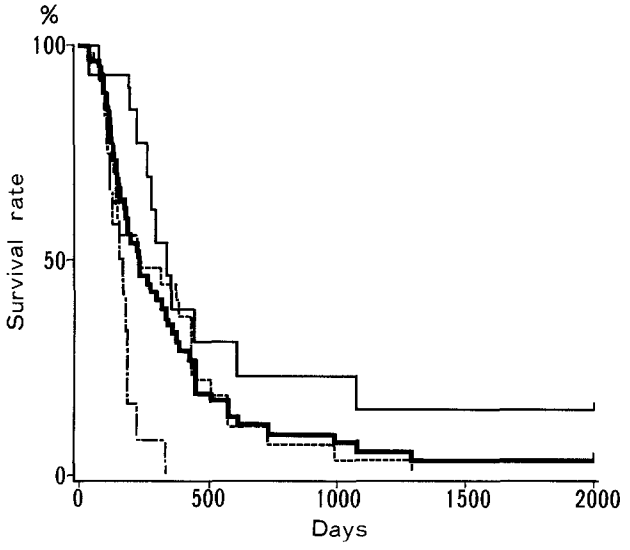
Discussion

The mechanism of FT antitumor action is such that FT is activated by 5-FU mainly in the liver microsomes, after which 5-FdUMP, an active metabolite of 5-FU, inhibits



	n	50% Survival in days	Survival rate (%) 1 y	2 y	3 y
CR+PR	52	336	47.3	20.1	14.4
MR+NC	93	183	30.2	11.0	6.9
PD	40	97	13.0	5.2	2.6
Total	185	185	31.5	12.6	8.2

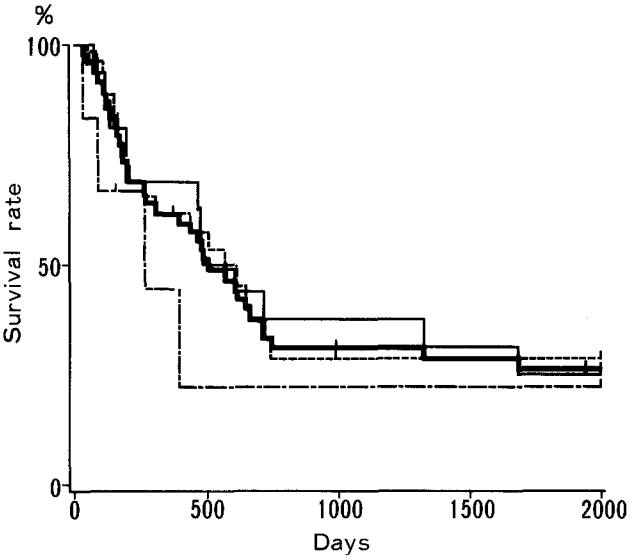
Fig. 1. Survival curves of stomach cancer patients treated with UFT



	n	50% Survival in days	Survival rate (%) 1 y	2 y	3 y
CR+PR	14	339	38.7	23.2	15.5
MR+NC	28	230	44.5	7.4	3.7
PD	12	158	0	0	0
Total	54	227	32.8	9.6	5.8

Fig. 2. Survivall curves of colorectal cancer patients treated with UFT

DNA synthesis. Uracil suppresses the degradation of 5-FU, but does not inhibit phosphorylation for activation of 5-FU, so that there is a higher 5-FU level in the blood and enhanced antitumor activity [7]. However, toxicity is



	n	50% Survival in days	Survival rate (%) 1 y	2 y	3 y
CR+PR	16	484	68.8	37.5	37.5
MR+NC	27	565	61.6	32.9	28.8
PD	6	264	44.4	22.2	22.2
Total	49	505	62.1	33.2	31.0

Fig. 3. Survival curves of breast cancer patients with UFT

also enhanced when 5-FU and uracil are combined, so that clinical applications have not been successful [10, 12, 16, 21–23]. On the other hand, since FT is transformed to 5-FU gradually in the liver, the 5-FU level is more highly increased in tumor tissue than in blood or normal tissue, because of the velocity of gradual activation from FT to 5-FU, the quantitative relationship between uracil's effect on degradation and phosphorylation of 5-FU, and the molar ratio between FT and uracil [1, 2, 27]. At a molar ratio of 1:4 between FT and uracil, the 5-FU level in tumor tissue was optimally increased compared with that in blood or normal tissue [5, 27], resulting in enhancement of the antitumor effect in both animals and humans. That the response rate observed in patients treated with prior chemotherapy including fluorinated pyrimidines was comparable to that in those administered preparations other than fluorinated pyrimidines [19] can be explained by the fact that antitumor activity was enhanced even in the patients refractory to fluorinated pyrimidine because of the increased 5-FU level in the tumor tissue resulting from the biochemical modulation of FT by uracil.

To evaluate the effectiveness of UFT, a study comparing it with FT as the parent compound will be of key importance. Although, strictly speaking, a randomized controlled study is required, in this study a historically comparative analysis was performed with the results of the FT phase II study (Table 4). Clinical effects were compared between UFT and FT at the individual dose by pooling data on cases from the same institutions concerned whenever the same standard was used for the evaluation [18, 30, 35]. UFT was given at a dose of 300–600 mg per day, and FT was given at a dose ranging from 600 to over 1400 mg. As seen in Table 3, UFT showed a higher response rate than

Table 3. Comparison of efficacy between UFT and FT by daily dosage in the historical comparative study

Agent	Dosage (mg)	Cases	Response					Response rate
			CR	PR	NC	(MR)	PD	CR + PR (%)
UFT	300	12	1	2	6	(1)	3	25.0
	400	10		1	5		4	10.0
	450	1			1			0
	600	104		31	51	(3)	22	29.8
	Total	127	1	34	63	(4)	29	27.6
FT	600	11		2	5	(1)	4	18.2
	800	66	1	11	36	(2)	18	18.2
	1000	3			3			0
	1200	41		5	28	(6)	8	12.2
	more than 1400	7		1	3	(1)	3	14.3
	Total	128	1	19	75	(10)	33	15.6

Table 4. Comparison of efficacy between UFT and FT against various types of cancer in the historical comparative study

Tumor	UFT							FT							χ^2 (Fisher)
	Cases	CR	PR	NC	(MR)	PD	Efficacy CR + PR (%)	Cases	CR	PR	NC	(MR)	PD	Efficacy CR + PR (%)	
Stomach	50	1	14	23	(3)	12	30.0	61		14	34	(4)	13	23.0	N.S.
Pancreas	8		3	3		2	37.5	2			1		1	0	N.S.
Gallbladder and bile duct	4			4			0	1			1			0	N.S.
Liver	9		3	4		2	33.3	3		1	1		1	33.3	N.S.
Colon and rectum	13		7	6			53.8	15		1	9		5	6.7	$P<0.01$
Lung	21		1	13	(1)	7	4.8	15			9	(1)	6	0	N.S.
Breast	13		4	7		2	30.8	14	1	1	10	(1)	2	14.3	N.S.
Others	9		2[a]	3		4	22.2	17		2[b]	10	(4)	5	11.8	N.S.
Total	127	1	34	63	(4)	29	27.6	128	1	19	75	(10)	33	15.6	$P<0.05$

[a] Kidney 1, prostate 1
[b] Kidney 1, thyroid 1

FT at each dose as well as in total quantity employed. The clinical effect was compared between the two drugs by cancer type, revealing a higher response rate of UFT than FT for each cancer. The response rate of UFT in colorectal cancer and the total for all subjects were significantly higher than with FT (Table 4).

A comparative analysis of the side effects of the two drugs was performed with reference to 551 patients included in the UFT phase II study and in 1502 patients receiving FT alone (data submitted to Ministry of Helath and Welfare after commercial approval). A comparison of side effect frequency at a UFT dosage of 300–600 mg and a standard FT dose of 800–1200 mg, showed that there were significantly fewer gastrointestinal symptoms with UFT than with FT. Hematological abnormality was also extremely rare in the UFT group (Fig. 4).

Because of the excellent selective toxicity of UFT against tumor tissue, the antitumor activity usual with FT could be dominantly enhanced and the side effects minimized by giving a daily dose of UFT that was half that of FT.

Subsequently, since it is essential for the life-prolonging effect to be known for evaluating on of the effect of a new anticancer agent, a cohort study was performed in 424 patients receiving UFT 5 years after the commencement of the therapy. The data on carcinoma of the stomach, colon and rectum and breast were comparable to those in previous reports [6, 8, 14, 29, 32]. For gastric cancer, Kurihara et al. [14], having reviewed studies with respect to cases treated with various kinds of chemotherapy, reported 50% survival times from 3.0 to 4.9 months and 1-year survival rates from only 2.0% to 14.4%. Reports of cases treated with FT alone showed 50% survival times of 152 days according to Furue et al. [6] and of 92 days according to Taguchi et al. [29]. In the patients treated with a combination of MMC and 5-FU by Furue et al. [6] the 50% survival time was 109 days, and one of 105 days was recorded by Taguchi et al. [29].

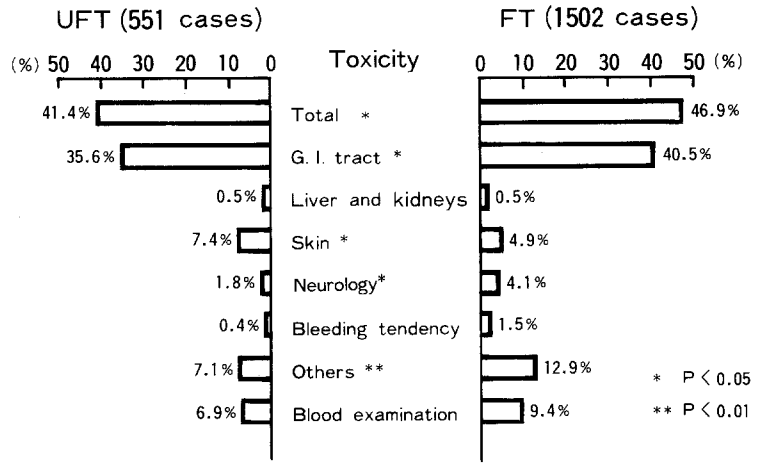


Fig. 4. Comparison of side effects between UFT and FT

The present results for stomach cancer, with 185 days for 50% survival time and 31.5% for the 1-year survival rate, are remarkable compared with previously reported data. In addition, the 50% survival time and 1-year survival rate obtained in this study in patients with colorectal cancer were 227 days and 32.8%, respectively. This is also significantly better than the results reported by Taguchi et al. [29]: 98 days for patients treated with FT alone and 175 days for those treated with MMC and 5-FU.

In conclusion, this study revealed significant UFT activity in a broad spectrum of cancer in the gastrointestinal tract, including carcinoma of the stomach, colon and rectum, and in cancer of the pancreas, gallbladder, bile duct and liver, breast and lung; its lower toxicity and its life-prolonging effect should also be mentioned.

Since favorable data have been obtained with the use of UFT alone, further study of UFT in various combinations with other agents or as postsurgical adjuvant chemotherapy is required.

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