receive laboratory examinations. To explore the associations between calculated fluid balance and the changes in clinical signs of dehydration and fluid retention, we analyzed data from patients who achieved oral fluid intake of 500 mL/day or less through the final 3 weeks and had complete fluid balance data. We chose this population, because we believe strict measurements of oral intake caused unacceptable ethical and practical burden for patients.

The patients received ordinary treatments from their institutions. From the time of study inclusion, the primary responsible physicians prospectively evaluated patients weekly as a part of routine practice, and recorded fluid balance variables, laboratory findings, and clinical signs of dehydration and fluid retention on a structured data-collecting sheet. As covariates, we recorded primary and metastatic tumor sites, performance status, amount of oral intake of fluids, presence or absence of vomiting, intestinal obstruction, requirement for intestinal/ascites/pleural drainage, and use of diuretics.

This study was approved by the Institutional Review Board of each hospital, and conducted in accordance with the Helsinki Declaration.

Measurements

Clinical Signs of Dehydration and Fluid Retention. The rationale for this assessment schedule was described in the original study.[10,11] The degree of dehydration was assessed on the basis of three physical findings: moisture on the mucous membranes of the mouth (0: moist, 1: somewhat dry, 2: dry), axillary moisture (0: moist, 1: dry), and sunkenness of eyes (0: normal, 1: slightly sunken, 2: sunken). These signs were selected due to their significant correlations with biological dehydration, as previously confirmed in elderly patients.[12–14] Ad hoc dehydration score (range 0–5) was calculated as the total of these three scores. A higher score thus indicated a higher level of dehydration.

The severity of peripheral edema was determined through the examination of seven regions: the hands, forearms, upper arms, feet, lower legs, thighs, and trunk. Peripheral edema severity was scored based on the degree of increased skin thickness in the middle of each region (0: none; 1: mild, thickness of <5 mm;

2: moderate, 5–10 mm; 3: severe, >10 mm). The peripheral edema score (range 0–21) was calculated as the total of the severity scores for the seven regions. A higher score indicated more severe edema.

Pleural effusion and ascites were each rated on a scale of 0–2 (0: physically nondetectable, 1: physically detectable but asymptomatic, 2: symptomatic or tense ascites). We did not use diagnostic imaging to determine pleural effusion and ascites severity, due to unacceptable burden for patients.

Fluid Balance. For calculations of fluid balance, we recorded volume of urine, fluid drainage (intestinal, pleural, or ascites), and vomiting as output data. These parameters were measured based on clinical requirements. The daily volume of fluid drainage and vomiting was defined as the mean value of total daily volume in the previous week. Fluid balance was calculated by subtracting the total daily output (the total amount of urine, vomiting, and intestinal, pleural, and ascites drainage) plus insensible water loss (assumed as 500 mL/day) from the total daily volume of artificial hydration.[2–4,9,15] Oral intake fluid was not included, because all patients enrolled in this analysis consumed 500 mL/day or less throughout the last 3 weeks.

Statistical Analyses

Due to its exploratory nature, we performed multiple analyses in this study.

Association Between Hydration Volume and Laboratory Findings. We divided patients into two groups: those who received artificial hydration of 1 L/day or more during both 1 week and 3 weeks before death (hydration group) and those who did not (nonhydration group). This classification was determined on the basis of actual data distributions, and the other classifications achieved similar results.

First, we compared the albumin, BUN/creatinine, sodium, and potassium levels in the last week between the hydration and nonhydration groups. Second, we compared the prevalence of hypoalbuminemia (<2.0 g/L), azotemia (BUN/creatinine >72), hypernatremia (>145 mmol/L), hyponatremia (<130 mmol/L), and hyperkalemia (>6.0 mmol/L) in the last week between the groups. Third, we examined the interactions

between hydration group and the changes in albumin, BUN/creatinine, sodium, and potassium levels during the last 3 weeks with repeated measurement analysis. The last analysis was conducted only on the patients who had laboratory examinations both 3 weeks and 1 week before death. To adjust for the potential effects of covariates, we compared the frequency of each covariate between the hydration and nonhydration groups, and thereafter, we conducted subgroup analyses for patients with covariates whose frequency was significantly different between the groups. In addition, we calculated adjusted P-values by entering the covariates into the repeated measurement analysis models.

Associations Between Calculated Fluid Balance and Clinical Signs of Dehydration and Fluid Retention. We compared the calculated fluid balances 1 week before death between the patients whose dehydration and edema scores increased (by three or more points) and ascites and pleural effusion scores increased (by one or more point) in the final 3 weeks and those whose scores did not increase. Then, we calculated correlation coefficients between calculated fluid balance and the changes in these scores during the last 3 weeks.

Univariate analyses were conducted using the Chi-square test (Fisher's exact methods), Student's *t*-test, or Mann-Whitney *U*-test, where appropriate. All analyses were performed using the Statistical Package for Social Science (ver. 11.5).

Results

Of 734 patients initially recruited, 424 patients were excluded due to short administration periods of less than 3 weeks ($n = 323$), longer survival over observation periods ($n = 35$), prior communication difficulty ($n = 33$), medical complications ($n = 27$), discharge ($n = 5$), or use of artificial enteral nutrition ($n = 1$). Thus, a total of 310 patients completed the original study, and 226 patients had abdominal malignancies. For this study, data from a total of 125 patients (55%) who received laboratory examinations during the last week were analyzed. There were no statistically significant differences in patient age, gender, primary site, performance status, or treatment

Table 1
Characteristics of Included and Excluded Patients with Abdominal Malignancies.

	Included ($n = 125$)	Excluded ($n = 101$)	P
Age	67 ± 13	69 ± 10	0.25
	% (n)	% (n)	
Gender (male)	49 (61)	46 (45)	0.53
Primary site			
Stomach	38 (48)	26 (26)	0.39
Colon	22 (27)	14 (20)	
Pancreas	14 (17)	12 (17)	
Rectum	14 (18)	12 (18)	
Bile duct	4.0 (5)	4.8 (7)	
Ovary	4.0 (5)	3.4 (5)	
Others	7.2 (9)	5.5 (8)	
Performance status at enrollment			
≤2	23 (29)	19 (19)	0.20
3	39 (49)	43 (43)	
4	38 (47)	39 (39)	
Treatment settings			
Oncology	26 (32)	17 (17)	0.11
Palliative care/home	74 (93)	84 (84)	

settings between the included and excluded patients (Table 1).

Association Between Hydration Volume and Laboratory Findings

Table 2 summarizes patient characteristics of the hydration and nonhydration groups. There were significant differences in the frequency of peritoneal metastases, the degree of oral intake of fluids, and the frequency of intestinal drainage between the groups. The mean hydration volume in the hydration group was 1458 ± 514 mL/day 3 weeks before death, 1296 ± 413 mL/day 1 week before death, and 857 ± 622 mL/day 24 hours before death. Hyperalimentation was performed in 59% of the hydration group ($n = 26$) 3 weeks before death and in 27% ($n = 12$) 24 hours before death. All artificial hydration was performed via intravenous routes.

Albumin, BUN/Creatinine, Sodium, and Potassium Levels in the Last Week

In the entire sample, in the subgroups of patients with peritoneal metastases, and in the subgroups of patients with oral intake of fluids <500 mL/day, the mean albumin levels were significantly lower in the hydration group than in the nonhydration group (Table 3).

Table 2
Patient Characteristics of Hydration and Nonhydration Group

	Hydration Group ($n=44$)		Nonhydration Group ($n=81$)		P
Age	66 ± 14		68 ± 12		0.41
	%	n	%	n	
Gender (male)	55	(24)	46	(37)	0.34
Primary site					0.082
Stomach	55	(24)	30	(24)	
Colon	18	(8)	23	(19)	
Pancreas	16	(7)	14	(11)	
Rectum	4.5	(2)	14	(11)	
Bile duct	2.3	(1)	4.9	(4)	
Ovary	0		6.2	(5)	
Others	4.5	(2)	8.6	(7)	
Metastatic sites					
Lung	14	(6)	25	(20)	0.15
Pleura	18	(8)	21	(17)	0.71
Liver	43	(19)	46	(37)	0.79
Peritoneum	77	(34)	59	(48)	0.043
Complications and treatments					
Oral intake fluids <500 mL/day 1 week before death	84	(37)	52	(42)	<0.001
Vomiting	39	(17)	27	(22)	0.19
Intestinal obstruction	66	(29)	54	(44)	0.21
Intestinal drainage	30	(13)	7.4	(6)	<0.001
Ascites drainage	18	(8)	9.9	(8)	0.18
Pleural drainage	2.3	(1)	2.5	(2)	1.0
Diuretics	34	(15)	41	(33)	0.47

There were no significant differences in mean BUN/creatinine, sodium, or potassium levels between the groups.

Prevalence of Hypoalbuminemia, Prerenal Azotemia, Hyper/Hyponatremia, and Hyperkalemia in the Last Week

In the entire sample and in the subgroup of patients with oral intake of fluids <500 mL/day, the prevalence of hypoalbuminemia was significantly higher in the hydration group than in the nonhydration group (Table 4). The prevalence of hyponatremia tended to be higher in the hydration group than in the nonhydration group, both in the entire sample and

in the subgroup of patients with oral intake of fluids <500 mL/day, with a marginal statistical significance. There were no significant differences in the prevalence of azotemia, hypernatremia, or hyperkalemia between the groups.

Interaction Between Hydration Group and the Changes in Albumin, BUN/Creatinine, Sodium, and Potassium Levels During the Last 3 Weeks

A total of 93 patients (74% of 125 analyzed patients) received laboratory examinations both 3 weeks and 1 week before death. There were no statistically significant differences in patient age, gender, and primary site between the

Table 3
Laboratory Findings in the Last Week

	All samples			Patients with Peritoneal Metastasis			Patients with Oral Intake Fluids <500 mL/day		
	Hydration Group ($n=44$)	Nonhydration Group ($n=81$)	P	Hydration Group ($n=34$)	Nonhydration Group ($n=48$)	P	Hydration Group ($n=37$)	Nonhydration Group ($n=42$)	P
Albumin (g/L)	2.4 ± 0.52	2.7 ± 0.50	0.005	2.4 ± 0.49	2.7 ± 0.55	0.025	2.4 ± 0.53	2.7 ± 0.50	0.005
BUN/creatinine	46 ± 20	40 ± 21	0.18	48 ± 20	40 ± 18	0.069	48 ± 20	42 ± 22	0.19
Sodium (mmol/L)	135 ± 6.4	136 ± 5.3	0.48	136 ± 6.6	135 ± 5.0	0.32	135 ± 6.6	136 ± 5.1	0.33
Potassium (mmol/L)	4.4 ± 0.72	4.4 ± 0.88	0.91	4.3 ± 0.73	4.3 ± 0.94	0.91	4.3 ± 0.72	4.3 ± 0.98	0.93

Table 4
Prevalence of Abnormal Laboratory Findingsin the Last Week

	All Samples					Patients with Peritoneal Metastasis					Patientswith Oral Intake Fluids <500 mL/day				
	Hydration Group (n = 44)		Nonhydration Group (n = 81)			Hydration Group (n = 34)		Nonhydration Group (n = 48)			Hydration Group (n = 37)		Nonhydration Group (n = 42)		
	%	n	%	n	P	%	n	%	n	P	%	n	%	n	P
Hypoalbuminemia (<2.0 g/L)	23	(10)	8.6	(7)	0.028	21	(7)	10	(5)	0.20	24	(9)	4.8	(2)	0.020
Prerenal azotemia[a]	11	(5)	6.2	(5)	0.37	12	(4)	4.2	(2)	0.39	14	(5)	7.1	(3)	0.39
Hypernatremia (>145 mmol/L)	6.8	(3)	4.9	(4)	0.70	8.8	(3)	2.1	(1)	0.31	8.1	(3)	4.8	(2)	0.66
Hyponatremia (<130 mmol/L)	27	(12)	14	(11)	0.074	21	(7)	19	(9)	0.91	27	(10)	12	(5)	0.087
Hyperkalemia (>6.0 mmol/L)		0	4.9	(4)	0.30	2.9	(1)	8.3	(4)	0.39		0	4.8	(2)	0.50

[a]BUN/creatinine >72.

patients who had laboratory data at the two points in time and those who had only one-point data (data not shown). Fig. 1 demonstrates that there was a statistically significant interaction between hydration group and changes in albumin level (2.8 ± 0.68 mg/dL 3 weeks before death to 2.4 ± 0.56 mg/dL 24 hours before death in the hydration group vs. 2.8 ± 0.53 to 2.6 ± 0.45 mg/dL in the nonhydration group). There were no significant interactions between the hydration group and changes in the BUN/creatinine, sodium, or potassium levels during the last 3 weeks (34 ± 15, 3 weeks before death, to 44 ± 17, 24 hours before death in the hydration group, vs. 31 ± 17 to 39 ± 20 in the nonhydration group; 134 ± 6.1 to 136 ± 6.6 mmol/L vs. 135 ± 4.7 to 136 ± 5.8 mmol/L; 4.4 ± 0.65 to 4.4 ± 0.68
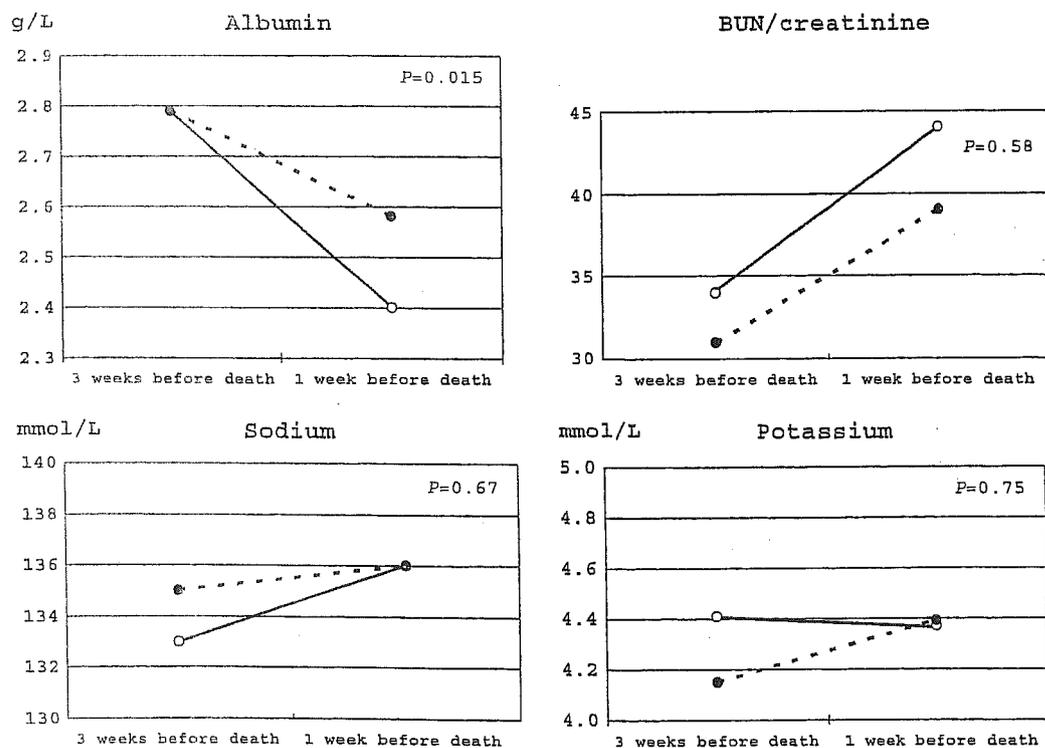

Fig. 1. Association between hydration practice and changes in laboratory findings. (O) Hydration group (n = 37); (●) nonhydration group (n = 56).

Table 5
Fluid Balance in the Final 3 Weeks ($n = 53$)

	3 Weeks Before Death	1 Week Before Death	24 Hours Before Death
Calculated fluid balance			
Median (range)	−400 (−1600, 757)	−521 (−1750, 493)	−421 (−2086, 1057)
Ranges			
<−1000 mL/day	9.4% ($n = 5$)	19% ($n = 10$)	13% ($n = 7$)
−1000 to −500 mL/day	38% ($n = 20$)	36% ($n = 19$)	32% ($n = 17$)
−499 to 0 mL/day	38% ($n = 20$)	34% ($n = 18$)	34% ($n = 18$)
1–500 mL/day	11% ($n = 6$)	11% ($n = 6$)	17% ($n = 9$)
>500 mL/day	3.8% ($n = 2$)	0	3.8% ($n = 2$)
Output data			
Urine volume (mean, mL/day)	951 ± 492	876 ± 478	590 ± 460
Drainage volume (median, mL/day)			
Vomiting	29 ($n = 12$)	71 ($n = 8$)	14 ($n = 7$)
Intestinal	160 ($n = 12$)	116 ($n = 12$)	127 ($n = 16$)
Ascites	214 ($n = 6$)	157 ($n = 5$)	0
Pleural effusion	286 ($n = 3$)	71 ($n = 3$)	186 ($n = 2$)

mmol/L vs. 4.2 ± 0.66 to 4.4 ± 0.91 mmol/L; respectively).

Associations Between Calculated Fluid Balance and the Changes in Clinical Signs of Dehydration and Fluid Retention

Of 113 patients who consumed 500 mL/day or less fluid intake orally throughout the last 3 weeks, 53 patients had complete fluid balance data. There were no statistically significant differences in patient age, gender, and primary site between the included and excluded patients, but the included patients were significantly more frequently recruited from oncology settings (data not shown). The percentages of patients receiving artificial hydration of 500 mL/day or more was 92% 3 weeks before death, 83% 1 week before death, and 72% 24 hours before death.

Table 5 summarizes the fluid balance data during the final 3 weeks. The percentage of patients with positive calculated fluid balance was less than 25% throughout the three study points.

The calculated fluid balance was not significantly different between the patients with deterioration in scores of dehydration, edema, ascites, and pleural effusion during the last 3 weeks and those without (Table 6). Moreover, the calculated fluid balance was not significantly linearly correlated with the changes in dehydration, edema, ascites, and pleural effusion scores ($\rho = 0.012$ and 0.93; $\rho = 0.051$ and 0.72; $\rho = 0.14$ and 0.30; $\rho = 0.085$ and 0.55, respectively).

Discussion

This is, to the best of our knowledge, the first multicenter prospective study to explore the association between artificial hydration practice and laboratory findings, as well as between fluid balance and clinical signs of dehydration and fluid retention in the last week of life in terminally ill cancer patients.

One of the important findings of this study was that active hydration was significantly associated with hypoalbuminemia. This interaction of artificial hydration with the changes in albumin levels during the last 3 weeks remained statistically significant after adjusting multiple

Table 6
Fluid Balance of the Patients With and Without Deteriorated Scores of Dehydration and Fluid Retention

	Mean (mL/day)	Median (mL/day)	P
Dehydration score[a]			0.79
+3 or more ($n = 11$)	−475 ± 453	−400	
+2 or less ($n = 42$)	−572 ± 547	−572	
Edema score[b]			0.87
+3 or more ($n = 20$)	−582 ± 542	−450	
+2 or less ($n = 33$)	−534 ± 524	−549	
Ascites score[c]			0.23
+1 or more ($n = 10$)	−365 ± 518	−250	
0 or less ($n = 43$)	−596 ± 524	−595	
Pleural effusion score[c]			0.14
+1 or more ($n = 5$)	−284 ± 773	93	
0 or less ($n = 48$)	−580 ± 497	−572	

[a]Calculated from three physical findings. A higher score indicates a higher level of dehydration, with possible range of 0–5.
[b]Calculated from seven physical findings. A higher score indicates a higher level of peripheral edema, with possible range of 0–21.
[c]Rated as 0 (physically nondetectable) to 2 (symptomatic).

covariates. The potential mechanism of this phenomenon includes dilution by a large amount of fluids in artificial hydration therapy, and this finding supports a clinical assumption that excessive artificial hydration could result in fluid retention through decrease in colloid osmotic pressure.[10,16,17]

The second important finding of this study was that, even when artificial hydration was not actively performed, sodium and potassium levels in the last week were within essentially normal ranges in a great majority of patients. In this study, median of calculated fluid balance was −400 mL/day or less throughout the last 3 weeks and only 20% of the patients had positive fluid balance. Nonetheless, hypernatremia and hyperkalemia were identified in less than 10% of the patients. These findings are consistent with preliminary empirical findings from hospice settings that, even in patients who received no artificial hydration, mean sodium and potassium levels were within normal ranges.[3,5,6] Therefore, it is assumed that serious sodium and potassium imbalance is not always common in terminally ill cancer patients, even if they do not receive active artificial hydration. These results suggest that the physiology of water metabolization in the terminal stage of cancer might be different from that in healthy or acute stage patients, because insensible water loss, depending on caloric expenditure, might be smaller in patients with cachexia and lower mental activity,[9,15] and/or because fluid shift could occur from the third space to the intravenous component. Physiological studies to clarify water metabolism and amount of water required for terminally ill cancer patients are strongly needed.

Of special note was that BUN/creatinine levels constantly increased in the last 3 weeks regardless of whether the patients received artificial hydration therapy or not. This finding supports a hypothesis suggested by an observational study on a small number of abdominal cancer patients that the pathophysiology of dehydration in terminally ill cancer patients is intravenous water depletion caused by fluid shift from the intravascular component to the interstitial spaces, not total body dehydration.[17] It suggests that artificial hydration therapy does not always alleviate water depletion under the condition in which administered water cannot be maintained in the intravascular component,

due to increased membrane permeability and/or decreased colloid osmotic pressure.

The third important finding of this study is that calculated fluid balance was not strongly associated with changes in clinical signs of dehydration and fluid retention. This finding reflects a hypothesis that not total fluid deficit but fluid shift from intravascular components to interstitial spaces is a major factor in the development of fluid retention in terminally ill cancer patients.[17] The clinical implication of this finding is that fluid balance study is not an appropriate alternative to direct evaluation of patient symptoms.

This study clearly has multiple major limitations, and interpretation of the findings requires special caution. First, laboratory and fluid balance studies were performed according to clinical requirements, and all patients did not receive these examinations. We believe, however, that this is an acceptable limitation of this study, because clinical research designed to obtain these examinations from all terminally ill patients is practically and ethically difficult and would result in unacceptable recruitment bias, and because patient backgrounds were not significantly different between the included and excluded patients. Second, this is an observational study, and therefore contains some treatment bias. Third, study subjects were limited to those with abdominal malignancies, and thus the results might not be applicable to other patients. Fourth, because calculated fluid balance did not include actually measured insensible water loss and oral intake volume, the fluid balance data calculated in this study might be over or underevaluated. Fifth, we investigated only fluid volume, and electrolytes or calories (hyperalimentation or not) administered for each patient was not considered. Sixth, reliability of the measurement schedule adopted in this study was not formally established. Finally, the small sample size made several statistical analyses difficult and limits generalization of the conclusions.

In conclusion, active artificial hydration could result in hypoalbuminemia, with no clear beneficial effects on normalizing BUN/creatinine, sodium, or potassium levels, and fluid balance does not strongly correlate with actual changes in clinical signs of dehydration and fluid retention. Calculated fluid balance would not be an appropriate alternative to

direct monitoring of patient symptoms. More study is clearly needed to determine the role of artificial hydration therapy in the last 3 weeks for the terminally ill cancer patients.

Acknowledgments

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Appendix
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Phase II study of a 4-week capecitabine regimen in advanced or recurrent gastric cancer

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Our objective was to evaluate the efficacy and safety of capecitabine in chemotherapy-naive patients with unresectable advanced or metastatic gastric cancer. An open-label multicenter phase II study was conducted for previously untreated patients with advanced or metastatic gastric cancer. Oral capecitabine $828\,mg/m^2$ twice daily was given on days 1–21 every 4 weeks. Baseline characteristics of 60 enrolled patients were: male/female 49/11, median age 64 years (range 28–74), good performance status (ECOG 0–1) in 98% of patients and 27 patients had prior gastrectomy (45%). A median of 4 treatment cycles were administered (range 1–37). Five patients were excluded from the efficacy analysis because they did not meet eligibility criteria. The overall response rate (RR) in the evaluable patient population ($n=55$) was 26% [95% confidence interval (95% CI) 15–39%] and a further 29% of patients had stable disease. The overall RR in the intent-to-treat population ($n=60$) was 23% (95% CI 13–36.0%). Median time to progression in the evaluable patient population was 3.4 months (95% CI 1.8–6.1) and overall survival time in the intent-to-treat population was 10.0 months (95% CI 6.4–13.6). The most frequent grade 3/4 drug-related adverse event was hand–foot syndrome (13%), but this was readily managed by treatment interruption and dose reduction. No patients developed grade 3/4 drug-related diarrhea, vomiting, leukopenia or thrombocytopenia. We conclude that this 4-week regimen of capecitabine showed promising activity and was well tolerated as first-line therapy for advanced/metastatic gastric cancer. Further investigation of this regimen is warranted. *Anti-Cancer Drugs* 17:231–236 © 2006 Lippincott Williams & Wilkins.

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Introduction

Since 5-fluorouracil (5-FU)-based chemotherapy prolongs survival compared with best supportive care alone [1], many phase III studies involving 5-FU-based combination regimens for advanced gastric cancer have been reported [2–4]. However, the definitive standard regimen has not yet been established and 5-FU monotherapy remains as one of the reference control regimens. The results of the randomized JCOG9205 phase III study comparing 5-FU continuous infusion (5-FUci) with 5-FU–cisplatin, and uracil/tegafur–mitomycin C have recently become available [4]. These show that median overall survival does not differ between 5-FUci and 5-FU–cisplatin, despite a significant difference in response rate (RR) and progression-free survival (PFS) favoring 5-FU–cisplatin [4].

Capecitabine (Xeloda) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU preferentially to tumor cells. After oral administration, capecitabine is rapidly and extensively absorbed through the intestine as an intact molecule, and is then metabolized to 5-FU in three steps. In the first step, capecitabine is hydrolyzed by carboxylesterase (primarily in the liver) to form 5′-deoxy-5-fluorocytidine (5′-DFCR). The next step is mediated by cytidine deaminase, which is highly active in tumor cells and in the liver, and converts 5′-DFCR to 5′-deoxy-5-fluorouridine (5′-DFUR). Thymidine phosphorylase (TP), which is significantly more active in tumor tissue than in adjacent healthy tissue, finally converts 5′-DFUR to 5-FU. With each successive conversion step, capecitabine potentially reduces the systemic exposure to 5-FU, while increasing 5-FU delivery to tumor tissues [5]. Consequently, capecitabine avoids some of the gastrointestinal toxicities (e.g. diarrhea) that are commonly observed with 5-FU.

Based on preliminary clinical studies [6–8], capecitabine 1255 mg/m^2 twice daily administered for 2 weeks followed by a 1-week rest period was adopted globally in many subsequent trials. However, in a Japanese phase I study using continuous administration of capecitabine [9], the maximum tolerated dose (MTD) was 1255 mg/m^2 twice daily, with skin fissures and gastric ulcers noted as the dose-limiting toxicities. Consequently, a 4-week intermittent regimen (3 weeks of drug administration and 1 week of rest) of capecitabine 828 mg/m^2 twice daily was recommended by the investigators as a Japanese regimen for phase II studies [9]. This lower dose and prolonged administration period was selected to sustain both safety and dose intensity. In a small pilot study in patients with advanced gastric cancer [10], this 4-week regimen of capecitabine yielded a RR of 24% in chemotherapy-naive patients and showed a good safety profile without severe diarrhea.

On the basis of these findings, we conducted a larger phase II study with capecitabine to confirm the activity and safety of this 4-week regimen in patients with advanced gastric cancer.

Patients and methods

Study design

This study was designed as an open-label multicenter phase II study in accordance with the Good Clinical Practice guidelines for clinical trials in Japan and the Declaration of Helsinki. The study protocol was approved by the ethics committee of each institution. Written informed consent was obtained from all patients.

Patients

All patients had to have histologically confirmed gastric cancer with measurable lesions. Eligibility criteria were as follows: ECOG performance status 0–2, an expected survival time of $\geq$ 3 months and an age at enrolment of 20–75 years. Patients were required to meet standard criteria for hematologic, hepatic and renal status: leukocytes 4000–12 000 cells/mm^3; platelets $\geq$ 100 000 cells/mm^3; hemoglobin $\geq$ 9.0 g/dl; GOT (AST), GPT (ALT) and Al-p $\leq$ 2.5 × upper limit of normal (ULN) for the center; total bilirubin and creatinine < 1.5 × ULN. Patients were required to be chemotherapy-naive (including post-operative adjuvant chemotherapy) for gastric cancer and to have received no radiotherapy to target lesions. Surgery and/or immunotherapy was to have been completed 4 and 2 weeks prior to the initiation qof capecitabine, respectively. Major exclusion criteria were as follows: active peptic ulcer, pregnant or lactating women, central nervous system metastases, inability to take meals due to underlying disease and blood transfusion within 2 weeks of the screening blood test.

Dosage and dose modifications

Capecitabine 828 mg/m^2 was taken orally twice daily within 30 min after breakfast and dinner. The actual dose of capecitabine administered was determined according to the patient's body surface area (BSA) as follows: BSA < 1.31 m^2 = 900 mg/dose, 1.31 m^2 $\leq$ BSA < 1.64 m^2 = 1200 mg/dose and BSA $\geq$ 1.64 m^2 = 1500 mg/dose. A dose of 600 mg twice daily was used when patients who were treated initially at the lowest dose level needed dose reduction. Each cycle of therapy consisted of 3 weeks of administration of capecitabine and a 1-week rest period. Patients were scheduled to receive at least 2 cycles of treatment unless they had disease progression, severe and uncontrollable adverse events or withdrew consent. Throughout the study, chemotherapy (other than capecitabine), immunotherapy, hormonal therapy and administration of systemic steroids were prohibited.

When drug-related grade 3 adverse events (excluding anorexia, nausea, vomiting, alopecia, malaise, taste abnormality, lymphopenia and increased bilirubin) occurred, capecitabine administration should be interrupted until the events had resolved to grade 0 or 1. Treatment could be restarted at the same dose after the first interruption. After the second interruption, the dose of capecitabine should be reduced to one level below the starting dose (i.e. 600, 900 or 1200 mg/dose as appropriate). Study treatment was discontinued in patients who developed grade 4 drug-related adverse events, except for lymphopenia.

Study assessments

Before enrollment, demographic characteristics, symptoms and signs of disease were evaluated in each patient. Laboratory, electrocardiography and imaging studies of all lesions were also performed. The results served as baseline data for the assessment of efficacy and safety. Toxicities were evaluated every 2 weeks during the first 2 cycles and every 4 weeks thereafter. Drug compliance was reviewed at the patients' regular visits by retrieving drug boxes and checking unused tablets. Survival in all patients was monitored for 1 year after the last patient was enrolled.

Evaluation of response and safety

Tumor responses were assessed every 4 weeks and evaluated according to WHO response criteria [11]. Evaluation was performed by the investigators and an Independent Review Committee (IRC).

Adverse events were assessed according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC) grading system [12]. Safety was evaluated in all patients who received capecitabine treatment. Hand–foot syndrome (HFS; palmar–plantar erythrodysesthesia) was classified based on clinical and functional domains as outlined in Table 1.

Table 1 Grading scale of HFS

Grade	Clinical domain	Functional domain
1	numbness, dysesthesia/paresthesia, tingling, painless	discomfort that does not disrupt normal activities
2	painful erythema, with swelling	discomfort that affects activities of daily living
3	moist desquamation, ulceration, blistering, severe pain	severe discomfort, unable to work or perform activities of daily living

Statistical methods

The target number of patients for accrual was 60. Given an expected RR of 25%, a threshold RR of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the efficacy analysis. The 95% confidence interval (CI) of the RR was calculated by the exact method, assuming a binomial distribution of data.

Treatment duration was defined as days from the initial to the last administration of capecitabine. Dose intensity was calculated by cumulative dose/treatment duration. Time to tumor progression (TTP) was calculated as the time from the first administration of capecitabine to disease progression or death, if the patient died before progression. Overall survival was defined as the time from study enrolment to death. These were calculated by the Kaplan–Meier method.

Results

Patient characteristics

A total of 60 patients were enrolled between February 1999 and April 2001. Their baseline characteristics are shown in Table 2. Median age was 64 years (range 28–74 years). The majority of patients had a good performance status (0 or 1). The major metastatic sites were lymph nodes and liver. All 60 patients received at least one dose of capecitabine and were included in the safety analysis. Although the investigators evaluated response in all patients, five patients did not meet the eligibility criteria (blood transfusion within 2 weeks preceding screening test, and elevated white blood cell count, bilirubin and AST at screening) and were excluded by the IRC.

Treatment duration

A median of 4 treatment cycles were administered (range 1–37). The median duration of treatment was 3.1 months (range 0.1–35.8 months). The median cumulative dose of capecitabine was 190 g (range 12–1629 g). Median dose intensity was 1870 mg/day (range 1198–3000 mg/day). Twenty-one of 60 patients (35%) were treated for at least 20 weeks and 10 patients (17%) were treated for more than 40 weeks. Reasons for treatment discontinuation were progressive disease (72%), drug-related adverse events (13%), adverse events not related to capecitabine (8%) and other (ineligible patient, salvage surgical therapy and withdrawal of consent). Compliance with capecitabine was maintained over 90% in all patients.

Table 2 Patient characteristics at baseline (*n* = 60)

	No. patients	%
Median age [years (range)]	64 (28–74)	
Male/female	49/11	82/18
ECOG performance status		
0	44	73
1	15	25
2	1	2
Gastrectomy		
Yes	27	45
No	33	55
Histology		
Differentiated	31	52
Undifferentiated	29	48
No. metastatic sites		
1	45	75
≥ 2	15	25
Sites of metastasis		
lung	2	3
liver	27	45
lymph node	41	68
others	6	10

Efficacy

The anti-tumor efficacy of capecitabine is shown in Table 3. The overall RR confirmed by the IRC in 55 evaluable patients was 26% (95% CI 15–39.0%), including 7% of patients who showed a complete response. The median duration of response in patients with a complete or partial response was 8.8 months (range 2.7–29.6 months). The median TTP was 3.4 months (95% CI 1.8–6.1 months). On the other hand, the overall RR in the intent-to-treat population was 23% (95% CI 13–36.0%). Median overall survival calculated in all 60 patients was 10.0 months (95% CI 6.4–13.6 months) and the 1-year survival rate was 42%. The Kaplan–Meier plot of overall survival is shown in Fig. 1.

Safety

Common drug-related adverse events were HFS (57%), anorexia (28%), nausea (27%) and diarrhea (20%). The majority were grade 1 or 2 (Fig. 2). The most frequent drug-related grade 3/4 adverse event was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. There were no episodes of grade 3/4 vomiting or diarrhea, which were defined as dose-limiting toxicities in preliminary studies conducted in the US and Europe [6,7].

Frequently reported drug-related laboratory abnormalities were: lymphopenia (63%), decreased erythrocytes (55%),

Table 3 Anti-tumor response of capecitabine

	No. patients (%)	
	Assessed by investigators (n=60; ITT population)	Confirmed by IRC (n=55; evaluable population)
Response		
complete response (CR)	3 (5)	4 (7)
partial response (PR)	11 (18)	10 (18)
stable disease (SD)	20 (33)	16 (29)
progressive disease	21 (35)	19 (35)
Not evaluable[a]	5 (8)	6 (11)
Overall RR [% (95% CI)]	23 (13–36)	26 (15–39)
Disease control (CR/PR + SD) rate (%)	57	55 (41–68)

[a]Inadequate post-baseline observation.

Fig. 1

10.0 months (95% CI 6.4–13.6)
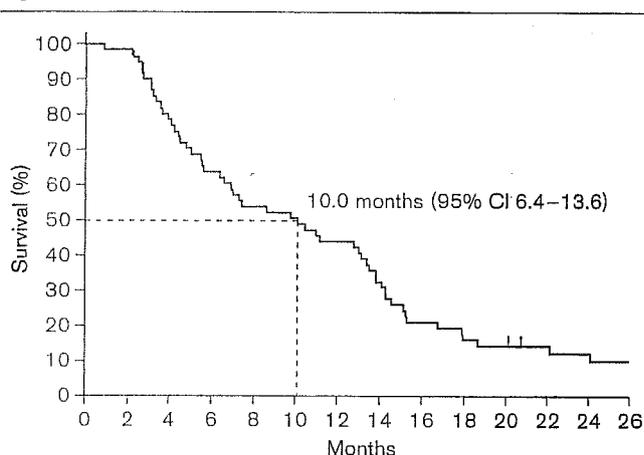
Overall survival (n=60).

Fig. 2
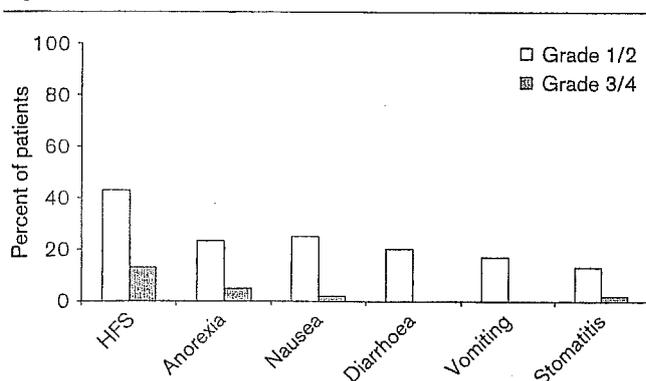
Common treatment-related clinical adverse events (more than 15% of patients).

decreased hemoglobin (50%), increased AST (GOT) (38%), hyperbilirubinemia (37%), hyperglycemia (37%), decreased hematocrit (37%), leukopenia (32%) and granulocytopenia (30%). Common grade 3/4 drug-related laboratory abnormalities were lymphopenia (43%) and hyperbilirubinemia (23%).

Treatment was discontinued in eight patients due to drug-related adverse events (increased bilirubin levels in three patients, HFS in two patients, and anorexia, rupture of abdominal aortic aneurysm and gastric perforation in one patient each). Dose reduction was needed in three patients with HFS, and one patient with grade 2 leukopenia and granulocytopenia. One patient died from rupture of an abdominal aortic aneurysm after the third cycle of treatment and this case was considered to be a treatment-related death.

Discussion

Capecitabine has shown consistently good efficacy and tolerability in solid tumors, especially in colorectal cancer [13,14] and breast cancer [15–17]. In addition, capecitabine offers the convenience of oral administration and has an improved tolerability profile compared with i.v. bolus 5-FU, resulting in less resource utilization in metastatic colorectal cancer [18,19]. There are also several promising reports of capecitabine monotherapy [20,21] and combination therapy [22,23] in advanced gastric cancer. Currently, a couple of phase III trials including capecitabine combination regimens are ongoing in Korea and the UK [24]. Most of these trials are based on a 3-week capecitabine schedule (2 weeks on and 1 week off).

We conducted a phase II study with a 4-week regimen of capecitabine (given on days 1–21) according to the recommendation of a Japanese phase I study [9], and showed that this regimen was active and well tolerated in advanced gastric cancer. The RR was 26%, median TTP was 3.4 months and median overall survival was 10.0 months. These efficacy results seem to be similar to those reported with the 3-week regimen of capecitabine in Korea (n = 44, RR 32%, median TTP 3.1 months and median overall survival 9.5 months) [20] and Mexico (n = 18, RR 25%, median TTP 21 weeks, and median overall survival 6.5 months) [21]. Although the dose intensity of capecitabine was lower in this study (median 1870 mg/day) than in the Korean study (median 3542 mg/day) which used the 3-week schedule [20], the median cumulative dose in our study (190 g) was almost equivalent to that in Korean study (183 g). This would account for the similar efficacy observed in both studies.

In terms of safety, the majority of treatment-related adverse events were grade 1 or 2. The predominant treatment-related grade 3/4 adverse event was HFS (13%) – a well-known adverse event associated with chronic fluoropyrimidine exposure and one of the most common adverse events associated with capecitabine treatment [19]. The prevalence and degree of HFS in this study were similar to those reported with the 3-week

regimen [20,21]. HFS was, however, never life threatening, and was managed relatively easily with therapy interruption and dose reduction. It is noteworthy that no patients experienced grade 3/4 diarrhea or vomiting in the present study with the 4-week regimen. This could be due to the different dose and schedule used or ethnic differences. The prevalence of severe diarrhea with capecitabine was lower in Japanese than in Caucasians in previous studies [6,7,9,10].

Although various laboratory abnormalities were observed, frequently occurring (more than 10%) treatment-related grade 3/4 abnormalities were limited to only two events, i.e. lymphopenia (43%) and hyperbilirubinemia (23%). In the current study, lymphocyte count was not specified in the inclusion criteria and most patients already had grade 1 or greater lymphopenia at baseline. However, grade 3/4 leukopenia was not observed and grade 3/4 granulocytopenia was seen in only one patient. The reason for the high incidence of hyperbilirubinemia observed in the present study was due to the toxicity criteria used. Specifically, the definition of grade 3 hyperbilirubinemia according to NCIC-CTC criteria is 1.5–3 × ULN. On the other hand, the grade 3 criterion according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 [25] is more than 3–10 × ULN. If this study was reviewed according to NCI-CTC criteria, the incidence of grade 3/4 hyperbilirubinemia would have been 8% and it is similar to that reported with other oral fluoropyrimidines [26]. From these results, the current regimen seems quite feasible in the treatment of advanced gastric cancer, although the data are not yet adequate to compare the safety profiles of the 3- and 4-week regimens.

Consequently, the efficacy and safety findings of the present study suggest that a 4-week regimen of capecitabine is a suitable alternative to the standard 3-week regimen. Further investigation of this regimen in advanced gastric cancer is warranted.

Acknowledgments

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連載

● 薬の知識

オキサリプラチン

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はじめに

近年，大腸癌の化学療法は長足の進歩を遂げている．現在，欧米において切除不能進行・再発結腸・直腸癌に対する標準化学療法は，塩酸イリノテカン(CPT-11)＋infusional 5-FU/leucovorin(LV)療法およびオキサリプラチン(L-OHP)＋infusional 5-FU/LV療法とされている(参考URL)．このどちらを初回化学療法に用いても生存期間に差は認められず，その効果は同等と考えられている[1]．本邦では2005年1月にinfusional 5-FU/l-LV療法が，4月にL-OHP＋infusional 5-FU/l-LV療法が承認され，ようやく世界的な標準化学療法を行う基盤が整った．

I．L-OHP

L-OHPはoxalateとdiaminocyclohexane(DACH)基を有する新たな白金錯体系抗癌剤である(図1)．おもな作用部位はほかの白金誘導体と同様にDNA adduct形成によるDNAの複製，転写の阻害と考えられている．L-OHPはシスプラチンやカルボプラチンとはまったく異なる白金誘導体に分類され，シスプラチン耐性を示す大腸癌細胞株(HT 29)に対しても in vitro, in vivo ともに強い殺細胞効果を示した．一般にほかの白金誘導体とは交差耐性を示さず，むしろ相乗的な効果を示すと考えられている．このようなL-OHPの既存の白金誘導体と異なる殺細胞活性は，大きなDACH基の関与が示唆されているが詳細は不明である．
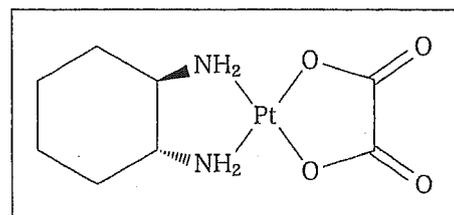

図1　オキサリプラチンの構造式

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図2 これまでに報告されている主要な FOLFOX レジメン
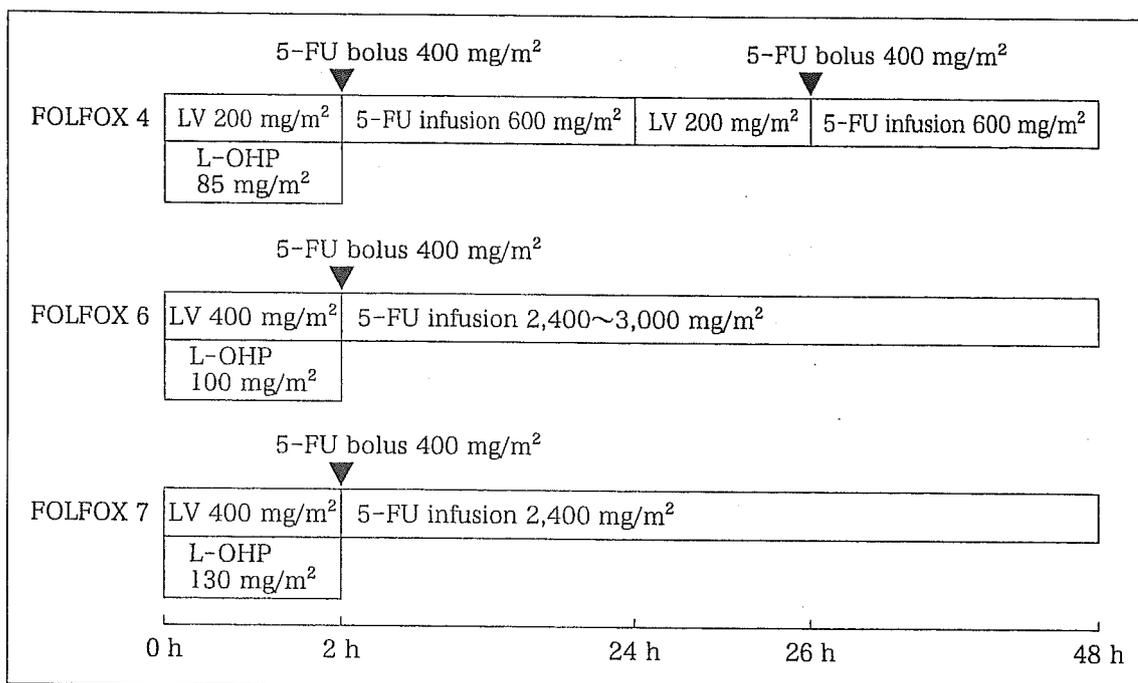すべて2週ごと投与. 本邦では L-OHP 85 mg/m²を超える投与量は承認されていない.
LV は本邦では *l*-LV のため半量となる.

II. L-OHP の臨床試験

1. 海外の成績

1990 年代の前半に 5-FU 治療耐性を示した転移性大腸癌に対する二次治療例あるいは初回治療例で L-OHP 単剤の効果と安全性が検討された. 既治療例では約 10%, 初回治療例では約 20%の奏効率が示され, 本剤の有効性が確認された. その後, 1990 年代の半ばに相乗効果を有する 5-FU/LV との併用療法が開発された. この開発はヨーロッパを中心に行われたため, infusional type の 5-FU/LV との併用 (FOLFOX レジメン)がもっとも多く検討されている. 現在までに, FOLFOX レジメンは 7 種類が検討されている(図2).

切除不能進行・再発結腸・直腸癌に対する L-OHP の位置づけを決定した重要な第Ⅲ相試験を紹介する.

1) L-OHP＋infusional 5-FU/LV(FOLFOX 4)対 infusional 5-FU/LV(LV 5 FU 2 または de Gramont レジメン)の転移性大腸癌初回治療例を対象とした第Ⅲ相試験[2]

両群で生存期間(中央値：16.2 カ月 vs. 14.7 カ月, p＝0.12)に差はみられなかったものの, 奏効率(50.7% vs. 22.3%, p＝0.0001)および主要評価項目である progression free survival (PFS)(中央値：9.0 カ月 vs. 6.2 カ月, p＝0.0003)では FOLFOX 4 群が有意に優れていた. しかし, 安全性では FOLFOX 4 群において神経毒性がみられ, 血液毒性や消化器毒性も頻度, 重篤度ともに高かった.

2) CPT-11＋bolus 5-FU/LV(IFL)対 L-OHP＋infusional 5-FU/LV(FOLFOX 4)対 CPT-11＋L-OHP(IROX)の転移性大腸癌初回治療例を対象とした第Ⅲ相試験[3]

IFL 群, FOLFOX 4 群, IROX 群の奏効率がそれぞれ 31%, 45%, 35%, time to pro-

gression(TTP)中央値がそれぞれ6.9カ月，8.7カ月，6.5カ月，生存期間中央値がそれぞれ15.0カ月，19.5カ月，17.4カ月であり，FOLFOX 4群はIFL群に比べて奏効率(p=0.002)，TTP(p=0.0014)，生存期間(p=0.0001)ともに有意に優れていた．また，FOLFOX 4群はIROX群に比べて奏効率(p=0.03)およびTTP(p=0.001)において有意に優れていたが，生存期間(p=0.09)に有意差はなかった．好中球減少，下痢などの重篤な有害事象もFOLFOX 4群で有意に少なく，唯一L-OHPの特徴である末梢神経障害が多かった．

初回治療だけでなくIFL治療耐性を示した症例においてもFOLFOX 4の有効性が証明されている[4]．また，2005年の米国臨床腫瘍学会(ASCO)で術後補助化学療法におけるFOLFOX 4の有用性も報告された．これらの臨床試験によって，FOLFOXレジメンは切除不能進行・再発結腸・直腸癌に対する世界的な標準化学療法と位置づけられている．

2．国内の成績

5-FU治療耐性を示した転移性大腸癌に対する二次治療例でL-OHP単剤の奏効率は11%であり，安全性に関しても海外の成績と同等であった[5]．また，L-OHPとbolus 5-FU/l-LVの併用療法の第I/II相試験が計画され，2004年のASCOでその結果が公表されている[6]．

そして，L-OHP単剤の成績や体内薬物動態は海外のこれまでの報告と差がないことから，早期に世界標準治療を導入するべく未承認薬検討会議において，2005年4月にL-OHPはinfusional 5-FU/l-LV療法との併用で承認された．

III．L-OHPの使用方法

実際の臨床で使用されるFOLFOX 4レジメンの具体的な投与方法について以下に示す．

1．Day 1の投与方法

①悪心・嘔吐予防目的でL-OHP投与前に5-HT$_3$受容体拮抗剤およびステロイド剤(デキサメタゾンなど)を点滴静注する．

②5%ブドウ糖溶液250 mlに溶解したL-OHP 85 mg/m^{2}と5%ブドウ糖溶液250 mlに溶解したレボホリナートカルシウム(l-LV)100 mg/m^{2}を輸液ポンプで120分かけて同時に点滴静注する．急性神経障害である咽頭喉頭感覚異常や呼吸困難感(発現率は1～2%，呼吸機能自体には影響を与えない)が出現した場合は，次回投与よりL-OHPを6時間かけて投与する．5-FUとl-LVの投与時間は変更なし(具体的には，L-OHPと5-FUが同時に投与されないように，L-OHP投与開始4時間後にl-LV投与を開始し，L-OHPとl-LVの投与終了後に5-FUの急速静注を実施する)．

③l-LV投与終了直後に，5-FU 400 mg/m^{2}を3分間程度の急速静注または5%ブドウ糖溶液50 mlに混じて全開点滴する．

④5-FUの急速静注後，5-FU 600 mg/m^{2}をディスポーザブルインフューザーまたは輸液ポンプで22時間かけて持続静注する．

2．Day 2の投与方法

L-OHPの投与を除き，Day 1と同様に行う．

5-FUの持続静注は，入院の場合は22時間当り500 ml以上の輸液に混じて末梢静脈より投与してもよいが，静脈炎を発生する可能性があるので十分な観察を行う．中心静脈カテーテ

ルまたは中心静脈ポートを留置し，5-FU を持続静注するほうが望ましい．

IV．有害事象および副作用

FOLFOX 4 レジメンのおもな有害事象および副作用は，①末梢神経障害，②消化器症状（悪心，嘔吐，下痢，口内炎，食欲不振，腹痛，便秘など），③疲労，④脱毛，⑤咳嗽，⑥骨髄抑制（白血球減少，好中球減少，貧血，血小板減少），⑦ GOT/GPT 上昇などである．末梢神経障害は 80〜90％に認められ，冷たいものに接触することで誘発あるいは悪化する四肢末端や口唇周囲の知覚不全，感覚異常（しびれなど）である．

感覚異常による機能障害（立つ，歩く，物を持つ，ボタンをかけるなどの動作において困難を伴う）を認めることがあり，この症状は L-OHP の累積投与量に依存して発現する．累積投与量 540 mg/m² で約 1％，780 mg/m² で約 20％，1,170 mg/m² で約 40％にみられる．ほとんどの有害事象や副作用は休薬期間に回復，軽快する．しかし，重篤な下痢や好中球減少の出現時には止痢剤，補液，顆粒球コロニー刺激因子（G-CSF）製剤などを適切に使用する．

おわりに

欧米における切除不能進行・再発結腸・直腸癌に対する治療成績は，CPT-11 と L-OHP の有効な使用により初回治療の奏効率で 40％以上，生存期間中央値で 20 カ月以上と格段の進歩を遂げた．わが国でも L-OHP が承認された今日，日本人における FOLFOX レジメンの有効性と安全性を確認し，さらに経口フッ化ピリミジン系薬剤や分子標的薬剤（bevacizumab，cetuximab など）との併用療法を早急に検討する必要がある．

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