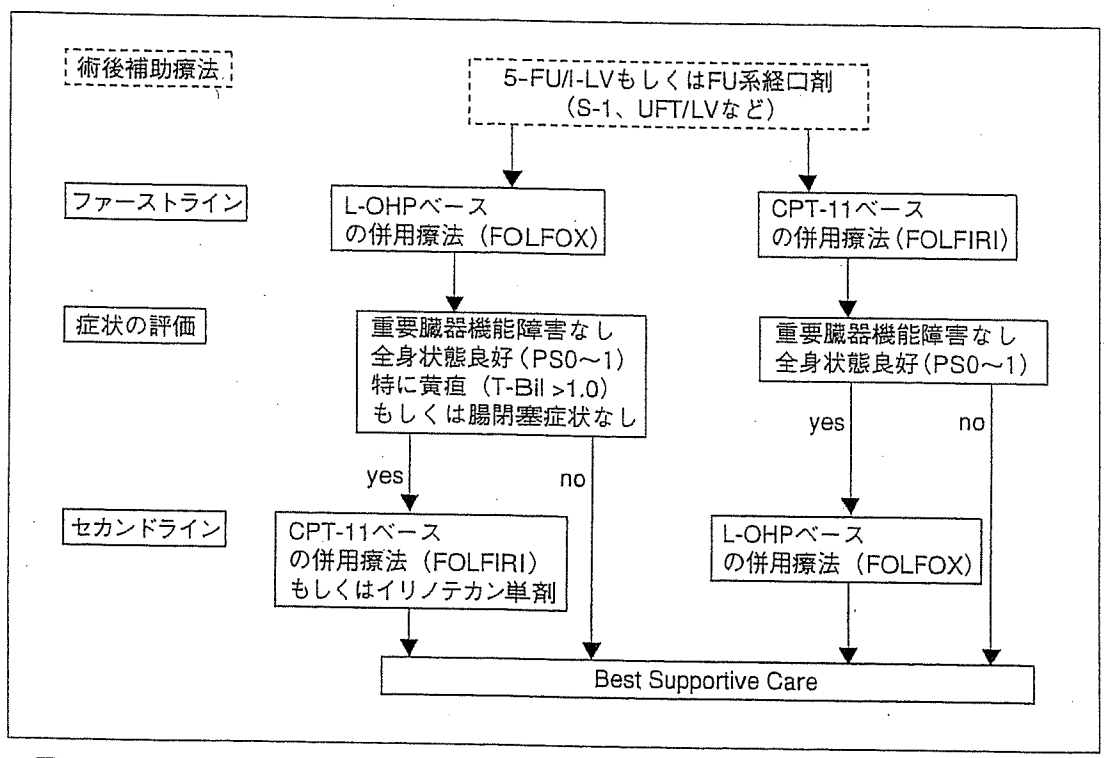


図1　セカンドライン以降の化学療法

- 転移性結腸・直腸がん症例に対するFOLFOXとFOLFIRIのクロスオーバーデザインの第Ⅲ相試験が行われ，セカンドラインではFOLFIRI群に比べ，FOLFOX群の無増悪期間中央値が4.2ヵ月と有意に延長していたが，全生存期間には有意差がなかった[4]。
- 5-FU抵抗性の転移性結腸・直腸がん症例に対する本邦のCPT-11単剤の成績は奏効率11%，MST 12ヵ月と実臨床でも有用性が示唆されている[5]。
- 5-FU抵抗性の転移性結腸・直腸がん症例に対するセカンドラインにおけるCPT-11とFOLFOXのクロスオーバーデザインの第III相試験が行われ，生存期間には有意差は認めなかったが，奏効率，有害事象頻度においては末梢神経毒性を除き，CPT-11群に比べ，FOLFOX群が有意に良好な成績であった[6]。
- 本邦ではようやく2005年4月よりファーストラインでFOLFIRIまたは，FOLFOXの標準治療が可能となった。未だ本邦のまとまった成績はない。
- これまでにセカンドライン以降のティーエスワン® (S-1)，ユーエフティ® (UFT)/LV療法の有用性に関する報告はない。

セカンドライン以降の化学療法はこう進める（図1）

- 全治療経過のなかでCPT-11，L-OHP，5-FU/LVの3剤を用いることで，生存期間が延長することが報告されている[7]。
- ファーストラインがFOLFOXの場合は，CPT-11ベースの併用療法（FOLFIRI）かCPT-11単剤による治療がセカンドラインとなる。
- ファーストラインがCPT-11ベースの併用療法（FOLFIRI）の場合はFOLFOXがセカンドラインとなる。
- 5-FU/LVまたは，S-1または，UFT/LV療法の補助化学療法中または終了後6ヵ月以内の再発の場合は，FU系薬剤は効果が乏しいと考えられる。次治療はPitotら[6]（表

1）の試験成績が参考となる。

- 現段階では基本的には5-FU/LV, CPT-11, L-OHPの3剤使用後のサードラインの治療法はなく，BSCとなる。

こんなとき，どうするか？

- PS 3以上の場合：化学療法は困難であるため，BSCとする。
- PS 2の場合：化学療法は困難なことも多く，BSCも選択肢のひとつである。患者が強く希望する場合は，十分なインフォームドコンセントのもとで治療を行う。ただし，70～80%の減量投与から開始するなどの工夫が必要である。
- 高齢者(主に75歳以上)：高血圧，糖尿病，脳・心血管障害などの合併症を有する症例も多く，より安全性の高い治療が望ましい。Infusional 5-FU/LV, S-1もしくはUFT/LVの投与が実施されることが多いが，これまでにこの対象群のセカンドライン以降での有用なデータは乏しい。
- 血清総ビリルビン値上昇症例（>1.0mg/dL），腹膜播種による便通異常を有する症例：CPT-11による重篤な副作用が出現しやすいので慎重に適応を考慮する[8]。
- 前化学療法による骨髄機能低下症例：原則として化学療法は行えない。十分な回復を待って治療を開始する。または減量投与も考慮する。

このように考えて治療をすすめる

- セカンドラインまでは積極的な治療を行うことが望ましいが，常に患者の状態（PS，検査データ，転移部位など）を把握し，適切な画像評価，安全性評価を行うことが重要である。著効例では，治癒を目指した切除手術も念頭に置き，効果の不十分な症例では，BSCへの移行のタイミングを常に意識することが大切である。
- セカンドラインにおいても主軸はFOLFOX, FOLFIRIの3剤併用療法である。患者によっては，CPT-11単剤治療や経口薬剤による治療も選択肢となる。

文　献

1）Rougier P et al : Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352 : 1407－1412 (1998)

2）Cunningham D et al : Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352 : 1413－1418 (1998)

3）Andre T et al : CPT-11 (irinotecan) addition to bimonthly,high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. Eur J Cancer 35 : 1343－1347 (1999)

4）Tournigand C et al : FOLFIRI followed by FOLFOX 6 or the reverse sequence in advanced colorectal cancer. J Clin Oncol 22 : 229－237 (2004)

5）Nishina T et al : Clinical study of irinotecan therapy in patients with fluoropyrimidine-resistant advanced colorectal cancer. Gan To Kagaku Ryoho 31 : 1361－1364 (2004)

6）Pitot HC et al : A randomized phase III equivalence trial of irinotecan (CPT-11) versus oxaliplatin／5-fluorouracil (5 FU) ／leucovorin (FOLFOX 4) in patients (pts) with advanced colorectal cancer (CRC) previously treated with 5 FU. Pro Am Soci Clin Oncol 23 : #3506 (2005)

7）Grothey A et al : Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 22 : 1209－1214 (2004)

8）Raymond E et al : Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. J Clin Oncol 20 : 4303－4312 (2002)

9）カンプト注®，トポテシン注®添付文書

Original Article

Artificial Hydration Therapy, Laboratory Findings, and Fluid Balance in Terminally Ill Patients with Abdominal Malignancies

Tatsuya Morita, MD, Ichinosuke Hyodo, MD, Taisuke Yoshimi, MD, Masayuki Ikenaga, MD, Yoichiro Tamura, MD, Akitaka Yoshizawa, MD, Akira Shimada, MD, PhD, Tatsuo Akechi, MD, PhD, Mitsunori Miyashita, RN, MHlthSc, and Isamu Adachi, MD, for the Japan Palliative Oncology Study Group

Department of Palliative and Supportive Care, Palliative Care Team and Seirei Hospice (T.M.), Seirei Mikatahara General Hospital, Hamamatsu; Department of Gastroenterology (I.H.), National Shikoku Cancer Center Hospital, Ehime; Department of Internal Medicine (T.Y.), Dozono Medical House (T.Y.), Kagoshima; Hospice (M.I.), Yodogawa Christian Hospital, Osaka; Department of Surgery (Y.T.), Kasumigaura National Hospital, Ibaragi; Department of Internal Medicine (A.Y.), Kanamecho Hospital, Tokyo; Department of Palliative Medicine (A.S.), Tohoku University Hospital, Miyagi; Psycho-Oncology Division (T.A.), National Cancer Center Research Institute East, Chiba; Psychiatry Division (T.A.), National Cancer Center Hospital East, Chiba; Department of Adult Nursing/Terminal and Long-Term Care Nursing (M.M.), The University of Tokyo, Tokyo; and Department of Palliative Medicine (I.A.), Shizuoka Cancer Center, Shizuoka, Japan

Abstract

To explore the association between hydration volume and laboratory findings, and between calculated fluid balance and changes in clinical signs of dehydration and fluid retention in terminally ill cancer patients, a secondary analysis of a large multicenter, prospective, observational study was performed. The study enrolled 125 abdominal cancer patients who received laboratory examinations in the last week before death. Patients were classified into two groups: the hydration group (n = 44), who received 1 L or more of artificial hydration per day both 1 and 3 weeks before death, and the nonhydration group (n = 81). The mean albumin level 1 week before death was significantly lower in the hydration group than in the nonhydration group, and the interaction between hydration group and decrease in the albumin level was statistically significant after adjusting multiple covariates (from 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. a decrease of 2.8 ± 0.53 to 2.6 ± 0.45 mg/dL in the nonhydration group, P = 0.015). There was no significant difference between the groups in the mean blood urea nitrogen/creatinine, sodium, or potassium levels 1 week before death. Among 53 patients who had oral fluid intake of less than 500 mL/day throughout the last 3 weeks and completed a fluid balance study, the median of calculated fluid balance was −400 mL/day 3 weeks before death, −521 mL/day 1 week before death, and −421 mL/day 24 hours before

Address reprint requests to: Tatsuya Morita, MD, Department of Palliative and Supportive Care, Palliative Care Team and Seirei Hospice, Seirei Mikatahara General Hospital, 3453 Mikatahara-cho, Hamamatsu, Shizuoka 433-8558, Japan. E-mail: tmorita@sis.seirei.or.jp

Accepted for publication: June 23, 2005.

0885-3924/06/$–see front matter
doi:10.1016/j.jpainsymman.2005.06.015

death. Calculated fluid balances did not significantly differ between the patients with deterioration of dehydration signs, edema, ascites, and pleural effusion during the final 3 weeks and those without. These data suggest that active artificial hydration might result in hypoalbuminemia, with no clear beneficial effects on normalizing blood urea nitrogen/creatinine, sodium, or potassium levels. Fluid balance did not significantly correlate with changes in dehydration—and fluid retention—signs. Calculated fluid balance is not an appropriate alternative to direct monitoring of patient symptoms. More studies are needed to determine the clinical efficacy of artificial hydration for terminally ill cancer patients. J Pain Symptom Manage 2006;31:130–139.

Key Words
Palliative care, dehydration, water depletion, rehydration, neoplasm

Introduction

The dehydration–rehydration problem is one of the most important issues in the recent literature on end-of-life care.[1] Although the primary focus of medical treatment should be placed on patient comfort in the late stages of cancer, an empirical survey revealed that laboratory findings still comprise an important factor when physicians determine the indications for artificial hydration therapy.[2] Therefore, it seems important to clarify the effects of artificial hydration therapy on laboratory data in terminally ill cancer patients. Existing empirical studies have suggested that blood urea nitrogen (BUN) and creatinine levels tend to be higher in patients who do not receive artificial hydration therapy than in patients who receive artificial hydration, but that mean sodium and potassium levels are essentially normal even when artificial hydration therapy is not performed.[3–6] However, these studies were single institution studies, and, to our best knowledge, there are no multicenter prospective studies to explore the association between hydration practice and laboratory findings in terminally ill cancer patients. Moreover, while a fluid balance study is a classical method for monitoring the treatment effects of intravenous hydration therapy,[7–9] no studies have been reported about its usefulness in palliative care settings.

The primary aims of this study were thus to explore the association between (1) hydration volume and laboratory findings and (2) calculated fluid balance and the changes in clinical signs of dehydration and fluid retention during the last 3 weeks of life in terminally ill cancer patients.

Methods

This was a secondary analysis of data collected during a multicenter, prospective, observational study to investigate the associations between hydration volume and patient symptoms in the last 3 weeks of life in terminally ill patients.[10,11] The participants were consecutive, terminally ill cancer patients treated in 14 oncology units, 19 palliative care units, and 4 home-based palliative care programs in Japan. Patients were considered potential participants if they met the following inclusion criteria: (1) older than 20 years; (2) life expectancy estimated by a physician to be 3 months or less; and (3) incurable malignancy of lung or abdominal origin (excluding hepatic malignancies). Exclusion criteria were (1) liver cirrhosis, renal failure, nephritis syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcemia, endocrine disorders, and vital organ complications unrelated to underlying malignancies; (2) surgical, radiological, or oncological treatments in the 3 weeks prior to study inclusion; (3) existing communication difficulty; and (4) the use of artificial enteral nutrition. Patients were enrolled from August 2002 to February 2003, and followed up until March 2003.

To explore the association between hydration volume and the laboratory findings in the final week of life, we analyzed data for patients who received laboratory examinations during the last week. Laboratory examinations were performed for clinical purposes, and we investigated potential sampling bias by comparing the backgrounds of the patients who did and did not

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

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)	

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

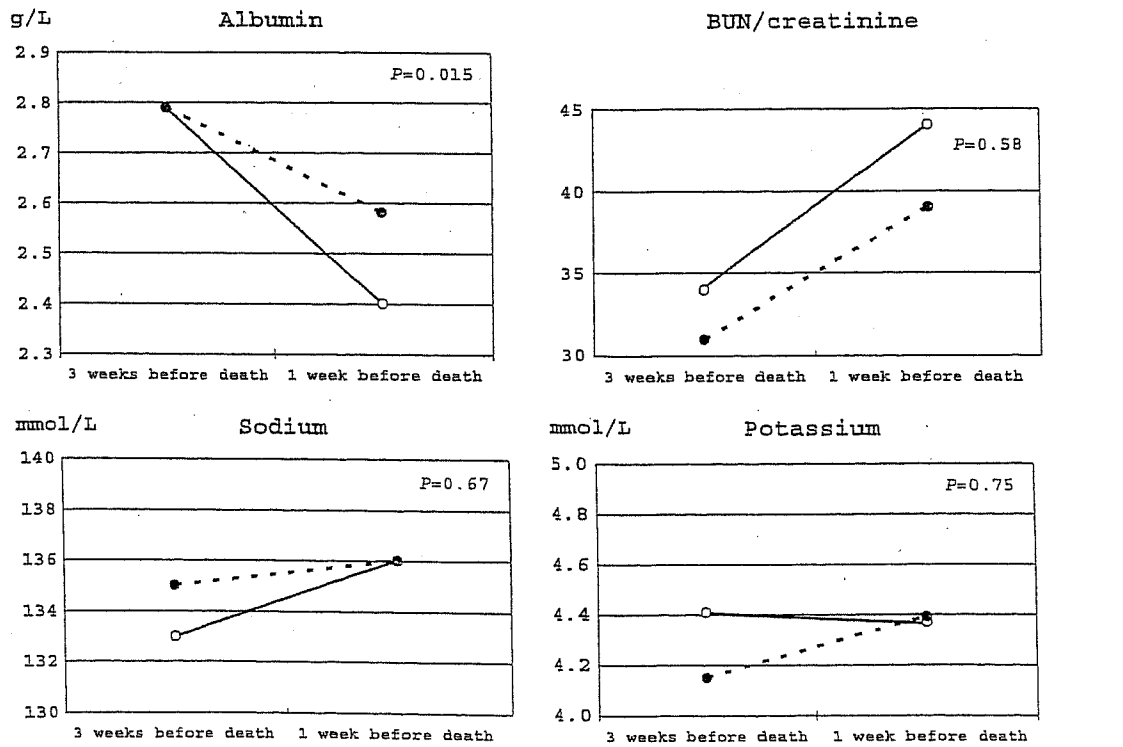


Fig. 1. Association between hydration practice and changes in laboratory findings. (○) Hydration group ($n=37$); (●) nonhydration group ($n=56$).

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

This work was supported in part by a Grant-in-Aid for Cancer Research (11–2) from the Ministry of Health and Welfare, Japan.

References

1. Sarhill N, Walsh D, Nelson K, Davis M. Evaluation and treatment of cancer-related fluid deficits: volume depletion and dehydration. Support Care Cancer 2001;9:408–419.

2. Morita T, Shima Y, Adachi I, Japan Palliative Oncology Study (J-POS) Group. Attitudes toward terminal dehydration of Japanese physicians: a nationwide survey. J Clin Oncol 2002;20:4699–4704.

3. Ellershaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage 1995;10:192–197.

4. Fainsinger RL, MacEachern T, Miller MJ, et al. The use of hypodermoclysis for rehydration in terminally ill cancer patients. J Pain Symptom Manage 1994;9:298–302.

5. Vull-Navich K, Smith S, Andrews M, et al. Comfort and incidence of abnormal serum sodium, BUN, creatinine and osmolality in dehydration of terminal illness. Am J Hosp Palliat Care 1998;15: 77–84.

6. Waller A, Hershkowitz M, Adunsky A. The effect of intravenous fluid infusion on blood and urine parameters of hydration and on state of consciousness in terminal cancer patients. Am J Hosp Palliat Care 1994;11:22–27.

7. Dougan LR, Finlay WEI. Fluid and electrolyte balance: assessment of the patients. Brit J Anaesth 1973;45:945–952.

8. Kavouras SA. Assessing hydration status, Curr Opin Clin Nutr Metab Care 2002;5:519–524.

9. Oh MS, Kim H. Basic rules of parenteral fluid therapy. Nephron 2002;92(Suppl 1):56–59.

10. Morita T, Hyodo I, Yoshimi T, et al. Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies. Ann Oncol 2005;16:640–647.

11. Morita T, Hyodo I, Yoshimi T, et al. Incidence and underlying etiologies of bronchial secretion in terminally ill cancer patients; a multi-center prospective observation study. J Pain Symptom Manage 2004;27:533–539.

12. Eaton D, Bannister P, Mulley GP, Connolly M. Auxiliary sweating in clinical assessment of dehydration in ill elderly patients. BMJ 1994;308:1271.

13. Gross CR, Lindquist RD, Woolley AC, et al. Clinical indicators of dehydration severity in elderly patients. J Emerg Med 1992;10:267–274.

14. McGee S, Abernethy WB, Simel DL. Is this patient hypovolemic? JAMA 1999;281:1022–1029.

15. Cox P. Insensible water loss and its assessment in adult patients: a review. Acta Anaesthesiol Scand 1987;31:771–776.

16. Andrews M, Bell ER, Smith SA, Tischler J, Veglia JM. Dehydration in terminally ill patients. Is it appropriate palliative care? Postgrad Med J 1993;93:201–208.

17. Morita T, Tei Y, Inoue S, Suga A, Chihara S. Fluid status of terminally ill cancer patients with intestinal obstruction: an exploratory observational. Support Care Cancer 2002;10:474–479.

Appendix

Japan Palliative Oncology Study Group

The members of this group are Taketoshi Ozawa, MD, Palliative Care Unit, Yokohama Kosei Hospital; Chikako Kato, MD, Hospice, St. Francis Hospital; Yoshiyuki Kizawa, MD, Palliative Care, Tsukuba Medical Center Hospital; Takeshi Okabe, MD, Okabe Clinic; Hiroyuki Kohara, MD, PhD, Palliative Care, National Sanyo Hospital; Yasuo Shima, MD, Palliative Care, National Cancer Hospital East; Kayako Shimamura, MD, Hospice, Kyuseigun Kiyose Hospital; Yoshikazu Chinone, MD, Palliative Care, Japanese Red Cross Medical Center; Yoshi Tsukiyama, MD, Department of Palliative Medicine, Wakayama Medical University; Junichi Tsunoda, MD, Palliative Care, Sannou Hospital; Kenji Nishitateno, MD, General and Medical Director, Peace House Hospice; Akitoshi Hayashi, MD, Director of Hospice Service, The Japan Baptist Hospital; Yoshifumi Honke, MD, Department of Palliative Care, Hiroshima Prefectural Hospital; Hideaki Nagai, MD, PhD, Department of Palliative Medicine, National Tokyo Hospital; Makoto Miyoshi, MD, Palliative Care, Kitakyushu Municipal Medical Center; Kinomi Yomiya, MD, Palliative Care, Saitama Cancer Center; Fumiki Asanuma, MD, Department of Surgery, Kitasato Institute Hospital; Yoshikazu Ashino, MD, Department of Surgery, Fukushima-rosai Hospital; Hisanao Ohkura, MD, Medical Oncology Division, Ibaraki Kenritsu Chuo Hospital & Cancer Center; Hiroyuki Otani, MD, Department of Internal Medicine, Second Teaching Hospital, Fujita Health University School of Medicine; Nobuhiro Tsukada, MD, Department of Internal Medicine, Saiseikai Center Hospital; Nobuhisa Nakajima, MD, Department of Surgery, Sapporo Social Insurance General Hospital; Akira Hoshino, MD, Department of Surgery, Iwate Prefectural Kitakami Hospital; Toshihiro Matsuura, MD, Department of Gastroenterology, Chubu National Hospital; Takatsugu Kawagoe, MD, Department of Surgery, Toki General Hospital; Takuya Aoki, MD, PhD, Respiratory Division, Department of Internal Medicine, Saiseikai Central Hospital; and Takayuki Kaburagi, MD, Internal Medicine, Ibaraki Kenritsu Chuo Hospital & Cancer Center.

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

Junichi Sakamoto[a], Keisho Chin[b], Ken Kondo[c], Hiroshi Kojima[d], Masanori Terashima[e], Yoshitaka Yamamura[f], Toshimasa Tsujinaka[g], Ichinosuke Hyodo[h], Wasaburo Koizumi[i] and on behalf of the Clinical Study Group of Capecitabine

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.

Anti-Cancer Drugs 2006, 17:231–236

Keywords: 4-week regimen, advanced gastric cancer, capecitabine, gastric cancer, recurrent gastric cancer

[a]Kyoto University Graduate School of Medicine, Kyoto, Japan, [b]Cancer Institute Hospital, Tokyo, Japan, [c]Nagoya National Hospital, Nagoya, Japan, [d]Aichi Cancer Center Aichi Hospital, Okazaki, Japan, [e]Fukushima Medical University, Fukushima, Japan, [f]Aichi Cancer Center, Nagoya, Japan, [g]Osaka National Hospital, Osaka, Japan, [h]NHO Shikoku Cancer Center, Matsuyama, Japan and [i]Kitasato University School of Medicine, Sagamihara, Japan.

Correspondence to J. Sakamoto, Department of Epidemiological and Clinical Research Information Management, Kyoto University Graduate School of Medicine, Yoshidakonoe-cho, Sakyo-ku, Kyoto 606-8501, Japan.
Tel: +81 757521511; fax: +81 75752 1518;
e-mail: sakamoto@pbh.med.kyoto-u.ac.jp

Sponsorship: Nippon Roche KK (Chugai Pharmaceutical Co., Ltd) provided the study drug and support during the study.

Received 7 September 2005 Accepted 5 October 2005

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 $\times$ upper limit of normal (ULN) for the center; total bilirubin and creatinine $<$ 1.5 $\times$ 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.

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

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.

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].

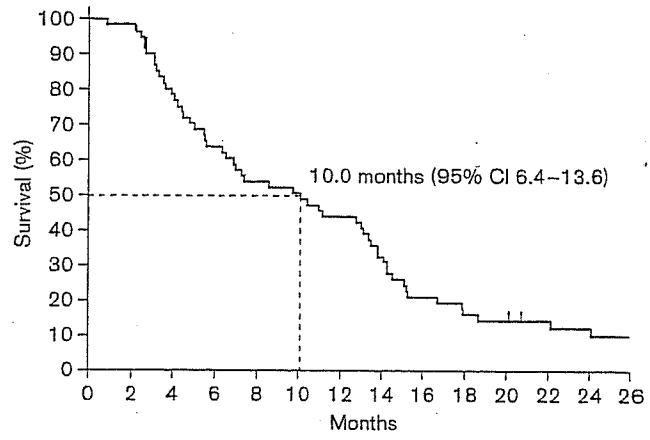
Frequently reported drug-related laboratory abnormalities were: lymphopenia (63%), decreased erythrocytes (55%),

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)

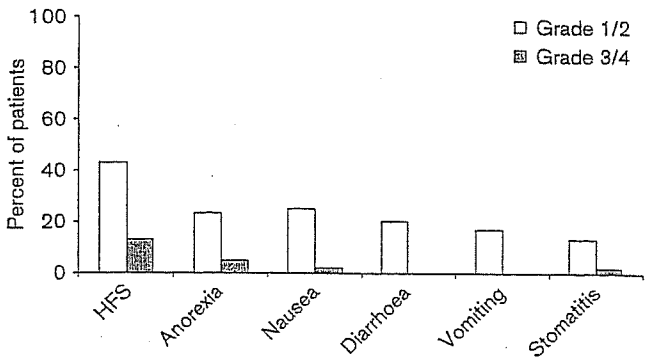
[a]Inadequate post-baseline observation.

Fig. 1



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%, mediar 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

We are indebted to Professor Minoru Kurihara, Professor Keiichi Nagao, Dr Tsuneo Sasaki, and Dr Junji Tanaka for their help in the assessment of efficacy; to Drs Hisanobu Niitani, Shigeru Tsukakoshi and Hiroshi Fujita for their assistance in the evaluation of safety; and to Dr Yasuo Ohashi for his helpful comments on the statistical analysis. We are also grateful to Drs Y. Kondo (Sapporo Kousei Hospital), N. Sairenji (Kanagawa Cancer Center), Y. Tamiya (Niigata Prefecture Yoshida Hospital), H. Takiuchi (Osaka Medical College), M. Higashino (Osaka City General Hospital), T. Suzuki (Chiba University), T. Ichikura (National Defence Medical College), S. Ujiie (Miyagi Cancer Center), H. Saitoh (Yamagata Prefecture Central Hospital), T. Akiya (Gunma Cancer Center) and K. Yamaguchi (Saitama Cancer Center), and special advisor Professor T. Taguchi.

References

1 Van Cutsem E, Haller D, Ohtsu A. The role of chemotherapy in the current treatment of gastric cancer. *Gastric Cancer* 2002; 5(Suppl 1):17–22.
2 Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, *et al.* Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; 15:261–267.
3 Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, *et al.* Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 2000; 18:2648–2657.
4 Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, *et al.* Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with untreatable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; 21:54–59.
5 Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, *et al.* Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumors by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998; 34:1274–1281.
6 Budman DR, Meropol NJ, Reigner B, Creaven PJ, Lichtman SM, Berghorn E, *et al.* Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. *J Clin Oncol* 1998; 16:1795–1802.
7 Mackean M, Planting A, Twelves C, Schellens J, Allman D, Osterwalder B, *et al.* Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. *J Clin Oncol* 1998; 16:2977–2985.
8 Van Cutsem E, Findlay M, Osterwalder B, Kocha W, Dalley D, Pazdur R, *et al.* Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. *J Clin Oncol* 2000; 18:1337–1345.
9 Saeki T, Takashima S, Terashima M, Satoh A, Toi M, Osaki A, *et al.* A Japanese phase I study of continuous oral capecitabine in patients with malignant solid tumors. *Int J Clin Oncol* 2005; 10:51–57.
10 Koizumi W, Saigenji K, Ujiie S, Terashima M, Sakata Y, Taguchi T, *et al.* A pilot phase II study of capecitabine in advanced or recurrent gastric cancer. *Oncology* 2003; 64:232–236.
11 WHO. *WHO handbook for reporting results of cancer treatment.* Geneva: WHO; 1979.
12 NCIC-CTC. *National Cancer Institute of Canada Common Toxicity Criteria grading system.* Toronto: NCIC; 1991.
13 Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, *et al.* Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; 19:2282–2292.
14 Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, *et al.* Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; 19:4097–4106.
15 O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, *et al.* Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002; 20:2812–2823.
16 Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, *et al.* Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999; 17:485–493.
17 Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, Buzdar A, *et al.* Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *Cancer* 2001; 92:1759–1768.
18 Twelves C, Boyer M, Findlay M, Cassidy J, Weitzel C, Barker C, *et al.* Capecitabine (Xeloda™) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. *Eur J Cancer* 2001; 37:597–604.
19 Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, *et al.* First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002; 13:566–575.

臨牀消化器内科 2006 Vol.21 No.1
©日本メディカルセンター

連載

● 薬の知識

オキサリプラチン

梶原　猛史*　兵頭一之介*,**

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．

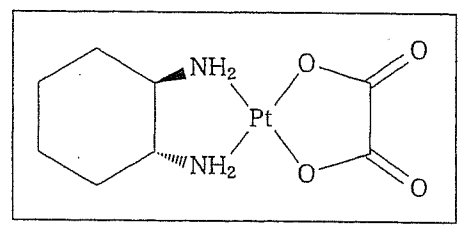


図1　オキサリプラチンの構造式

Key words：オキサリプラチン，大腸癌

Takeshi Kajiwara／Ichinosuke Hyodo
*独立行政法人国立病院機構四国がんセンター消化器内科(〒790-0007 愛媛県松山市堀之内13)
**現 筑波大学大学院人間総合科学研究科臨床医学系消化器内科

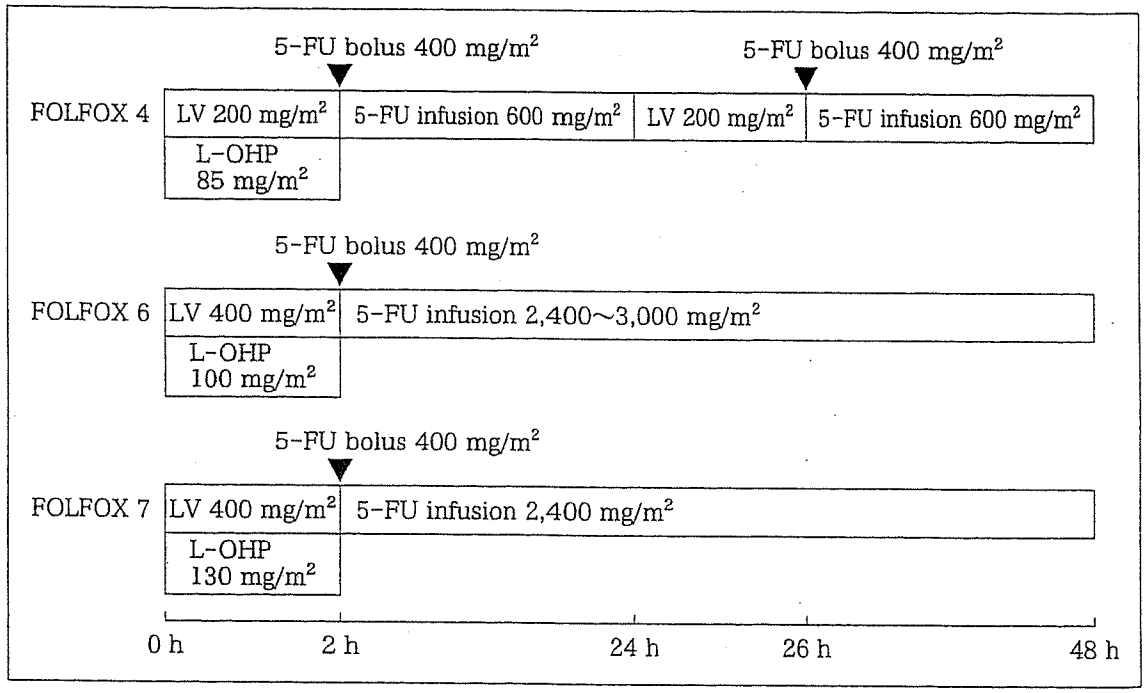


図2　これまでに報告されている主要なFOLFOXレジメン
すべて2週ごと投与．本邦ではL-OHP 85 mg/m²を超える投与量は承認されていない．
LVは本邦では*l*-LVのため半量となる．

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 m*l*に溶解したL-OHP 85 mg/m^2と5%ブドウ糖溶液250 m*l*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)．

③*l*-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 m*l*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 m*l*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