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CLINICAL INVESTIGATION

Radiological Insertion of Denver Peritoneovenous Shunts for Malignant Refractory Ascites: A Retrospective Multicenter Study (JIVROSG-0809)

Shunsuke Sugawara · Miyuki Sone · Yasuaki Arai · Noriaki Sakamoto · Takeshi Aramaki · Yozo Sato · Yoshitaka Inaba · Yoshito Takeuchi · Teruko Ueno · Kiyoshi Matsueda · Michihisa Moriguchi · Takahiro Tsushima

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Abstract
Purpose Peritoneal venous shunts (PVSs) are widely used for palliating symptoms of refractory malignant ascites and are recognized as one of the practical methods. However, reliable clinical data are insufficient because most previous reports have been small studies from single centers. We conducted a retrospective, multicenter study to evaluate the safety and efficacy of radiologically placed PVSs in patients with malignant refractory ascites.
Methods A total of 133 patients with malignant ascites refractory to medical therapies were evaluated for patient characteristics, technical success, efficacy, survival times, adverse events, and changes in laboratory data.
Results PVSs were successfully placed in all patients and were effective (i.e., improvement of ascites symptoms lasting 7 days or more) in 110 (82.7%). The median duration of symptom palliation was 26 days and median survival time was 41 days. The most frequent adverse event was PVS dysfunction, which occurred in 60 (45.1%) patients, among whom function was recovered with an additional minimally invasive procedure in 9. Abnormalities in coagulation (subclinical disseminated intravascular coagulation) occurred in 37 (27.8%) patients, although only 7 (5.3%) developed clinical disseminated intravascular coagulation. Other major adverse events were gastrointestinal bleeding (9.8%), sepsis (3.8%), and acute heart failure (3.0%). PVS was least effective in patients with elevated serum creatinine, bloody ascites, or gynecologic tumor.
Conclusions Radiological PVS is a technically feasible and effective method for palliating the symptoms from refractory malignant ascites, but preoperative evaluation and monitoring the postprocedural complications are mandatory to preclude severe adverse events after PVS.

Keywords Denver shunt · Interventional radiology · Malignant ascites · Palliative therapy · Peritoneovenous shunt

S. Sugawara (✉) · M. Sone
Department of Radiology, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan
e-mail: suga_shun@hotmail.com

Y. Arai · N. Sakamoto · Y. Takeuchi
Division of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

T. Aramaki · M. Moriguchi · T. Tsushima
Division of Diagnostic Radiology, Shizuoka Cancer Center, 1007, Shimo-nagakubo, Nagaizumi-cho, Suntoh-gun, Shizuoka 411-8777, Japan

Y. Sato · Y. Inaba
Department of Interventional and Diagnostic Radiology, Aichi Cancer Center Hospital, 1-1, Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

T. Ueno · K. Matsueda
Department of Diagnostic Imaging, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31, Ariake, Kohtoh-ku, Tokyo 135-8550, Japan

Present Address:
S. Sugawara
Department of Radiology, Ebara Hospital, 4-5-10, Higashi-yukigaya, Ohta-ku, Tokyo 145-0065, Japan

Introduction

Malignant ascites in patients with advanced cancer often is resistant to medical treatment. Symptoms from ascites result in a progressive deterioration in quality of life (QOL). Whereas diuretics and paracentesis have been

traditionally used to relieve symptoms, their use among physicians is inconsistent [1, 2]. In particular, although paracentesis can provide immediate relief, the effects are temporary and may be complicated by hypotension, secondary peritonitis, and the loss of protein and electrolytes contained in ascites fluid, among others [1, 2].

One means of palliating the various symptoms of refractory ascites is peritoneovenous shunts (PVSs) [3–15]. A variety of shunts have been designed [16–18]. One widely used technique for nonsurgical peritoneovenous shunting is radiological insertion of the Denver shunt. To date, however, most reports of PVSs for malignant refractory ascites have been derived from small studies at single centers only, and the lack of large, prospective, safety and efficacy studies has hampered evidence-based decision making on the use of PVSs and limited their routine use in malignant refractory ascites [5, 6, 9–11, 14, 15, 19, 20].

We evaluated the safety and efficacy of radiologically inserted PVSs in patients with refractory malignant ascites at five Japanese institutions. This study was conducted by Japan Interventional Radiology in Oncology Study Group (JIVROSG) as JIVROSG-0809.

Materials and Methods

Patients

Inclusion criteria were cytologically confirmed or clinically diagnosed malignant ascites, malignant ascites refractory to medical therapy, and ascites-induced deterioration in quality of life (QOL). Patients with ascites due to liver cirrhosis were excluded. The study protocol was approved by the institutional review board of all participating institutions before data collection.

From May 2001 to July 2008, 133 of 139 patients who underwent percutaneous insertion of PVSs met the selection criteria at five Japanese institutions and were enrolled (see Appendix Table 5).

Procedure for PVS Placement

All PVSs were inserted by interventional radiologists in the angiography suite by using a previously reported technique [20–23]. Percutaneous placement was performed under local anesthesia with image guidance by ultrasonography or fluoroscopy. PVSs were inserted on the right side except in patients with a central venous port in the right subclavian vein. Intravenous analgesic and sedative use was conducted in accordance with the local practice of the participating hospital, as was prophylactic use of antibiotics, catecholamines, or gabexate mesylate.

The PVS system consisted of a 16-F peritoneal catheter with side holes, a 12-F venous catheter, and a chamber with a one-way valve, which connected the two catheters. Preprocedural paracentesis was performed when ascites was prominent. Initially, a 3-cm to 5-cm long skin incision was made over the lower rib cage and a pocket for the chamber was created with forceps. The chamber was placed on the lower rib cage to allow it to be manually compressed to prevent occlusion of the system. Through a subcutaneous tunnel, the venous catheter was pulled out via a small incision on the upper chest wall and inserted into the subclavian vein using a Seldinger technique with a 12-F peel-away introducer under image guidance. The peritoneal catheter was inserted into the abdominal cavity with a 16-F peel-away introducer using a similar technique. After checking the position of the entire system by fluoroscopy, the incisions were closed with silk, nylon, or absorbable thread. The procedure time, defined as the time from local anesthesia to the completion of suturing, was recorded.

Study Outcomes

The primary outcome of interest was the clinical efficacy of the PVS, which was evaluated from subjective symptoms and classified into two groups: (1) effective, defined as duration of improvement of symptoms of ascites of 7 days or more; and (2) ineffective, duration of improvement of less than 7 days. In patients with multiple symptoms from ascites, the PVS was judged effective when at least one symptom was improved for 7 days or more without the other symptoms becoming worse.

Secondary outcomes included patient characteristics, toxicity profile, changes in laboratory data, overall survival time (OS), and duration of palliation. Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3. Grade 2 to 5 hematologic and nonhematologic AEs observed by the attending physicians were collected from the case report forms. Laboratory data before and after PVS placement were collected for blood counts, prothrombin times (PT), fibrinogen, fibrin degradation products (FDPs), and blood chemistry. Shunt dysfunction was defined as PVS system-related AE, and it was evaluated in another category. OS was defined as the time from the first PVS placement to death as a result of any cause. The palliation period was defined as the total duration of symptom palliation.

Statistical Analysis

Demographic and baseline variables, including survival time, were summarized by descriptive statistics. Survival time, duration of symptom palliation (<4 W or not) were compared using the χ^2 test and Mann–Whitney U test.

Pre- and postoperative body weight and abdominal girth were compared by using the Mann–Whitney *U* test. Factors associated with efficacy and toxicity (preoperative laboratory data, characteristics of ascites, and primary disease) were identified on the χ^2 test and Mann–Whitney *U* test. Statistical significance was set at 0.05. SPSS software, version 17 (SPSS, Chicago, IL) was used for all analyses.

Results

Patient Demographics

Characteristics of the total of 133 consecutive patients are listed in Table 1. Gastrointestinal (GI) cancer (43.6%) was the most common primary tumor. Performance status was 3 or 4 in 36.9% of patients. The most frequent symptoms from ascites were abdominal distention (98.5% of patients) and anorexia (65.4%). Cytological examination of ascites was performed in 54.8% of patients and malignant cytology was reported in 36.8%. Preoperative abdominal girth was 87.4 ± 10.1 cm (n = 71) and preoperative body weight was 55.6 ± 11 kg (n = 107).

Table 1 Baseline characteristics of patients

Characteristic	No. of patients (N = 133)	%
Age (yr)		
Mean	58.3	
Median	58	
Range	27–82	
Sex		
Male	71	53.4
Female	62	46.6
Site of primary tumor		
Colorectal cancer	33	24.8
Gastric cancer	25	18.8
Pancreatic cancer	21	15.8
Liver/bile duct cancer	16	12
Breast cancer	10	7.5
Ovarian cancer	9	6.8
Others	19	14.3
Performance status (ECOG[a])		
0	0	0
1	19	14.3
2	52	39.1
3	44	33.1
4	5	3.8
Unknown	13	9.8
Symptom		
Abdominal distention	131	98.5
Anorexia	87	65.4
Nausea/vomiting	10	7.5
Dyspnea	7	5.3
Lower extremity edema	7	5.3
Abdominal pain	6	4.5
Malaise	4	3.0
Back pain	3	2.3
Gait difficulty	1	0.8
Characteristics of ascites		
Property		
Clear	71	53.4
Bloody	21	15.8
Chylous	9	6.8
Bilious	1	0.8
Not evaluated	31	23.3
Viscosity		
Serous	90	67.7
Mucinous	9	6.8
Not evaluated	34	25.6
Cytology		
Malignant	49	36.8
Nonmalignant	24	18
Not performed	59	44.4
Unknown	1	0.8

[a] Eastern Cooperative Oncology Group

PVS Placement

PVS was successfully placed in all patients (100%) without any procedure-related AE. One patient developed grade one pneumothorax, which did not require additional intervention. The median procedure time was 60 *(range, 11–160) min, and the median length of hospital stay after PVS placement was 17 (range, 1–130) days.

Efficacy

PVS placement satisfied the efficacy criteria in 110 (82.7%) patients (Fig. 1). Palliation of symptoms until death, which was one criterion of efficacy, was achieved in 58 patients (43.6%). With regard to individual symptoms, PVS was effective for abdominal distention in 94 of 131 patients (71.8%), anorexia in 37 of 87 (42.5%), and nausea/vomiting in 5 of 10 (50%).

Median follow-up period was 41 (range, 1–481) days and was continued until death in 115 (86.5%) patients. Median time to symptom palliation was 2 (range, 1–9)

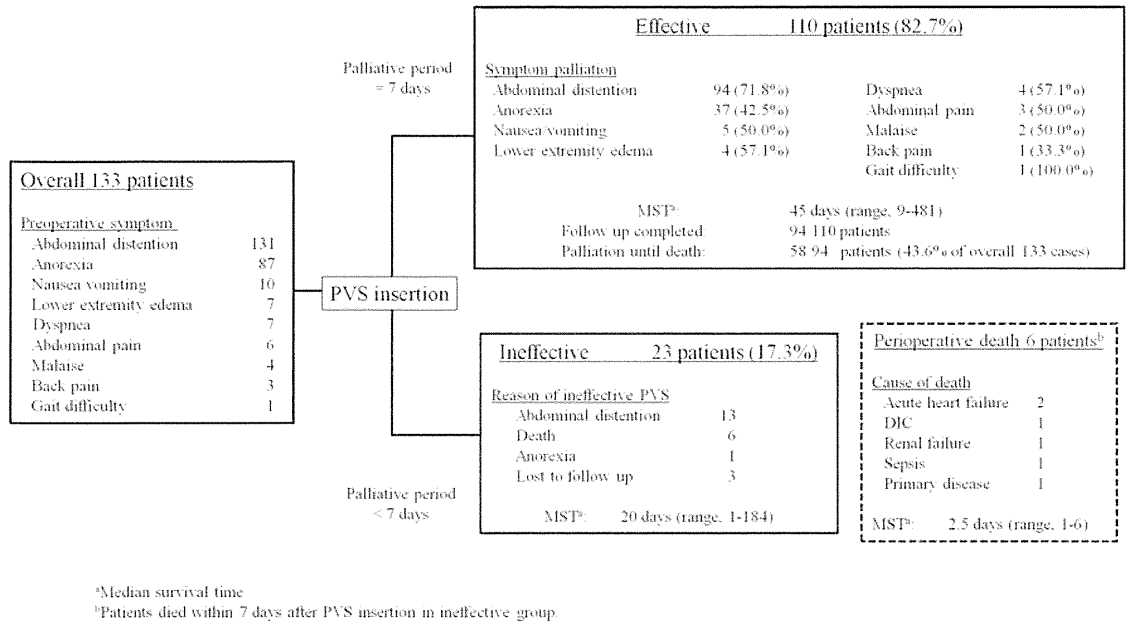


Fig. 1 Efficacy and safety of PVS insertion

days, median duration of palliation was 26 (range, 1–330) days, median duration of hospitalization was 17 (range, 1–130) days, and median survival time was 41 (range, 1–481) days.

At 7 days after PVS placement, mean abdominal girth and body weight decreased significantly (decrease ratio: −6.2% and −3.2%; $P < 0.001$), and no significant change was seen in performance status ($P = 0.342$).

Adverse Events

The profile of nonhematologic AEs, except for primary tumor progression, is listed in Table 2. Sixty patients (45.1%) demonstrated 85 AEs over grade 2, of whom 44 patients developed AEs of grade 3 or higher. Six patients died within 7 days after PVS placement (Fig. 1). Preoperative serum creatinine level was 3.9 mg/dl in the patient who died of renal failure. After 7 days, fatal AEs (grade 5) except for primary tumor progression occurred in 11 patients, due to DIC in 3, GI bleeding in 3, and DIC with GI bleeding, GI bleeding with liver dysfunction, myocardial infarction, bowel perforation, pneumonitis in one patient each.

GI bleeding was found in 13 patients (9.8%): upper GI bleeding in 7 patients; lower GI bleeding in 2; upper and lower GI bleeding in 2; biliary tree bleeding in 1; and unknown origin in 1. Among these patients, observation or conservative therapy was selected in seven patients. Additionally, transfusion in four patients, endoscopic variceal ligation for esophageal varices in one, and embolization therapy using interventional radiological technique in one were performed. Clinical DIC was found in seven patients (5.3%), and five patients died of DIC. Grade 5 DIC and GI bleeding occurred in the same two patients. Abnormalities in coagulation without clinical symptoms (subclinical DIC) after PVS insertion were seen in 37 (27.8%) patients, but they did not progress to clinical DIC. Other severe nonhematologic AEs that appeared in more than one patient included sepsis (3.8%), bowel obstruction (3.8%), acute heart failure/pulmonary edema (3%), venous thrombosis (2.3%), pleural effusion (2.3%), respiratory failure (2.3%), fever (1.5%), and liver dysfunction/failure (1.5%).

Regarding grade 2 or higher AEs involving hematologic and other laboratory data, a total of 98 patients (73.7%) demonstrated 189 AEs (Table 3). Anemia was the most frequent AE, developing in 71 (53.4%) patients. This occurred within 7 days in 88.7% of these patients, and the change in grade was 2 or less in 97.2%.

Patency and Function of the PVS

PVS dysfunction (recurrence of symptoms) was observed in 60 (45.1%) patients (Fig. 2). PVS imaging findings by chamber shuntography, Doppler ultrasound, or radionuclide scanning revealed occlusion in 11 patients and patency in 19 (Fig. 2). Of these 60 patients, paracentesis was required in 22. Ten patients underwent a secondary intervention involving the PVS, nine of whom achieved symptom palliation.

Factors Associated with Safety and Efficacy

Subgroup analyses were performed for preexisting abnormalities in laboratory data, primary tumor site, and ascites

Table 2 Adverse events

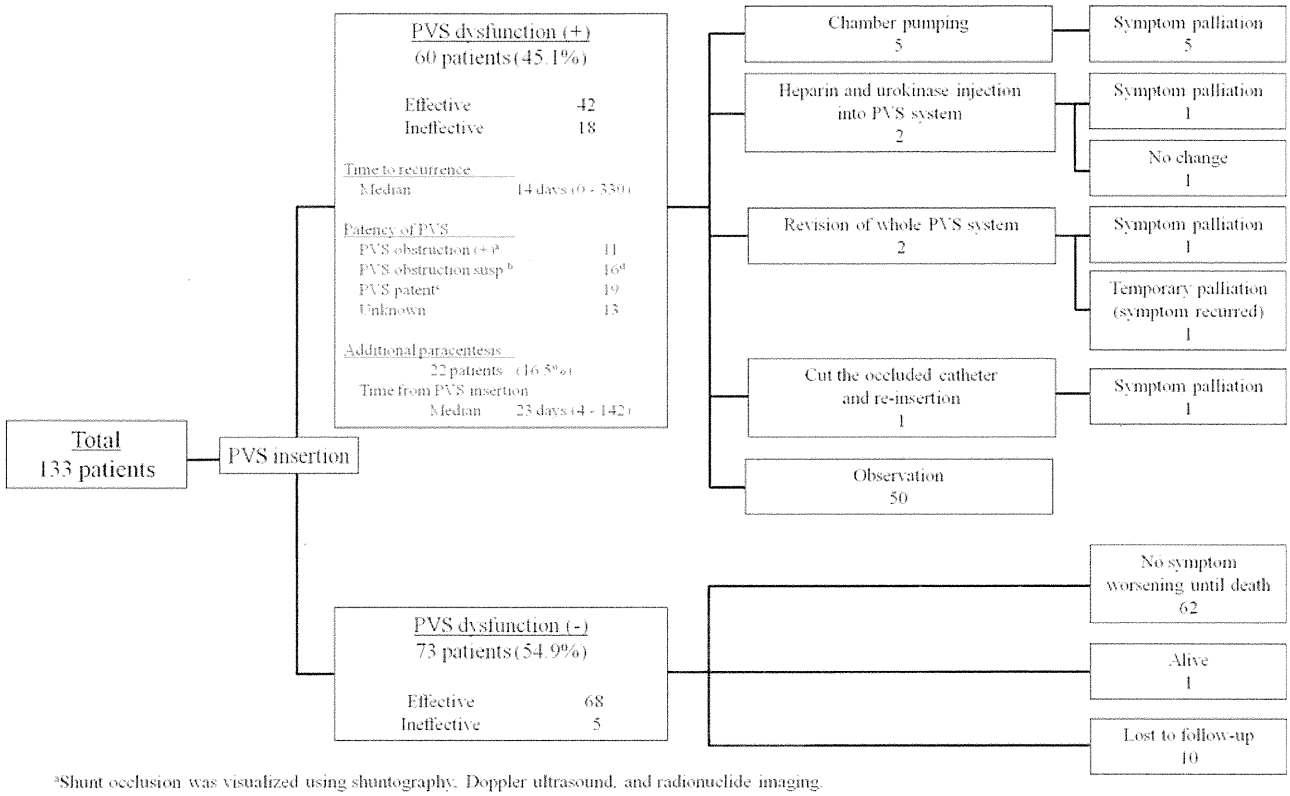
Adverse event	Overall	%	Days to onset (range)	Grade ≥3	%
Any	60 pts	45.1		44	33.1
GI bleeding	13	9.8	10 (2–28)	11	8.3
Fever	11	8.3	1.9 (0–6)	2	1.5
Venous thrombosis	8	6	4 (2–17)	3	2.3
Pulmonary embolism	1	0.8	15	1	0.8
Clinical DIC	7	5.3	2 (1–7)	7	5.3
Pleural effusion	6	4.5	7 (3–11)	3	2.3
Respiratory failure	3	2.3	2 (0–3)	3	2.3
Pneumonitis	1	0.8	42	1	0.8
Sepsis	5	3.8	5 (2–51)	5	3.8
Bowel obstruction	5	3.8	24 (3–123)	5	3.8
Bowel perforation[a]	1	0.8	36	1	0.8
Nausea	1	0.8	6	1	0.8
Acute heart failure/pulmonary edema	4	3	0.5 (0–2)	4	3
Myocardial infarction	1	0.8	41	1	0.8
Cerebrovascular ischemia	1	0.8	40	1	0.8
Liver dysfunction/failure	2	1.5	10.5 (1–20)	2	1.5
Abdominal pain	1	0.8	20	1	0.8
Renal failure	1	0.8	1	1	0.8
Hyperglycemia	1	0.8	10	1	0.8
Diarrhea	3	2.3	1	–	–
Wound dehiscence	2	1.5	Unknown	–	–
Wound infection	2	1.5	17 (17)	–	–
Fatigue	1	0.8	1	–	–
Edema	1	0.8	3	–	–
Pneumothorax	1	0.8	0	–	–
Hypotension	1	0.8	1	–	–
Rigors/chills	1	0.8	1	–	–

[a] Bowel perforation was thought to be unrelated to PVS insertion

Table 3 Laboratory data adverse events

	No.	%	Change in grade[a] after PVS				Days from PVS placement		
			+1	+2	+3	+4	1	2–7	8–14
Any	98 patients	73.7							
Leukopenia	6	4.5	0	4	1	1	1	4	1
Anemia	71	53.4	43	26	2	–	48	15	8
Thrombocytopenia	12	9	1	7	2	2	3	6	3
Hypoalbuminemia	26	19.5	26	–	–	–	10	6	10
Fibrinogen, decreased	8	6	–	3	4	1	2	4	2
Bilirubin, increased	17	12.8	10	7	–	–	9	2	6
ALT, increased	11	8.3	7	4	–	–	1	4	6
AST, increased	16	12	10	5	1	–	6	5	5
Creatinine, increased	4	3	4	–	–	–	1	1	2
Hypernatremia	1	0.8	–	–	1	–	–	–	1
Hyponatremia	6	4.5	–	5	1	–	–	2	4
Hyperkalemia	4	3	1	3	–	1	–	–	4
Hypokalemia	7	5.3	–	3	4	–	5	2	–

[a] Grade was defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3



[a]Shunt occlusion was visualized using shuntography, Doppler ultrasound, and radionuclide imaging.
[b]Shunt occlusion was suspected for the cause of symptom recurrence clinically, although shunt occlusion was not visualized.
[c]Shunt patency was confirmed by imaging.
[d]For the cause of shunt dysfunction, one case of fibrin sheath formation in superior vena cava or subclavian vein and 1 case of tumor growth with encasement of peritoneal catheter was suspected.

Fig. 2 Patency and PVS function

characteristics, with additional analysis for the duration of symptom palliation and survival time. Of these, grade 2 or higher elevated serum creatinine ($P = 0.014$) and bloody ascites ($P = 0.045$) at baseline were significantly associated with a shorter duration of palliation (4 weeks or less; Table 4). Patients with gynecologic tumors had a shorter duration of symptom palliation than other patients ($P = 0.047$), but these included more patients with bloody ascites ($P = 0.018$). Patients with gastric cancer had statistically significantly short survival times (4 weeks or less; $P = 0.046$), whereas those with a grade 2 or greater decrease in serum albumin demonstrated a tendency to shorter duration of symptom palliation, albeit that this was not statistically significant ($P = 0.053$; Table 4).

Discussion

In this study, we investigated experience in a number of institutions with radiologically inserted Denver PVS in 133 patients with malignant ascites. PVSs were effective in 110 (82.7%) patients with malignant refractory ascites, and the median duration of symptom palliation was 41 days. Technical success was achieved in all patients without any major procedure-related AEs. These findings are consistent with previous reports of radiological insertion of PVSs (62–87.5%), confirming the feasibility and safety of radiological insertion of a PVS in patients with refractory malignant ascites [3, 21–23].

Our findings also confirmed previous results that the onset of symptom improvements was rapid [22]. Consistent with this, however, PVS insertion may result in rapid changes in circulatory dynamics as well as the rapid introduction of various agents present in ascites into the circulation. Although causality has not been clarified and a range of contributing factors may be present, the high rates of major AEs seen in the present and previous studies [2, 4, 6, 9–11, 15, 19–24] remain important considerations, and emphasize the importance of pre-procedural evaluation of general patient status, including cardiac and renal functions, and meticulous postprocedural management for 48 h to detect DIC or other AEs [1, 4].

The clinical effectiveness rate of PVS placement in our patients with malignant ascites of 82.7% is comparable to those of previous reports [1, 2, 4, 8, 12, 19, 23, 25]. In our study, PVS placement was particularly effective for

Table 4 χ^2 test analysis of preoperative variables and duration of symptom palliation/survival time

Variable	*N*	Grade[a]	*N* (%)	Duration of symptom palliation		*P* value	Duration of survival time		*P* value
				≥4 weeks (*n* = 64)	<4 weeks (*n* = 69)		≥4 weeks (*n* = 89)	<4 weeks (*n* = 44)	
Primary tumor	133								
Colorectal cancer			33 (24.8)	21 (32.8)	12 (17.4)	0.063	27 (30.3)	6 (13.6)	0.059
Gastric cancer			25 (18.8)	8 (12.5)	17 (24.6)	0.117	12 (13.5)	13 (29.5)	0.046[b]
Pancreatic cancer			21 (15.8)	13 (20.3)	8 (11.6)	0.254	17 (19.1)	4 (9.1)	0.216
Liver/bile duct cancer			16 (12)	8 (12.5)	8 (11.6)	1	12 (13.5)	4 (9.1)	0.653
Breast cancer			10 (7.5)	6 (9.4)	4 (5.8)	0.651	7 (7.9)	3 (6.8)	1
Ovarian cancer			9 (6.8)	3 (4.7)	6 (8.7)	0.566	5 (5.6)	4 (9.1)	0.701
Gynecologic cancer			12 (9)	4 (6.3)	8 (11.6)	0.44	7 (7.9)	5 (11.4)	0.733
Ascites	133								
Clear			71 (53.4)	32 (50.0)	39 (56.5)	0.562	48 (53.9)	23 (52.3)	1
Bloody			20 (15)	5 (7.8)	15 (21.7)	0.045[c]	8 (9)	12 (27.3)	0.012[b]
Chylous			9 (6.8)	7 (10.3)	2 (2.9)	0.134	7 (7.9)	2 (4.5)	0.726
Serous			90 (67.7)	39 (60.9)	51 (73.9)	0.158	56 (62.9)	34 (77.3)	0.142
Mucinous			9 (6.8)	4 (6.3)	5 (7.2)	1	6 (6.7)	3 (6.8)	1
Abnormal LD	*N*			(*n* = 63)	(*n* = 69)		(*n* = 88)	(*n* = 44)	
Leukocytosis	132	>2	3 (2.3)	2 (3.2)	1 (1.4)	0.936	3 (3.4)	0 (0)	0.536
				(*n* = 63)	(*n* = 69)		(*n* = 88)	(*n* = 44)	
Anemia	132	>2	72 (54.5)	34 (54)	38 (55.1)	1	48 (54.5)	24 (54.5)	1
		>3	17 (12.9)	10 (15.9)	7 (10.1)	0.471	11 (12.5)	6 (13.6)	1
				(*n* = 63)	(*n* = 67)		(*n* = 88)	(*n* = 42)	
Creatinine, increased	130	>1	55 (42.3)	24 (38.1)	31 (46.3)	0.444	36 (40.9)	19 (45.2)	0.781
		>2	17 (13.1)	3 (4.8)	14 (20.9)	0.014[b]	9 (10.2)	8 (19.0)	0.264
				(*n* = 62)	(*n* = 64)		(*n* = 86)	(*n* = 40)	
Hyponatremia	126	>1	79 (62.7)	35 (56.5)	44 (68.8)	0.214	53 (61.6)	26 (65)	0.868
		>3	24 (19)	11 (17.7)	13 (20.3)	0.888	17 (19.8)	7 (17.5)	0.954
				(*n* = 61)	(*n* = 66)		(*n* = 86)	(*n* = 41)	
Hypoalbuminemia	127	>2	98 (77.2)	42 (68.9)	56 (84.8)	0.053	63 (73.3)	35 (85.4)	0.196
		>3	7 (5.5)	3 (4.9)	4 (6.1)	1	5 (5.8)	2 (4.9)	1

[a] Grade was defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3

[b] $P < 0.05$ with χ^2 test

LD laboratory data

abdominal distention, although anorexia was not sufficiently palliated. Various pathophysiologic mechanisms other than ascites may play a role in anorexia, including effects intrinsic to the tumor itself, gastrointestinal obstruction, and AEs from the PVS.

Body weight and abdominal girth were significantly reduced 7 days after PVS insertion, which objectively demonstrates the efficacy of PVSs. A previous report recommended measuring body weight and abdominal girth to evaluate PVS efficacy [9]; however, measurement of abdominal girth is not particularly reproducible because the measurement may depend on the observer or position of the patient, which is sometimes difficult to do in patients at end of life. The efficacy of PVS should be evaluated based on subjective changes in symptoms, taking into consideration that PVS insertion is a palliative intervention.

Patients with gastrointestinal malignancies have shorter life expectancy than those with gynecological malignancies [1, 8–10, 15, 26]. Consistent with this, survival time in patients with gastric cancer in this study was significantly shorter than that for other patients, which was probably due to the disease itself. Considering that symptom palliation may improve QOL, the poor prognosis of the primary disease should not be overly emphasized in evaluating indications for PVS placement. Our study did not demonstrate improvements in performance status (Fig. 1), which also has been reported previously [11].

Shunt dysfunction, a frequent AE in previous studies, was observed in 45.1% of our patients [2, 6, 9, 13, 15, 19, 23, 25]. Causes of shunt dysfunction include mechanical obstruction, such as a kink in the catheter, venous thrombosis in the subclavian or central vein, and a fibrin sheath around the catheter [2, 4, 5, 8, 15, 20, 23, 24]. These causes are sometimes revealed by imaging using ultrasonography, shuntography, or contrast-enhanced computed tomography [20, 23], and function often can be recovered by additional minimally invasive intervention. Imaging procedures to determine the cause of shunt dysfunction should be undertaken.

In our study, abnormalities in coagulation without clinical symptoms (subclinical DIC) after PVS insertion were seen in 37 (27.8%) patients, and only 7 patients (5.3%) developed clinical DIC. These results are comparable to previous studies [1–4, 7, 10–12, 15, 19]. The reported incidence of clinical DIC varies, ranging from 0–33%, and the relevant coagulopathy has not been identified [1, 3, 9–12, 21, 22, 24]. The detection of clinical DIC after PVS placement using laboratory data only appears to be difficult.

Decreases in serum creatinine and BUN levels were seen in the postoperative period. Possible reasons include increases in circulatory blood volume and renal blood flow, which result in increased urine volume [14]. The progression of anemia after PVS insertion may be due to the inflow of ascites into the circulatory system, with resulting transient dilution of blood cells [4, 7, 11, 14]. Severe AEs, such as DIC and GI bleeding, which may occur after PVS insertion [5, 19, 21, 22], should be considered in these patients.

In the subgroup analysis, we found that renal dysfunction was associated with a short duration of symptom palliation. Furthermore, acute renal failure was a cause of early postprocedural death. Bieligk et al. [9] reported that preoperative renal function is predictive of prognosis after PVS insertion. These findings highlight the importance of assessing renal function before PVS placement. In particular, careful consideration should be given to determining the placement in patients with insufficient urine volume, who may be unable to tolerate the rapid increase in plasma volume immediately after PVS insertion [7–9, 15].

A low preoperative serum albumin level was associated with a short duration of symptom palliation. A possible explanation is that the low colloid osmotic pressure of this condition may lead to extravascular transudation of water and impaired production of a sufficient urine volume in response to increased circulatory blood volume after PVS, resulting in unsatisfactory reduction in ascites volume.

Other prognostic factors associated with a short duration of symptom palliation included bloody ascites, gynecologic primary tumor, and a high white blood cell (WBC) count before PVS placement. Bloody ascites is known to be an unfavorable factor and probably results from thrombosis in the PVS system [1, 15]. Gynecological malignancies tend to have a short palliation period, and most of the patients with gynecological malignancies in this study had bloody ascites.

Several limitations of the study warrant mention. First, given its retrospective case series design, evaluation of AEs, duration of symptom palliation, and survival time may have been biased. Furthermore, because it was a multicenter study, the methods used to evaluate these variables were likely not uniform. Unlike previous studies, our study consisted of a large number of patients from multiple institutions; particularly given the difficulty of prospective evaluation of palliative treatment for terminal patients, the present study may provide helpful information for clinical decision making in PVS placement for patients with refractory malignant ascites. Second, the appropriateness of the timing of our evaluation of PVS efficacy, at 7 days after the procedure, is uncertain. Additionally, if ascites was removed with PVS insertion, it can palliate symptoms separately from an effect of the PVS. The various studies on PVS for malignant ascites conducted to date did not establish a definite postprocedural period for evaluation but were rather limited to survival time and shunt dysfunction rate or shunt patency time [3, 5, 6, 9–12, 14, 15, 19–24]. Although no consensus on how to evaluate PVS efficacy has been established, our procedure of determining efficacy 7 days after PVS insertion is reasonable, given that survival time in patients with malignant ascites is limited. In addition, patients with advanced malignancies may deteriorate rapidly, due to the primary disease and other pathophysiologies (e.g., bowel obstruction, renal dysfunction) further confounding evaluation. This difficulty highlights the current lack of knowledge on assessing outcomes in end-of-life decision making and underscores the need for further study on this area.

In conclusion, the present study suggests that radiological PVS insertion is technically feasible and yields an adequate rate of symptom palliation in patients with symptomatic refractory ascites. Although shunt dysfunction is a frequent AE, recovery of function may be obtained with appropriate additional interventions. Because changes in laboratory data, including subclinical DIC, and cardiac dysfunction or other nonhematologic AEs may occur after PVS insertion, preoperative evaluation of cardiac and renal function and postoperative management of systemic conditions are essential to preclude severe AEs after PVS.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

See Table 5.

Table 5 Five Japanese institutions enrolled in this study

Institution	No. of enrolled patients ($N = 133$)	%
Aichi Cancer Center Hospital and Research Institute	29	21.8
Iwate Medical University Hospital	23	17.3
The Cancer Institute Hospital of Japanese Foundation for Cancer Research	20	15
National Cancer Center	26	19.5
Shizuoka Cancer Center	35	26.3

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Case Report

Hepatic Arterial Infusion Chemotherapy Prior to Standard Systemic Chemotherapy in Patients with Highly Advanced Unresectable Liver Metastases from Colorectal Cancer: A Report of Three Patients

Toshihiro Iguchi[a]*, Hitoshi Idani[b], Shinya Asami[b], Hisashi Endo[c], Yoshitaka Inaba[d], Yasuaki Arai[e], and Susumu Kanazawa[f]

Departments of [a]Radiology, [b]Surgery, and [c]Medical Oncology, Fukuyama City Hospital, Fukuyama, Hiroshima 721-8511, Japan, [d]Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan, [e]Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo 104-0045, Japan, and [f]Department of Radiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

We administered hepatic arterial infusion chemotherapy (HAIC) prior to FOLFOX to three patients with unresectable liver metastases from colorectal cancer. The patients' disease state was found to be highly advanced based on both computed tomography findings and liver function tests. The treatment strategy included an initial administration of HAIC to control liver metastases and improve liver function in order to facilitate the subsequent safe administration of FOLFOX without drug loss. As the HAIC regimen, 1,000 mg/m^2 of 5-FU was administered weekly by continuous 5-h infusion after performing laboratory investigations through an implanted port-catheter system. After 3 HAIC cycles administered over 3 consecutive weeks, the mean alkaline phosphatase levels decreased from 969.3 IU/l to 422 IU/l due to shrinkage of the liver metastases. Thereafter, FOLFOX without drug loss could be safely initiated for all patients. Two patients succumbed 488 and 333 days after HAIC was initiated; the third patient is still alive and has been followed-up for 1215 days. The combined use of HAIC and standard systemic chemotherapy could be a feasible and efficacious treatment in highly advanced cases of liver dysfunction.

Key words: colorectal cancer, hepatic arterial infusion chemotherapy, liver metastasis, port-catheter system

Systemic chemotherapy is usually the preferred treatment for unresectable liver metastases from colorectal cancer [1]. With recent advances in new drugs and the standardization of chemotherapy regimens for colorectal cancer, patient survival has been prolonged. Currently, FOLFOX (5-fluorouracil (5-FU)/leucovorin with oxaliplatin) and FOLFIRI (5-FU/leucovorin with irinotecan) are used as standard chemotherapy regimens [1, 2], and the median survival with these regimens is reported to be 20.6-21.5 months [2]. The addition of bevacizumab to these regimens further prolongs the survival [3]. However, in patients with highly advanced unresectable liver metastases, it is vital but very difficult to select the initial treatment regimen because it is often impossible to perform further treatment if the initial treatment

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*Corresponding author. Phone:+81-84-941-5151; Fax:+81-84-941-5159
E-mail:iguchi@ba2.so-net.ne.jp (T. Iguchi)

fails. Fakih MG has reported that three patients with metastatic colon cancer and severe liver dysfunction were treated by FOLFOX [4]. After the initial improvement in disease status, disease progression was noted in 2 patients at 4 and 7 months from the inception of therapy, while treatment was ongoing in the third patient at 5 months.

Repeated hepatic arterial infusion chemotherapy (HAIC) through an implanted port-catheter system is an effective therapy for unresectable liver metastases from colorectal cancer [5-7]. Compared to systemic chemotherapy, HAIC increases the possibility of tumor response and might improve liver function by shrinking liver metastases [7-10]; however, a comparison was not made between HAIC with FOLFOX and HAIC with FOLFIRI in those reports. The administration of high doses of 5-FU, which is used as an HAIC regimen in Japan, is particularly associated with a good tumor response and patient-survival rates, and has fewer and less severe adverse events [5, 11].

We administered HAIC prior to FOLFOX to 3 patients with highly advanced unresectable liver metastases from colorectal cancer; further treatment in the event of failure of the initial treatment was considered impossible in these patients. The treatment strategy involved an initial administration of HAIC to control liver metastases and improve liver function in order to facilitate the subsequent safe administration of FOLFOX without drug loss. This strategy was formulated on the basis of the high tumor-response rate and the fewer and less severe adverse effects associated with HAIC.

Case Report

This report was approved by our institutional review board, and written informed consent was obtained from each patient.

Between November 2006 and April 2007, 69 patients were admitted to undergo initial therapy for colorectal cancer at our institution. Of those patients, three consecutive patients (2 men and 1 woman; mean age, 56.0 years) had highly advanced synchronous liver metastases. In all three patients, liver metastases were judged to be unresectable due to liver dysfunction and multiple metastases in both the right and left lobes of the liver. The primary cancer sites were the descending colon (n = 1), sigmoid colon (n = 1), and rectum (n = 1). The patient characteristics are shown in Table 1.

Our treatment strategy was as follows. First, surgical resection of primary colorectal cancer was performed. Next, we repeatedly administered HAIC through an implanted port-catheter system as the initial treatment for liver metastases, considering our patients' advanced state of disease, as indicated by both the computed tomography (CT) findings (Aquilion 64; Toshiba, Tokyo, Japan) and the results of liver function tests. As the HAIC regimen, 1,000 mg/m^2 of 5-FU was administered weekly by continuous 5-h infusion after performing laboratory investigations [5]. The levels of alkaline phosphatase (ALP) were more than 2.5 times the upper limit of normal (ULN; 875 IU/l) due to the liver metastases; thus, this value was used as an index for HAIC continuation. HAIC was administered weekly to control the liver metastases until the ALP levels were within 1.5 times the ULN (525 IU/l). Thereafter, FOLFOX without drug loss was started.

The patients underwent curative surgical resection of primary colorectal cancer and lymph node metastases. Metastases in N1 lymph nodes were observed in 2 patients; 1 patient showed N2 lymph node metastases. Extrahepatic metastases in the lung, bone, brain,

Table 1 Patients Characteristics

Case	Age (y.o)/ Sex	Primary Site	Liver Function before starting HAIC/after HAIC					Tumor Marker before starting HAIC/after HAIC		Liver Metastases Volume (%)[§] before starting HAIC/after 3 times HAIC	Follow-up Period(d)	Alive/ Dead
			ALP (IU/l)	LDH (IU/l)	AST (IU/l)	ALT (IU/l)	T-BIL (mg/dl)	CEA	CA19-9			
1	58/F	D-colon	971/349	710/303	37/23	27/8	0.4/0.5	3,258.9/389.3	11,184/1,302	42.8/33.9	333	Dead
2	55/M	S-colon	927/401	1,045/312	59/27	54/27	0.4/0.4	65.4/42.1	70/56	53.6/45.2	1,215	Alive
3	55/M	rectum	1,010/516	714/303	32/22	26/22	0.7/0.6	92.8/23.6	13/1.4	31.9/22.3	488	Dead

D-colon, descending colon; S-colon, sigmoid colon; HAIC, hepatic arterial infusion chemotherapy; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-BIL, total bilirubin. [§]Liver metastases volume (%) was esitmated using the following formula: liver metastases volume (ml)/[normal liver parenchymal volume (ml) + liver metastases volume (ml)] × 100.

and peritoneum were not observed in the patients.

Radiological placement of the port-catheter system was performed at 14, 20, and 21 days after surgery (Fig. 1). All placement procedures were performed in an angiography suite under local anesthesia. Prior to catheter placement, the patients underwent angiography and arterial embolization to allow arterial mapping and prevent extrahepatic influx of 5-FU; these procedures were performed using a 4-French angiographic catheter (Clinical Supply, Gifu, Japan) that was inserted from the left femoral artery. The extrahepatic arteries that branched from the hepatic artery such as the right gastric artery and the posterior superior pancreatoduodenal artery were embolized with microcoils (Trufill; Cordis, Miami Lakes, FL, USA) through a 2.1-French microcatheter (Sniper 2; Clinical Supply) inserted coaxially. Next, a 4-French angiographic catheter was inserted from the right femoral artery and advanced to the common hepatic artery via the celiac artery. An indwelling catheter (W spiral catheter; PIOLAX, Yokohama, Japan) with a side hole was then inserted using the catheter-exchange method. The catheter tip was inserted into the gastroepiploic artery such that the side hole was placed in the common hepatic artery. The gastroepiploic artery around the tip of the indwelling catheter was embolized using microcoils through a microcatheter inserted coaxially via the angiographic catheter inserted from the left femoral artery. Finally, the proximal end of the indwelling catheter was connected to a port implanted in the subcutaneous pocket created in the right thigh. No complications such as hematoma, infections, and hepatic artery injuries and occlusions occurred during or after the procedure.

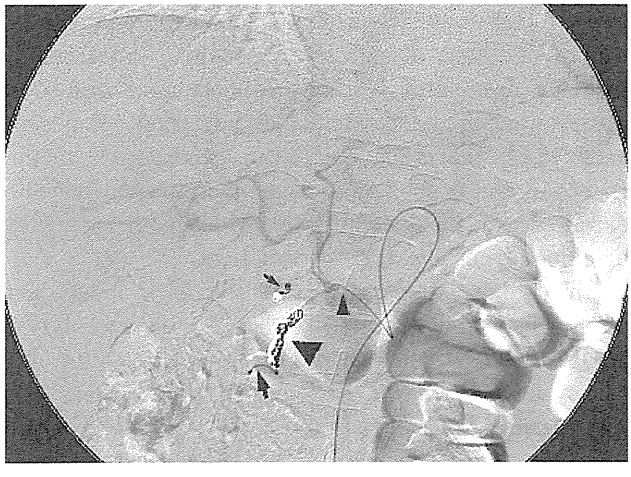

Fig. 1 Arteriogram via port shows that all hepatic arteries are well-visualized. The catheter tip is inserted into the gastroepiploic artery (arrow). The side hole is placed into the common hepatic artery (small arrowhead). To prevent an extrahepatic influx of anticancer agents, the gastroduodenal artery (arrowhead) and right gastric artery (small arrow) are embolized with microcoils.

On the following day, digital subtraction angiography and CT were performed during injection of a contrast medium through the implanted port-catheter system to confirm that the catheter was not dislodged and to ensure that the entire liver was perfused adequately [12]. Thereafter, HAIC was administered through the port-catheter system. After the administration of 5-FU, this system was flushed and filled with 2 ml heparin solution (1,000 IU/ml). The results of the liver function tests of the patients before starting HAIC were as follows: mean ALP, 969.3 IU/l; mean lactate dehydrogenase (LDH), 823 IU/l; mean aspartate aminotransferase (AST), 42.7 IU/l; mean alanine aminotransferase (ALT), 35.7 IU/l; and mean total bilirubin (T-BIL), 0.5 mg/dl (Table 1). In all patients, the percentage of liver involvement with metastases exceeded 30% (mean, 42.8%), as determined using contrast-enhanced CT and a workstation (Ziostation; Ziosoft, Tokyo, Japan).

After starting HAIC, no adverse events were observed in any of the patients. The ALP levels and other liver function parameters decreased to < 1.5 times the ULN after 3 HAIC cycles administered over 3 consecutive weeks (Table 1). The results of the liver function tests performed after HAIC administration were as follows: mean ALP, 422 IU/l; mean LDH, 306 IU/l; mean AST, 24 IU/l; mean ALT 19 IU/l; and mean T-BIL, 0.5 mg/dl. Though three patients had stable disease, according to RECIST criteria [13], on contrast-enhanced CT, the percentage of liver involvement with metastases decreased (mean, 33.8%) (Fig. 2). Thereafter, FOLFOX without drug loss could be safely initiated for all patients, and the chemotherapy regimen was changed to FOLFIRI after FOLFOX had failed.

FOLFOX and FOLFIRI were administered a total of 12 times in case 1 and 11 times in case 3, respectively. The systemic chemotherapy failed to produce a positive response in these patients and could not be continued. Their performance status worsened be-

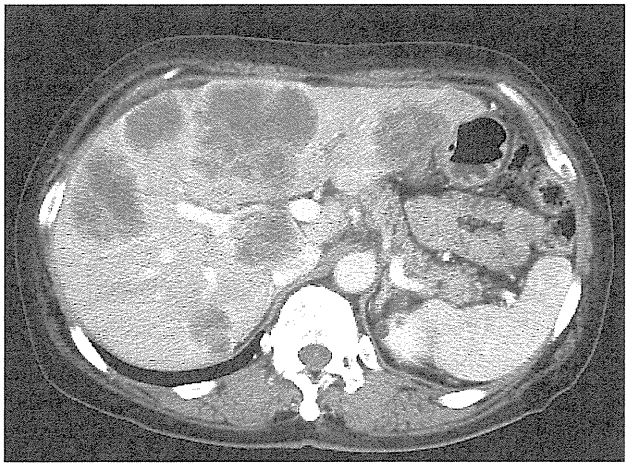

Fig. 2A A 58-year-old woman with multiple liver metastases from cancer of the descending colon. Contrast-enhanced CT image obtained before the initiation of HAIC showing multiple unresectable liver metastases in both the right and left lobes of the liver.

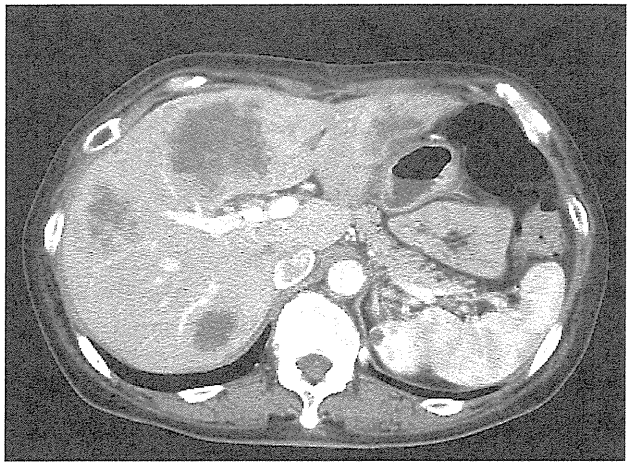

Fig. 2B Contrast-enhanced CT image obtained after 3 HAIC cycles showing smaller liver metastases. The percentage of liver involvement with metastases improved from 42.8% to 33.9%.

cause their liver metastases progressed; HAIC was therefore readministered to both patients (16 times for one patient and 6 times for the other). The case 1 patient succumbed to the disease 488 days after HAIC was initiated: case 3 succumbed after 333 days.

In case 2, FOLFOX and FOLFIRI were administered a total of 24 times. Afterward, another systemic chemotherapy was administered because he failed to respond to these treatment regimens. At present, he is still alive and has been followed-up for 1215 days.

Discussion

HAIC for unresectable liver metastases from colorectal cancer was evaluated in 3 different meta-analyses [8-10]; compared with systemic chemotherapy, HAIC was associated with a superior response rate, but it did not improve patient survival. Conversely, in Japan, it has been reported that the response rate of patients to HAIC is 78%, and the median survival time is 25.8 months after intermittent HAIC with high doses of 5-FU [5]. It seems that these positive results were an outcome of a number of contributing factors, including appropriate techniques for port-catheter system placement and evaluation of drug distribution using CT during arteriography [5, 12]. Additionally, this regimen has the advantage of being considerably cheaper than the current standard systemic chemotherapy and usually has fewer and less severe adverse events than systemic chemotherapy [5].

On the basis of its superior tumor response and the possibility of improved liver function, HAIC was administered prior to systemic chemotherapy in order to treat advanced unresectable liver metastases. HAIC was useful because it improved liver function in our patients by shrinking liver metastases and enabling the safe administration of standard systemic chemotherapy without drug loss. A positive relationship between dose intensity and response rate has been documented in the treatment of advanced colon cancers [14]; therefore, a lower prospective tumor response and a shorter prospective survival may be expected with the administration of chemotherapy with drug loss from the start of treatment.

In all our patients, because the ALP levels had already been elevated to more than 2.5 times the ULN, HAIC was continued until this level was within 1.5 times the ULN; this ALP value ($\geq$ 2.5 times the ULN) came under grade 2 of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Elevated ALP ($\geq$ 2 times the ULN) is one of the factors associated with poor prognosis in metastatic colorectal cancer patients treated with 5-FU, oxaliplatin, or oxaliplatin [15, 16]. In our patients, the mean ALP levels decreased from

969.3IU/l to 422IU/l due to shrinkage of the liver metastases after only 3 consecutive HAIC cycles. Standard systemic chemotherapy was initiated after the HAIC-mediated improvement in liver function because the abovementioned meta-analysis evaluation revealed that HAIC does not improve patient survival over that achieved with systemic chemotherapy [8-10].

It might have been possible to safely initiate systemic chemotherapy in our patients without prior HAIC. However, if standard systemic chemotherapy had failed because it could not be completed (*e.g.*, incomplete administration or administration with drug loss), further treatment might have been impossible because of the progression of advanced liver metastases. The combined use of HAIC and standard systemic chemotherapy in patients with highly advanced liver metastases seems to effectively facilitate the administration of subsequent systemic chemotherapy without drug loss. In order to prove that our treatment strategy may be a viable treatment option for such patients, it is necessary to accumulate more cases in multicenter and to determine the success rates and/or responses as well as possible adverse events.

In conclusion, we safely administered FOLFOX without drug loss in 3 patients with highly advanced unresectable liver metastases from colorectal cancer after the improvement in liver function caused by the shrinkage of liver metastases due to prior HAIC.

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ORIGINAL ARTICLE

A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial)

Tetsuya Hamaguchi · Kuniaki Shirao · Atsushi Ohtsu · Ichinosuke Hyodo · Yasuaki Arai · Hiroya Takiuchi · Hirofumi Fujii · Motoki Yoshida · Hiroshi Saito · Tadamichi Denda · Wasaburo Koizumi · Hiroaki Iwase · Narikazu Boku · Gastrointestinal Oncology Study Group of Japan Clinical Oncology Group

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Abstract
Background Preclinical studies have shown that mitomycin C (MMC) acts synergistically with irinotecan (CPT-11). In this phase II study, we evaluated the efficacy and toxicity of MMC/CPT-11 therapy as second-line chemotherapy for patients with fluoropyrimidine-resistant advanced gastric cancer.
Methods Eligible patients had evidence of tumor progression despite prior treatment with fluoropyrimidine-based regimens or had relapsed within 6 months after completion of therapy with adjuvant fluoropyrimidines. Treatment consisted of MMC (5 mg/m^2) and CPT-11 (150 mg/m^2) administered i.v. every 2 weeks. The primary endpoint was the response rate (RR). Our hypothesis was that this combination therapy was efficacious when the lower boundary of the 95% confidence interval (CI) of the RR exceeded 20% of the threshold RR.

T. Hamaguchi (✉) · K. Shirao
Division of Gastrointestinal Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: thamaguc@ncc.go.jp

K. Shirao
Department of Medical Oncology, Faculty of Medicine, Oita University, Oita, Japan

A. Ohtsu
National Cancer Center Hospital East, Research Center for Innovative Oncology, Chiba, Japan

I. Hyodo
Department of Internal Medicine, National Hospital Organization Shikoku Cancer Center, Ehime, Japan

Y. Arai
Department of Diagnostic Radiology, Aichi Cancer Center Hospital, Aichi, Japan

H. Takiuchi · M. Yoshida
Cancer Chemotherapy Center, Osaka Medical College Hospital, Osaka, Japan

H. Fujii
Department of Medical Oncology, Tochigi Cancer Center, Tochigi, Japan

M. Yoshida
Department of Gastroenterology, Kumamoto Regional Medical Center, Kumamoto, Japan

H. Saito
Department of Gastroenterology, Yamagata Prefectural Central Hospital, Yamagata, Japan

T. Denda
Division of Hematology/Oncology, Chiba Cancer Center Hospital, Chiba, Japan

W. Koizumi
Department of Internal Medicine, Kitasato University East Hospital, Kanagawa, Japan

H. Iwase
Department of Gastroenterology, National Hospital Organization Nagoya Medical Center, Aichi, Japan

N. Boku
Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Results Between April 2002 and July 2003, 45 eligible patients were registered and analyzed. Among the 45 patients, 40 (89%) had previously received chemotherapy for metastasis and 24 (53%) had a performance status (PS) of 0. Thirteen partial responses were obtained among the 45 patients, resulting in an overall RR of 29% (95% CI, 16–42%). The median time to progression was 4.1 months, and the median survival time was 10 months, with a 1-year survival rate of 36%. Grade 4 neutropenia was observed in 29% of the patients, whereas febrile neutropenia occurred in 9%. The incidence rates of grade 3 nausea and diarrhea were 13 and 2%, respectively.

Conclusions Although this study did not achieve the per-protocol definition of activity, the progression-free survival and overall survival appeared to be promising, with acceptable tolerability. Thus, MMC/CPT-11 therapy as second-line chemotherapy for fluoropyrimidine-resistant advanced gastric cancer presents a potential treatment option in patients with a good PS.

Keywords Gastric cancer · Mitomycin-C · Irinotecan · Fluoropyrimidine-resistant · Second-line chemotherapy

Introduction

Gastric cancer is the most common malignancy in Asian countries, with approximately 50,000 deaths in Japan annually [1]. The treatment of choice for this malignancy is primary tumor resection. In patients with curatively resected stage I–III gastric cancer, the 5-year survival proportion is >50%; however, this proportion remains at <10% in stage IV or recurrent disease. Randomized trials have demonstrated that fluorouracil-based regimens improve survival proportions in patients with advanced gastric cancer (AGC) compared with best supportive care (BSC) alone as first-line chemotherapy [2–4]. Moreover, combination chemotherapy results in superior outcomes compared with monotherapy. In Japan, the efficacy and toxicity of the combination of an oral fluoropyrimidine (S-1) and platinum was previously evaluated in the phase III SPIRITS (S-1 plus cisplatin vs. S-1 alone for first-line treatment of AGC) trial. S-1 plus cisplatin resulted in superior overall survival (OS) compared with S-1 alone [hazard ratio (HR), 0.77; 95% confidence interval (CI), 0.61–0.98%; $P = 0.04$], with an impressive median OS of 13.0 months [5]. The Japan Clinical Oncology Group (JCOG) 9912 trial (5-fluorouracil [FU] alone vs. S-1 alone vs. irinotecan [CPT-11] plus cisplatin [CDDP] combination for the first-line treatment of AGC) was also conducted in Japan. S-1 showed significant noninferiority for progression-free survival (PFS) and OS compared with 5-FU alone; however, CPT-11 plus CDDP showed no significant superior effects on PFS and OS compared with 5-FU alone [6]. In Japan, S-1 plus CDDP combination therapy is considered the standard first-line treatment for AGC.

Thuss-Patience et al. [7] reported at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) that CPT-11 monotherapy significantly prolonged OS compared with BSC as second-line chemotherapy. Although that report was the first randomized phase III study investigating second-line chemotherapy for AGC, no objective responses were observed. Thus, a consensus regarding the standard regimen for second-line chemotherapy has not yet been obtained.

Many AGC patients who failed to respond to first-line chemotherapy showed symptoms of pain, weight loss, or nausea due to their progressive disease. Thus, the induction of a tumor response is as important as delaying tumor progression for as long as possible. Patients who received combination chemotherapy showed higher response rates than those who received single-agent chemotherapy alone. Therefore, combination chemotherapy is preferable to single-agent chemotherapy for palliation. Moreover, combination chemotherapy may prolong OS compared with single-agent chemotherapy alone.

CPT-11 is a potent topoisomerase I inhibitor and is effective against AGC. In a phase II trial, the response rate (RR) to CPT-11 alone was 16% in previously treated AGC patients [8]. The administration of a CDDP and CPT-11 combination in AGC patients resulted in a higher RR and longer time to progression (TTP) [9–11]. As mentioned above, CDDP/CPT-11 did not significantly prolong OS over 5-FU, but induced a significantly higher RR than 5-FU in the JCOG9912 trial [6]. A 5-FU, leucovorin (LV), and CPT-11 combination produced a higher RR and longer TTP than CDDP/CPT-11 in AGC patients [12]. In another randomized phase III trial, 5-FU/LV/CPT-11 showed a trend to have superiority in TTP over CDDP/5-FU (5.0 vs. 4.2 months, respectively; HR, 1.23; 95% CI, 0.97–1.57%; $P = 0.088$), and a better safety profile [13]. These results support the finding that CPT-11 is active against AGC.

Mitomycin C (MMC) is also effective against AGC. Preclinical studies have shown that a MMC and CPT-11 combination synergistically inhibits tumor growth in vitro [14]. This is due to the possible induction of topoisomerase I gene expression by MMC, thereby increasing tumor cell sensitivity to CPT-11. A phase I/II study of this combination recommended an MMC dose of 5 mg/m^2 and a CPT-11 dose of 150 mg/m^2 administered biweekly [15]. The dose-limiting toxicities of this combination regimen when administered at 10 mg/m^2 for MMC and 150 mg/m^2 for CPT-11 were grade 4 neutropenia with or without febrile neutropenia and grade 3 diarrhea. The overall RR was 50% (15/30 patients), and 5 of 14 patients (36%) with prior chemotherapy showed a partial response (PR). We

previously showed that MMC and CPT-11 combination chemotherapy was effective and well tolerated in patients with fluoropyrimidine-resistant metastatic colorectal cancer; the RR, median TTP, and median survival time (MST) were 34% (95% CI, 20–49%), 4.2 months, and 11.9 months [16], respectively.

These results led us to conduct the present phase II clinical trial to investigate the efficacy and toxicity of MMC/CPT-11 therapy in patients with AGC resistant to a fluoropyrimidine-containing regimen in the JCOG0109-DI study.

Patients and methods

Eligibility

A patient was considered eligible if there was evidence of a refractory response to one prior chemotherapy containing fluoropyrimidine, which was any of the following types of history of chemotherapy:

1. In the case of unresectable gastric cancer, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine, or confirmed immediately after the discontinuation for any reason other than disease progression.
2. In the case of recurrent gastric cancer, recurrence detected within 24 weeks from the last dose of postoperative adjuvant chemotherapy containing fluoropyrimidine, and further chemotherapy was not administered after recurrence.
3. In the case of recurrent gastric cancer detected 25 weeks after the last dose of postoperative adjuvant chemotherapy, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after the discontinuation for any reason other than progression.
4. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the effect of neoadjuvant chemotherapy containing fluoropyrimidine was stable disease, progressive disease, or not evaluated, and recurrence was identified after curative resection. Chemotherapy was not performed following recurrence.
5. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the chemotherapy effect was a complete response or PR, and progression was detected during one chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after discontinuation for any reason other than progression.

Disease progression and the nonefficacy of neoadjuvant chemotherapy were believed to represent clinical failure by treating physicians. Elevation of the level of a tumor marker, such as carcinoembryonic antigen (CEA), was not accepted as adequate evidence for treatment failure. Documentation of evidence of a refractory response by computed tomography (CT) and magnetic resonance imaging was required.

For the other eligibility criteria, patients must be between 20 and 75 years of age, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate baseline bone marrow function [white blood cell (WBC) and platelet counts $\geq$4,000 and 100,000/mm^3, respectively], adequate hepatic function (serum bilirubin level $\leq$1.5 mg/dl and both serum aspartate aminotransferase and alanine aminotransferase levels $\leq$100 U/l), adequate renal function (serum creatinine level $\leq$1.5 mg/dl), adequate respiratory function (arterial partial pressure of oxygen $\geq$70 mmHg), and have received no blood transfusion within 14 days before enrollment. All patients were required to have $\geq$1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Patients were excluded if they had symptomatic brain metastasis, symptomatic ascites and/or pleural effusion, previous history of MMC or CPT-11 chemotherapy, preexisting diarrhea of >4 times/day, suspicion of existing active bleeding which needed blood transfusion at 14 days prior to registration in this study, or a high risk of a poor outcome due to concomitant nonmalignant disease (i.e., cardiac, pulmonary, renal, or hepatic disease; poorly controlled diabetes; or uncontrolled infection), or severe psychiatric disease. Pregnant or lactating women were excluded.

The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating hospital. All patients gave their written informed consent.

Treatment plan

The treatment schedule consisted of one MMC dose (5 mg/m^2, bolus injection), then CPT-11 (150 mg/m^2, 90-min i.v. infusion) repeated every 2 weeks, as described previously [16]. All patients were treated on an outpatient basis and were recommended to receive both a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone to prevent emesis. Subsequent treatment cycles were withheld until the WBC and platelet counts were $\geq$3,000 and 100,000/mm^3, respectively; diarrhea was $\leq$grade 1; and there were no infection symptoms such as pyrexia ($\geq$38°C). When the treatment course was delayed within 8 days from the planned schedule, the same dosage levels as those used previously were administered. When the treatment course was delayed beyond 8 days and within 21 days from the planned schedule, one lower dose level (CPT-11 level -1,

125 mg/m^2; level -2, 100 mg/m^2) than the previous level was administered, while the MMC dose was maintained at 5 mg/m^2. The treatment course was discontinued if it could not be started within 21 days from the planned schedule. When grade 4 leukopenia or thrombocytopenia occurred in a previous treatment course causing a delay within 8 days, the same dosage levels as those used previously were administered. When grade 2 diarrhea or higher was observed in a preceding course, dosages 1 level lower than the previous dosages were administered.

Treatment was repeated until disease progression or when severe toxicity was observed. The total MMC dose was limited to 50 mg/m^2, to prevent cumulative toxicity (e.g., interstitial pneumonia and hemolytic uremic syndrome), and thereafter CPT-11 alone was administered. This indicates that the maximum number of total treatment cycles of MMC/CPT-11 therapy is 10 cycles.

Evaluation of response and toxicity

During protocol treatment, the patient's signs and symptoms, as well as laboratory data (i.e., WBC with differential counts, liver function tests, urea nitrogen, creatinine, electrolytes, and urinalysis) were examined biweekly. Adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria version 2.0. Tumor response was assessed by CT every 4 weeks. The response of measurable and evaluable disease sites was assessed by each investigator in accordance with RECIST, and then reviewed by central review at the group meeting.

Statistical analysis

For this study, the primary endpoint was the RR and the secondary endpoints were OS and toxicity. Here, we used the standard design (attained design) of the Southwest Oncology Group [17]. Based on reports of RRs of 22% with paclitaxel alone [18] and 16% with CPT-11 alone [8] in the second-line setting and an RR of 36% in phase I/II studies of MMC/CPT-11 therapy [15], the RR in this study was expected to be within 30–40% for a future phase III trial. Here, the required sample size was calculated to be 45 patients, with the following parameters: $\alpha = 0.05$, $\beta = 0.10$, threshold response rate $(p_0) = 20\%$, and expected response rate $(p_a) = 40\%$. Interim analysis was performed when the number of enrolled subjects reached 25. The significance level for the interim analysis was set as $P < 0.02$. Furthermore, when the number of patients who reached RR was <5 at the interim analysis, the study was prematurely discontinued because it would have been difficult to exceed the expected RR despite further patient accumulation, or because it would not be worth advancing this regimen to an ensuing clinical study. When the study was not completed after the interim analysis, the number of patients was increased to 45 in order to allow the null hypothesis (threshold RR) to be tested. When α was <0.05, or when the lower boundary of the 95% CI of the RR exceeded 20% of the threshold RR, this therapy was considered to be efficacious as chemotherapy for gastric cancer patients who had received pretreatment. That is, when ≥16 of 45 patients had a PR, this study was judged to be positive. Here, patient enrollment was not temporarily discontinued.

OS was defined as the time from the registration date to death as a result of any cause. PFS was defined as the time from the registration date to the first documentation of objective tumor progression. Time-to-event and OS data were summarized using the Kaplan–Meier method.

Results

Patient population and study treatment

Between April 2002 and July 2003, 45 patients (33 men, 12 women) from 12 hospitals were enrolled and analyzed. Table 1 shows the demographic data, baseline disease, and regimens of prior chemotherapy. The median age was 64 years (range 36–75), and all patients had a good PS of 0 or 1. Eighteen patients (40%) had diffuse-type gastric cancer. As for prior chemotherapy, 40 (89%) had previously received chemotherapy for metastasis, whereas 5 had received adjuvant chemotherapy. In the first-line chemotherapy, 33 patients (73%) had received 5-FU or S-1 alone.

In all 45 patients, MMC/CPT-11 therapy was administered 281 times, and the median number of doses was 6 (range 1–10). Of the 45 patients, 10 (22%) completed the planned 10 chemotherapy cycles. In the remaining 35 patients, the reasons for treatment discontinuation were disease progression in 25, toxicity in 6, patient's refusal in 3, and death in 1. Regarding CPT-11 administration, 11 patients (24%) required -1 level dose reduction and 8 (18%) required -2 level reduction because of leukopenia and thrombocytopenia.

Efficacy

Of the 45 patients, 13 showed a PR (RR: 28.9%; 95% CI, 15.6–42.1%) (Table 2). The median PFS was 4.1 months (Fig. 1). The median OS time was 10.1 months (95% CI, 7.3–12.6 months), and the 1-year survival rate was 38% (Fig. 2).

Because the lower boundary of the 95% CI of the RR (15.6%) did not exceed the threshold RR (20%), the

Table 1 Patient characteristics ($n = 45$)

Age (years)	
Median	64
Range	36–75
Gender	
Male	33
Female	12
ECOG performance status	
0	24
1	21
2	0
Borrmann macroscopic type of primary cancer	
0	1
1	1
2	17
3	18
4	5
Unknown	3
Histological type	
Intestinal	25
Diffuse	18
Unclassified	2
Prior chemotherapy	
5-FU alone	18
S-1 alone	15
S-1 + CDDP	6
MTX + 5-FU	2
Others	4

ECOG Eastern Cooperative Oncology Group, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *MTX* methotrexate

Table 2 Evaluation of response ($n = 45$)

Tumor response	Patients	
	n	% (95% CI)
Complete response	0	0
Partial response	13	28.9 (15.6–42.1)
Stable disease	17	37.7 (23.6–51.9)
Progressive disease	14	31.1 (17.6–44.6)
Not evaluated	1	4.4 (0–6.5)
Survival	Months (95% CI)	
PFS	4.1 M (2.5–5.7)	
OS	10.1 M (7.3–12.6)	

CI confidence interval, *PFS* progression-free survival, *OS* overall survival

MMC/CPT-11 combination as second-line chemotherapy could not be definitively concluded as efficacious for further investigation.

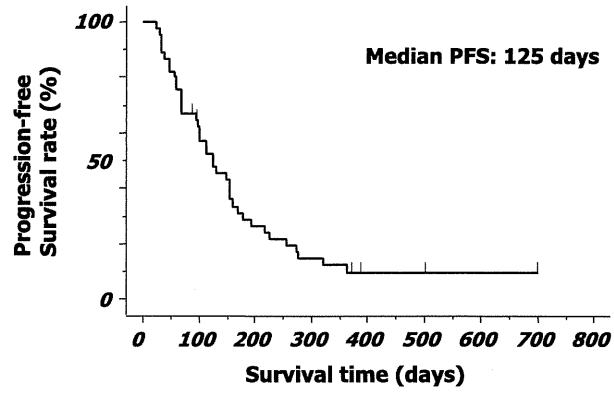

Fig. 1 Kaplan–Meier estimates of progression-free survival (*PFS*) rates

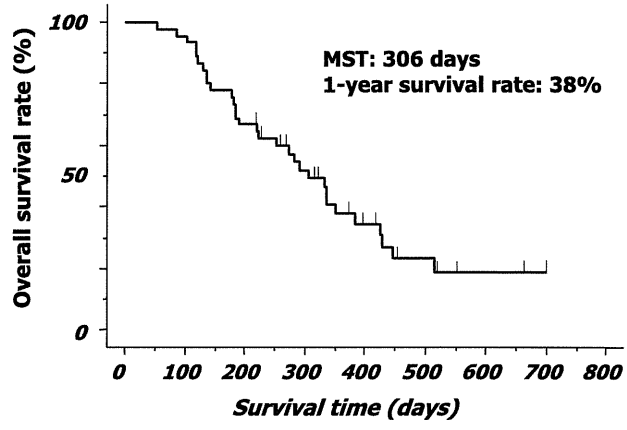

Fig. 2 Kaplan–Meier estimates of overall survival. *MST* Median survival time

Toxicity

The toxicities of the MMC/CPT-11 therapy are summarized in Table 3, with myelosuppression and gastrointestinal toxicity as major toxicities. Grade 3 and 4 neutropenia occurred in 24 and 29% of the patients, respectively, whereas grade 3 and 4 thrombocytopenia developed in only 7%. As for the nonhematological toxicities, the incidence rate of grade 3 diarrhea was 2%, and nausea and vomiting were mild. Early death due to interstitial pneumonitis within 30 days from the last chemotherapy occurred in 1 patient, which was considered by the JCOG Data and Safety Monitoring Committee to have been possibly related to the treatment.

Discussion

In second-line chemotherapy for AGC, the potential benefits remain unclear because of the few prospective studies that have been conducted thus far. These trials demonstrated that

Table 3 Grade 2–4 adverse events according to NCI-CTC ver. 2.0 ($n = 45$)

	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Hematological WBC	24	8	5	29
Neutrophils	10	11	13	53
Hb	25	3	3	13
Platelets	1	2	1	7
Febrile neutropenia	0	4	0	9
Non-hematological Anorexia	13	11	0	24
Nausea	11	6	0	13
Diarrhea	4	1	0	2
Infection with grade 3/4 neutropenia	0	2	0	4
Infection without neutropenia	4	2	0	4

NCI-CTC National Cancer Institute-Common Toxicity Criteria, *Hb* hemoglobin

the RRs to second-line chemotherapy in phase II trials for gastric cancer were similar to those observed for other cancers which are more commonly treated after the failure of first-line chemotherapy. Furthermore, 2 Japanese randomized trials (i.e., SPIRITS [5] and JCOG9912 [6]) achieved a median OS of 13.0 months despite the relatively short median PFS of about 4–6 months. Although both JCOG9912 and our previous phase III study (JCOG9205 [19]) utilized 5-FU continuous infusion (c.i.) and 5-FU/CDDP, the obtained median PFS was 2 months and the OS in JCOG9912 was much longer than that in JCOG9205. In the present study, the proportion of patients who received second-line chemotherapy was >70%, which is higher than that obtained in our previous study (53%). The results of previous phase II trials consistently suggest that patients treated with second-line chemotherapy may survive longer than those provided with BSC, although the survival benefit of the second-line chemotherapy has not yet been clarified.

According to the 26 prospective phase II studies reported in the literature, obtained using the search expressions "gastric cancer" and "second-line chemotherapy" in PubMed, the average and median RRs were 18.8 and 20.0% (0–34.6%), respectively [18, 20–44]. Although the present study did not disprove the null hypothesis about RR, it is suggested that MMC/CPT-11 therapy with an RR of 28.9% may possess some antitumor activity as second-line chemotherapy.

As for survival, the present study showed a median survival time of 10.1 months (95% CI, 7.3–12.9 months), and a 1-year survival proportion of 38%. These data are similar to those obtained in the first-line chemotherapy setting and appeared to be better than those obtained using several other regimens, showing a survival period of 3.5–13 months compared with the reported median survival period of 7–10 months in untreated patients. However, it is very difficult to compare phase II studies due to differences in patient background and subsequent therapy. One reason for improved survival may be good clinical selection of a patient. At the baseline evaluation, the median age of the patients in the present study was 64 years (range, 36–75), and all the patients had a good PS of 0 or 1. Another reason for the improved survival was the high proportion of tumor stabilization (66.7%) after the administration of the MMC/CPT-11 regimen. Therefore, it is considered that MMC/CPT-11 therapy may provide some survival benefit.

The toxicity of the MMC/CPT-11 regimen can be considered tolerable and manageable. Hematological toxicity was within the expected range, including grade 4 neutropenia, observed in 13 patients (29%) and grade 3 febrile neutropenia in 4 patients (9%). According to a Japanese prospective pharmacogenomic study of CPT-11, homozygotes and double heterozygotes of *6 and *28 (*6/*6, *28/*28 and *6/*28) were significantly associated with severe neutropenia. The UGT1A1 gene test prior to receiving this regimen may be useful to decide the starting dose of CPT-11 or to decide whether the patient should receive CPT-11 and MMC combination chemotherapy or CPT-11 monotherapy [45]. Although treatment-related death was observed in 1 patient (2%) in the present study, the occurrence of adverse events was similar to that in JCOG9911-DI, a phase II study of the same regimen for colon cancer; thus, MMC/CPT-11 therapy was considered tolerable. In the present study, the proportion of patients with toxicity was similar to that of patients where MMC/CPT-11 therapy was used as second-line treatment against colorectal cancer [16].

From the above results, the present phase II study of MMC/CPT-11 therapy for FU-based chemotherapy-refractory gastric cancer is judged to be negative on the basis of the decision rule defined in the protocol. This may be due to the threshold RR being set very high owing to the lack of data as the basis for setting the threshold level and expected RR, because of the small number of phase II studies of second-line treatment when this protocol was developed. In fact, the RR cannot be considered poor compared with that in phase II studies performed in other treated patients (as shown in Table 2), with a favorable