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.
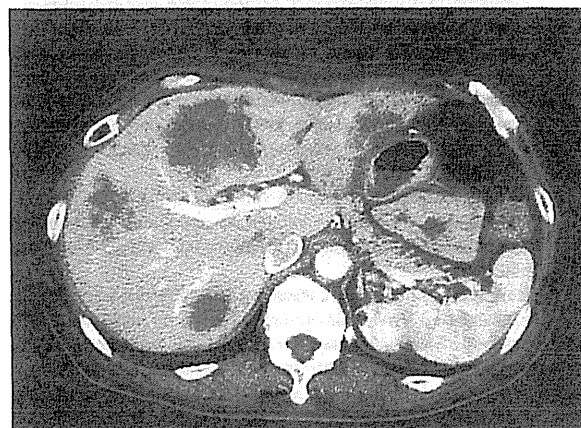

Fig. 2B   Contrast-enhanced CT image obtained after 3 HAIC cycles showing smaller liver metastases. The percentage of liver involvement with metastases improved from 42.8% to 33.9%.

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

969.3 IU/l to 422 IU/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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Phase II Clinical Study on Stent Therapy for Unresectable Malignant Colorectal Obstruction (JIVROSG-0206)

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Purpose: A phase II study of stent therapy for unresectable malignant colorectal obstruction was conducted to ascertain the clinical efficacy, safety, and procedural feasibility.

Methods: Inclusion criteria comprised unresectable obstruction of the rectum or sigmoid colon; no other apparent stenosis; performance status by Eastern Cooperative Oncology Group $\leq$3; and maintained major organ function. The treatment protocol was to place an uncovered metal stent through the anus in an obstructive portion under x-ray fluoroscopic guidance. The patients were followed for 4 weeks after therapy, and the degree of improvement in subjective symptoms lasting $\geq$2 weeks was assessed as effective when the patient was decompressed with stent, or ineffective when not decompressed. Rate of clinical efficacy was defined as the proportion of effective cases.

Results: The participants of the study comprised 33 patients (13 men and 20 women; mean age, 60 y). Rate of procedure completion was 97.0% (32/33). Treatment was effective in 27 patients, ineffective in 4, and unassessable in 1, yielding a clinical efficacy rate of 81.8% (27/33). Death owing to underlying disease (n=3), stent removal owing to anal pain (n=1), and occlusion at another location (n=1) were noted. No recurrences were seen among clinically effective cases. Adverse reactions included grades 2 to 3 diarrhea (n=12), pain (n=5), bleeding (n=1), and dysuria (n=1), but no grade 4 adverse reactions or treatment-related deaths were identified.

Conclusions: Stent therapy for unresectable malignant colorectal obstruction is effective, safe, and feasible.

Key Words: malignant colorectal obstruction, metal stent, palliation, supportive care, phase II study

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In patients with acute colorectal obstruction owing to unresectable malignancy, colostomy or a transanal ileus tube has been used to decompress the obstructed bowel as a palliative treatment.[1–3] However, considering their general status, poor prognosis, and quality of life, a less-invasive treatment is desirable as an alternative mode of palliation.

Since self-expanding metal stents were first reported to relieve acute colorectal obstruction in 1991,[4] colorectal stenting has found increasing acceptance for use in palliation, because the technique is less invasive than colostomy and does not lower the quality of life compared with the placement of an ileus tube over a long period.[5–9] This approach has been used not only for palliation, but also as a bridge to surgery for potentially resectable colorectal tumors with obstruction.[10,11]

Few prospective clinical trials have been conducted to ascertain the safety and efficacy of colorectal stenting. On the basis of this background, this multicenter phase II study of stent therapy for patients with unresectable colorectal obstruction was conducted by Japan Interventional Radiology in Oncology Study Group (JIVROSG).

MATERIALS AND METHODS

Study Design and Patient Eligibility

We designed a multicenter phase II clinical study to evaluate the clinical efficacy of stent therapy for unresectable malignant colorectal obstruction. Clinical efficacy was evaluated as the primary end point and the incidence and severity of adverse events and procedural feasibility were evaluated as secondary end points.

This study was carried out for patients with malignant obstruction in whom stent was used as a definitive therapy and not as a bridge to future surgical intervention. As inclusion criteria, unresectable malignant colorectal obstruction had to satisfy the following conditions: the presence of stricture or obstruction of the rectum or sigmoid colon from unresectable malignant tumor with symptoms of acute large bowel obstruction; range of colorectal stricture or obstruction extending between the area 5 cm from the anal verge and the level of the iliac crest as seen from contrast enema and including cases in which the rectum or sigmoid colon was resected earlier; no apparent stenosis in the gastrointestinal tract on the oral side from the target colorectal obstruction from a clinical perspective; maintenance of principal organ function (no apparent heart failure, platelet count $\geq$50,000/mm², total serum bilirubin level $\leq$3.0 mg/dL, and serum creatinine $\leq$2.0 mg/dL); performance status according to the Eastern Cooperative Oncology Group classification of $\leq$3; expectation of patient survival >4 weeks; and written informed consent obtained from patients before participation.

Patients in whom a colostomy was desirable, in whom a high possibility of resection of the rectum or sigmoid colon obstruction or a need for preoperative decompression for final surgery was observed, or in whom bleeding from the rectum or sigmoid colon obstruction required hemostatic procedures, were excluded.

The study was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating hospitals.

Treatment Protocol and Evaluation Method

In this study, stent therapy for unresectable malignant colorectal obstruction was defined as the placement of an uncovered metal stent in the obstructed portion of the rectum or sigmoid colon caused by an unresectable malignant tumor, using a transanal technique under x-ray fluoroscopic guidance (Fig. 1).

Contrast enema was performed using a water-soluble contrast medium, and the length of the stricture or obstructed portion of the rectum or sigmoid colon was measured. A guide wire was inserted through the anus far enough to pass through the obstructed portion under x-ray fluoroscopic guidance. A stent introducer was placed over the guide wire and inserted to place the stent in the target location. Concurrent use of an endoscope was allowed, and no regulations were enforced regarding whether balloon dilation was performed before or after stent placement.

As colorectal stents are not approved in Japan, the stents used were the uncovered Ultraflex stent system (Boston Scientific, Natick, MA) for the esophagus (Fig. 2). Assuming some migration, selection of lengths ≥3 cm longer than the stricture was recommended. The length of this stent delivery catheter is restricted to 100 cm and the target area was limited to the rectum apart from a close region of the anus to preserve the anal function and the sigmoid colon.

A 4-week evaluation and observation period was established after the stent therapy, during which subjective and objective symptoms were checked, blood tests were conducted, and abdominal radiographs were taken the day after treatment and each week thereafter. Level of improvements in subjective symptoms on the day after treatment and on each
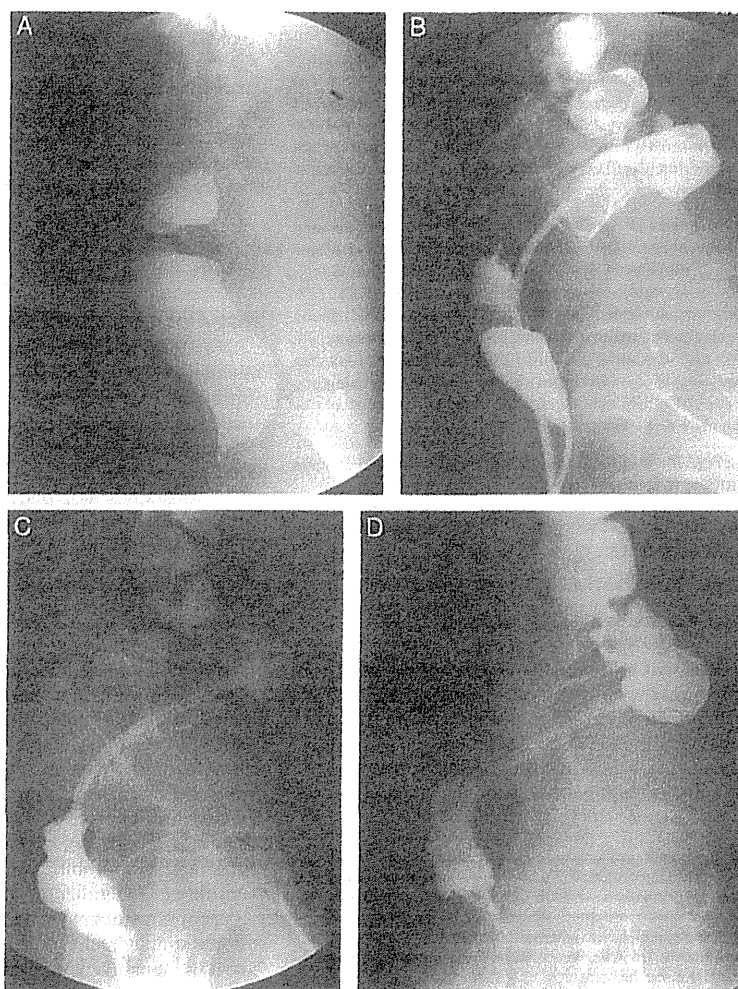
FIGURE 1. A 47-year-old woman who underwent rectal stenting for Schnitzler metastasis using an uncovered Ultraflex stent (length, 15 cm; diameter, 18 mm). A, Contrast enema using a water-soluble contrast medium showed that the rectum was completely obstructed. B, A catheter was passed through the obstructed portion and contrast medium was injected. C, A guide wire was inserted through the anus far enough to pass through the obstructed portion. A stent delivery catheter was placed over the guide wire under x-ray fluoroscopy. D, The stent was appropriately placed on the obstructed portion.
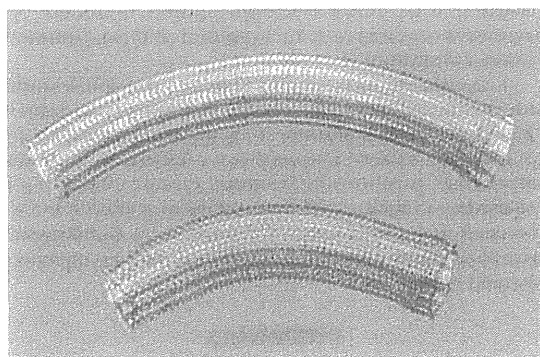
FIGURE 2. Uncovered Ultraflex esophageal stent.

subsequent week was evaluated. Treatment was considered to be "effective" in cases of improvement in defecation, gas elimination status, and abdominal symptoms for ≥ 2 weeks or "ineffective" when no improvement in symptoms was seen, whether the patient was decompressed with the stent or not decompressed. The rate of clinical efficacy was taken to be the proportion of effective cases compared with the total number of registered cases. Adverse reactions were assessed using National Cancer Institute-Common Toxicity Criteria (version 2.0). Procedural feasibility was assessed based on the rate of treatment protocol completion. The follow-up investigation was conducted after 4 weeks.

Statistics

When conducting a 1-sample binomial test for the number of cases in which severe adverse reactions or a need to assess the efficacy rate exist, the predicted value of complications for adverse reactions is 10%, and $\geq 30\%$ of cases with severe adverse reactions are inadmissible, 30 cases would be required under conditions of $\alpha = 0.05$, $\beta = 0.20$. For the efficacy rate, when the expected efficacy rate is taken to be 80% and the threshold efficacy rate to be 50%, 19 cases are required under conditions of $\alpha = 0.05$, $\beta = 0.20$. Accordingly, 30 cases were considered necessary in this study, and predicting a deviation from the protocol in 10% of these cases, the scheduled number of registered cases was 33.

RESULTS

The participants of the study comprised 33 patients who were enrolled between February 2003 and September 2007, all of whom satisfied the inclusion criteria. A patient summary is shown in Table 1

The rate of procedure completion was 97.0% (32/33), indicating the feasibility of the procedure. In 1 patient in whom the procedure failed, the obstructed portion was rigid and the stent delivery catheter could not be passed through. Table 2 shows the details of the procedure. No complications were seen accompanying the procedure. The clinical efficacy rate was 81.8% (27/33). Treatment was effective in 27 patients, ineffective in 4 patients, and unassessable in 1 patient because the effects could not be assessed for >2 weeks. The procedure failed in 1 patient. In the 27 patients in whom the procedure was clinically effective, no reobstruction was seen during the observation period. Confirmed events during the observation period were death from underlying disease in 3 patients

TABLE 1. Characteristics of the 33 Patients

Age (y)	
Median (range)	60 (34-84)
Sex	
Male	13
Female	20
ECOG performance status	
0	0
1	17
2	7
3	9
Earlier therapy	
None	23
Resection	10
Radiotherapy	5
Intrinsic stricture	
Primary rectosigmoid cancer	11
Recurrent rectosigmoid cancer	7
Extrinsic stricture	
Peritoneal cancer dissemination	13
Recurrent uterine cancer	2
Sricture length (cm)	
Mean (range)	7.8 (3-20)

ECOG indicates Eastern Cooperative Oncology Group.

(effective, n=2; unassessable, n=1), stent removal because of severe anal pain in 1 patient (ineffective, n=1), and gastrointestinal tract stenosis on the oral side in 1 patient (ineffective, n=1). Confirmed grades 2 to 3 adverse reactions were diarrhea in 12 patients (36.4%), pain in 5 patients (15.2%), bleeding in 1 patient (3.0%), and dysuria in 1 patient (3.0%). No grade 4 adverse reactions or treatment-related deaths were encountered. In the 27 patients who could be followed for 4 weeks after the stent placement, no stent movement beyond the obstructed portion was seen on abdominal radiography.

According to the follow-up investigation until November 2007, the median of a total follow-up period after the procedure was 78 days (3-1303 d). Finally, 4 patients were alive, 27 were dead, and 2 were censored because of transfer to another hospital. Cumulative median survival time after stent therapy was 91 days (95% confidence interval, 60-122 d) in all the 33 patients. In the 25 long-term effective cases over 4 weeks, reobstruction was seen in 4 cases on median 115 days after stent placement. In the reobstruction cases, stent replacement was performed in 2 cases and no reintervention was done in 2 others because of poor patient's condition.

TABLE 2. Stenting Procedures

Predecompression using transanal ileus tube	11
Procedure with endoscopy	13
Predilation using balloon	4
Stenting	
Success	32
Failure	1
No. stents	
1	28
2	4
Length of stent (cm)	
7	3
10	15
15	18

DISCUSSION

Since the report by Song et al[12] in 1991, stent therapy for gastrointestinal obstruction has been widely used, mainly for esophageal stenosis. In Japan, stent therapy was approved for malignant esophageal obstruction in 1996, and has been used as palliation for esophageal obstruction caused by malignant tumors and esophagobronchial fistula. Other than the esophagus, stents are used for gastric, duodenal, and colorectal obstruction,[13] and in other countries duodenal and colorectal stents are commercially available.[14]

Many reports have described the effectiveness of stents for colorectal obstruction, from palliation for unresectable obstruction to being a bridge to surgery for potentially resectable obstruction. In Japan, similar reports are occasionally seen, but the medical procedure of stent placement other than in the esophagus was not recognized, and colorectal stents that can be used in other countries have not yet been approved and thus cannot be used. Therefore, although some reports have suggested the use of such techniques, no prospective clinical trials have verified the safety and effectiveness of colorectal stents. This multicenter phase II clinical trial was aimed at confirming the clinical efficacy of stent therapy for unresectable malignant colorectal obstruction, using an esophageal stent that was one of the few gastrointestinal stents that could be obtained in Japan. At the time this study was conducted, the gastrointestinal stents that could be used were the Ultraflex stent (Ultraflex esophageal stent system; Boston Scientific, Natick, MA) and Z-stent (Cook-Z stents; William Cook Europe, Bjaeverskov, Denmark). The Ultraflex stent was available in both uncovered and covered types, but the Z-stent was available in covered types only. This study was restricted to uncovered stents only out of concern for migration,[15] and so was limited to the use of uncovered Ultraflex stents. In addition, as users were prohibited from modifying stent placement kits, the possible range of stent placement was limited by the length of the delivery system that was provided.[16] As a result, we used the stents for obstruction in the region from the rectum to the sigmoid colon.

In this study, the success rate for stent placement in the target area was 97%, indicating high procedural feasibility. Improvements of clinical symptoms were seen in 82% of enrolled patients, thus clinical efficacy was also good. However, even when stent placement was successful, 15.6% (5/32) of patients did not show improvement of clinical symptoms. This was similar to past reports.[8,17–19] Reasons for those unimproved patients were the existence of a separate stenosis on the oral side from the area of stent placement, decreased gastrointestinal function from widespread peritonitis carcinomatosis, and stent removal because of intense pain caused by stimulation of the stent edge on the lower rectum. As these causes cannot be accurately determined before stent placement, we recognize the difficulty of selecting only those patients who will show improvements in clinical symptoms. No complications were seen during stent placement, and adverse reactions such as diarrhea, pain, and bleeding after placement of the stent were similar to those in past reports.[8,17–19] Unacceptable stent migration completely beyond the obstructed portion was not seen within 4 weeks. No grade 4 adverse reactions, digestive tract perforations, or treatment-related deaths were encountered, and safety was judged to be within the acceptable range.

Limitations of this study include a lack of objectivity, as improvements in subjective symptoms were taken as the indicator of efficacy, and insufficient evidence for taking a period of 2 weeks for improvements in symptoms as indicative of effective treatment. Moreover, the stent used was an esophageal stent, and the length, diameter, flexibility, and expansive force may not be optimal for the treatment of colorectal obstruction.

In conclusion, these results indicated that this treatment method offers sufficient procedural feasibility and leads to a high level of improvement in symptoms, indicating that this treatment method should prove effective in alleviating symptoms in patients with terminal cancer with this kind of condition. In future, evaluations through clinical trials will be needed to assess whether this treatment could become a standard palliative treatment for patients showing symptoms of colorectal obstruction.

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CLINICAL INVESTIGATION

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

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Teruko Ueno · Kiyoshi Matsueda · Michihisa Moriguchi · Takahiro Tsushima

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

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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

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

Table 1 continued

Characteristic	No. of patients ($N = 133$)	%
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

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 ($n = 107$).

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)
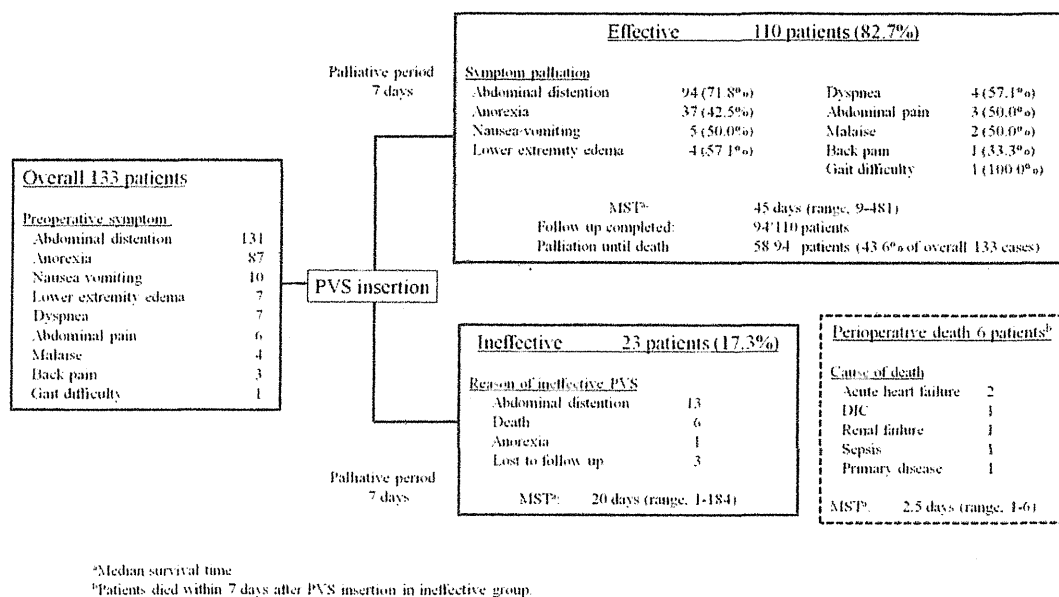
Palliative period
7 days

Overall 133 patients

Preoperative symptom
Abdominal distention   131
Anorexia   87
Nausea vomiting   10
Lower extremity edema   7
Dyspnea   7
Abdominal pain   6
Malaise   4
Back pain   3
Gait difficulty   1

PVS insertion

Effective   110 patients (82.7%)

Symptom palliation
Abdominal distention   94 (71.8%)   Dyspnea   4 (57.1%)
Anorexia   37 (42.5%)   Abdominal pain   3 (50.0%)
Nausea-vomiting   5 (50.0%)   Malaise   2 (50.0%)
Lower extremity edema   4 (57.1%)   Back pain   1 (33.3%)
                                        Gait difficulty 1 (100.0%)

MST*   45 days (range, 9-481)
Follow up completed: 94/110 patients
Palliation until death 58-94 patients (43.6% of overall 133 cases)

Ineffective   23 patients (17.3%)

Reason of ineffective PVS
Abdominal distention   13
Death   6
Anorexia   1
Lost to follow up   3

MST*   20 days (range, 1-184)

Perioperative death 6 patients[b]

Cause of death
Acute heart failure   2
DIC   1
Renal failure   1
Sepsis   1
Primary disease   1

MST*   2.5 days (range, 1-6)

Palliative period
7 days

*Median survival time
[b]Patients died within 7 days after PVS insertion in ineffective group

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

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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

Fig. 2 Patency and PVS function
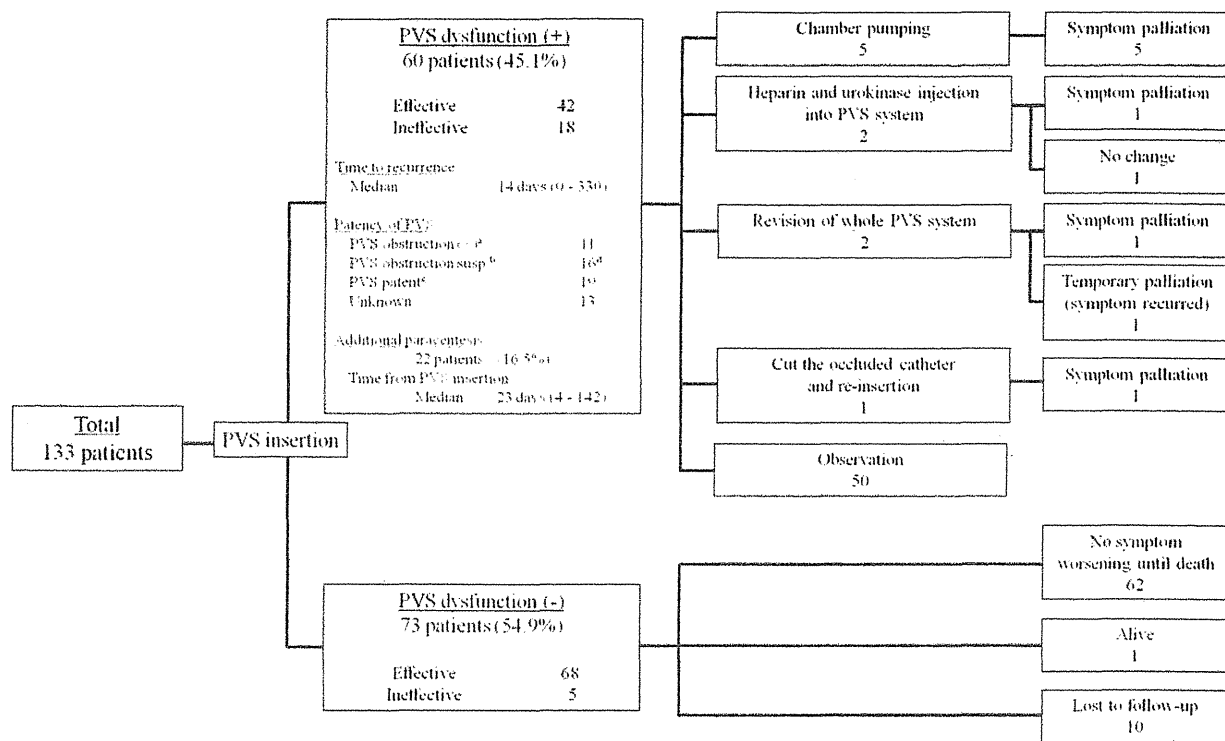
aShunt occlusion was visualized using shuntography, Doppler ultrasound, and radionuclide imaging.
bShunt occlusion was suspected for the cause of symptom recurrence clinically, although shunt occlusion was not visualized.
cShunt patency was confirmed by imaging
dFor the cause of shunt dysfunction, one 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.

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.

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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Original Article

Transcatheter Arterial Infusion Chemotherapy with a Fine-powder Formulation of Cisplatin for Advanced Hepatocellular Carcinoma Refractory to Transcatheter Arterial Chemoembolization

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Objective: The aim of this study was to assess the safety and efficacy of transcatheter arterial infusion chemotherapy using a fine-powder formulation of cisplatin for patients with advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization.
Methods: We retrospectively examined the data of 84 consecutive patients with transcatheter arterial chemoembolization-refractory hepatocellular carcinoma who underwent transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin. Cisplatin was administered at the dose of 65 mg/m^2 into the feeding artery of the hepatocellular carcinoma. The treatment was repeated every 4–6 weeks, until the appearance of evidence of tumor progression or of unacceptable toxicity.
Results: Of the 84 patients, one patient (1.2%) showed complete response and two patients (2.4%) showed partial response, representing an overall response rate of 3.6% (95% confidence interval, 0.7–10.1). Of the remaining, 38 patients (45.2%) showed stable disease and 41 (48.8%) showed progressive disease. The median overall survival, 1-year survival rate and median progression-free survival in the entire subject population were 7.1 months, 27% and 1.7 months, respectively. Major Grade 3 or 4 adverse events included thrombocytopenia in 12 patients (14%) and elevation of the serum aspartate aminotransferase in 33 patients (39%). The gastrointestinal toxicities were mild and reversible.
Conclusions: Transcatheter arterial infusion chemotherapy using a fine-powder formulation of cisplatin appears to have only modest activity, although the toxicity was also only mild, in patients with transcatheter arterial chemoembolization-refractory hepatocellular carcinoma.

Key words: hepatocellular carcinoma — transcatheter arterial infusion chemotherapy — cisplatin — transcatheter arterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is treated by one or more of a wide variety of treatment options available, depending on the tumor characteristics, including the number and size of tumors, and the presence/absence of tumor thrombosis and extrahepatic metastases (1,2). In patients with early-stage HCC, curative therapies can be applied, including resection, liver transplantation or local ablation therapy. However, the

prognosis of patients with HCC is still unsatisfactory, mainly because of the high frequency of recurrence post-therapy (3–9). Transcatheter arterial chemoembolization (TACE) has been performed for unresectable advanced HCC in patients who are unsuitable candidates for local ablation therapy or surgical treatment. To date, nine randomized control trials (RCTs) of transcatherter arterial embolization or TACE versus best supportive care have been reported (10–18). Three of these RCTs and two meta-analyses have demonstrated a survival benefit of this treatment modality in HCC patients (10,16,17,19,20). On the basis of these results, TACE has been the most commonly employed treatment modality in patients with unresectable advanced HCC, especially those with intermediate-stage disease, who are unsuitable candidates for local ablation therapy (21). However, unfortunately, the disease eventually progresses to becoming refractory to TACE.

Transcatheter arterial infusion chemotherapy (TAI) could be expected to have better antitumor efficacy and lesser toxicity than systemic chemotherapy, because it is associated with only a local increase in the concentrations of anticancer drugs, and therefore, a lower incidence of systemic adverse effects. The reported response rates to TAI with a single agent vary in the range of 9–33% (22–25), and those to TAI using combination regimens vary in the range of 44–73% (26–29). Thus, TAI has high antitumor activity and is widely used in clinical practice, especially in Japan, although no survival benefit has been established yet, because no randomized studies of TAI have been conducted until date.

Cisplatin for Intra-arterial Injection (IA-call®, Nippon Kayaku Co., Ltd) is a powder formulation and represents an improvement over the standard liquid type of cisplatin formulation for intra-arterial administration. Since the solubility of this agent is 2.86 times higher than that of standard cisplatin, the injection time can be shortened. In a clinical study of this agent for advanced HCC, a favorable tumor response rate of 33.8% was reported (25), and this agent was approved for use in the treatment of HCC by the Ministry of Health, Labour and Welfare of Japan, in July 2004. However, it has not been clarified whether this agent might also be effective for TACE-refractory HCC. Therefore, we conducted a retrospective investigation of the efficacy and safety of TAI using cisplatin in patients with HCC refractory to TACE.

PATIENTS AND METHODS

PATIENTS AND TREATMENT

From July 2004 to September 2008, 84 consecutive patients with TACE-refractory HCC underwent TAI using cisplatin at the National Cancer Center Hospital, Tokyo, or the National Cancer Center Hospital East, Chiba, Japan. TACE-refractory tumors were defined as those showing an increase in size or <25% reduction in size of the hypervascular lesions visualized on dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) at 1 month after TACE (30).

TAI was performed by introducing a catheter into the proper, right or left hepatic artery, or another feeding artery by the Seldinger technique, and injecting cisplatin at the dose of 65 mg/m^2 over 20–40 min. Until the appearance of evidence of tumor progression and/or of unacceptable toxicity, the treatment was repeated every 4–6 weeks for up to six cycles. Antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist (granisetron 1 mg) plus dexamethasone 8 mg was used at the physician's discretion. Patients received adequate hydration for protection against cisplatin-induced renal dysfunction, and the urine output was carefully monitored, especially during the first 3 days after intra-arterial administration of cisplatin, and intravenous furosemide was administered if the output was judged to be inadequate. In principle, the cisplatin dose was reduced if the patient's creatinine clearance decreased to below 50 ml/min.

This retrospective study was conducted with the approval of the Institutional Review Board of the National Cancer Center and conducted in accordance with the ethical principles stated in Japanese ethics guidelines for epidemiologic studies.

RESPONSE AND TOXICITY EVALUATIONS

The antitumor effect was evaluated by dynamic CT and/or MRI performed 1 month after each treatment cycle, and after the completion of six cycles, follow-up examinations were performed every 1–3 months. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (31). The best overall response was recorded for each patient. Progression-free survival was defined as the interval between the date of the initial TAI treatment using cisplatin and either the date of documentation of disease progression (either radiologic or symptomatic progression) or the date of death owing to any cause. Overall survival was measured from the date of the initial TAI treatment using cisplatin to the date of death or last follow-up. Survival curves were estimated using the Kaplan–Meier method. Toxicities were assessed using the Common Terminology Criteria for Adverse Events, version 3.0. Statistical analyses were performed using Dr SPSS II (SPSS Japan Inc., Tokyo, Japan).

RESULTS

PATIENT CHARACTERISTICS

The baseline characteristics of the 84 patients enrolled in this study are shown in Table 1. The diagnosis of HCC was made either by histologic examination (44 patients, 52%), or distinctive findings on CT, MRI and/or angiography associated with elevated serum levels of α-fetoprotein or protein induced by vitamin K antagonist II (40 patients, 48%). Of the total, 42 patients each were classified as the Child–Pugh classes A and B, whereas there were no patients of the

Table 1. Patient characteristics (*n* = 84)

Age, median (range)	68 (37–82)
Gender, *n* (%)	
Male	69 (82)
Female	15 (18)
ECOG performance status, *n* (%)	
0	56 (67)
1	26 (31)
2	0 (0)
3	2 (2)
T factor[a]	
T1	2 (2)
T2	34 (40)
T3a	17 (20)
T3b	31 (37)
Portal vein tumor thrombosis, *n* (%)	
Present	26 (31)
Absent	58 (69)
Ascites, *n* (%)	
Present	24 (29)
Absent	60 (71)
Hepatitis virus marker status, *n* (%)	
HBsAg-positive	12 (14)
HCVAb-positive	55 (65)
Child–Pugh class, *n* (%)	
A	42 (50)
B	42 (50)
Number of previous TACE sessions	
Median (range)	4 (1–17)
Reason for TACE-refractory disease, *n* (%)	
Progressive disease	69 (82)
Stable disease (under 25% decrease)	15 (18)
AFP (ng/dl)	
Median (range)	660.2 (1.7–4 06 500)
PIVKA II (mAU/ml)	
Median (range)	600 (11–96 390)

ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; TACE, transcatheter arterial chemoembolization; AFP, α-fetoprotein; PIVKA, protein induced by vitamin K antagonist.
[a]T factor was evaluated according to Sobin et al. (32).

Child–Pugh class C. Twenty-six patients (31%) had tumor thrombosis in the main and/or first portal vein. Prior therapies other than TACE were hepatectomy (37 patients, 44%), local ablation therapy (33 patients, 39%), TAI (13 patients, 15%) and systemic chemotherapy (10 patients, 12%) with non-platinum-containing regimens. The median number of previous sessions of TACE was 4 (range 1–17), and the

median period from the first TACE to the date on which the tumors were judged to be TACE-refractory was 15.8 months (range 1.0–78.0). The anticancer agents used for the previous TACE sessions were epirubicin in 79 patients, adriamycin in 17 patients and mitomycin C in 5 patients.

TREATMENT DELIVERY AND EFFICACY

In total, 167 cycles of TAI were administered to the 84 patients, with a median of one cycle (range 1–7) per patient. The median cisplatin dose per treatment session was 100 mg (range 50–135). A total of 83 patients received the standard dose of cisplatin in the first session, and the remaining one patient required a 50% reduction in the dose of cisplatin even from the first treatment cycle because of pre-existing renal dysfunction.

Of the study population, one patient showed complete response and two showed partial response, representing an overall response rate of 3.6% [95% confidence interval (CI), 0.7–10.1]. Stable disease was noted in 38 patients and progressive disease in 41 patients. The remaining two patients were not evaluable as they were lost to follow-up. After treatment discontinuation, 50 (60%) patients received supportive care only, 32 (38%) received additional anticancer therapy and 2 (2%) were lost to follow-up. The additional anticancer therapies were TACE with epirubicin or mitomycin in 18 patients, TAI using non-platinum drugs in 7 patients (including 5-fluorouracil with systemic interferon in 3 patients, epirubicin in 3 patients and zinostatin-stimalamer in 1 patient), systemic chemotherapy in 5 patients (including S-1, i.e. a mixture of tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate, in 3 patients and uracil–tegafur plus mitoxantrone in 2 patients) and immunotherapy in 2 patients. By the time of the analysis, except for eight patients who were still alive but showed disease progression, all of the patients had died. The median progression-free survival was 1.7 months (95% CI, 1.1–2.3) and the median overall survival was 7.1 months (95% CI, 4.9–9.3), with a 1-year survival rate of 27% (Fig. 1).

ADVERSE EVENTS

Data of all 84 patients were analyzed for adverse events. The adverse events are summarized in Table 2. In regard to the hematologic adverse events, thrombocytopenia was the most common, with 12 (14%) patients developing Grade 3 or 4 thrombocytopenia; however, none of the patients required platelet transfusions. Grade 3 or 4 leukopenia and neutropenia occurred in only 6 and 4% of the patients, respectively. There were no events of febrile neutropenia.

The main non-hematologic adverse events were elevation of the serum aspartate aminotransferase (AST) and serum alanine aminiotransferase (ALT). Grade 3 or 4 elevation of the AST and ALT was observed in 33 (39%) and 5 (6%) patients, respectively. Gastrointestinal adverse events, such as nausea, vomiting and anorexia, were frequently observed
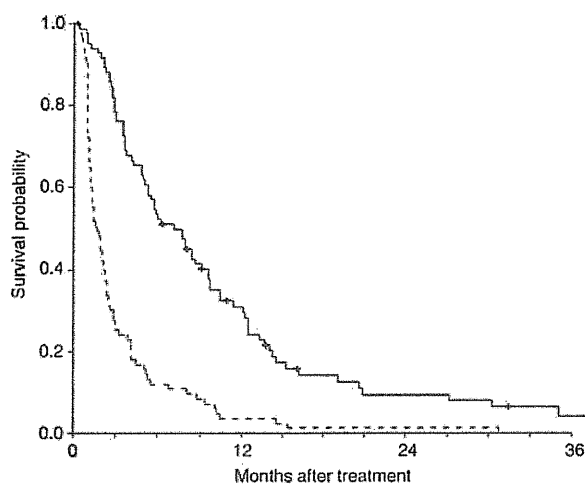
Figure 1. Overall survival (continuous line) and progression-free survival (dotted line) in the 84 patients. The marks on the curve represent censored cases.

Table 2. Adverse events

	No. of patients				Gr 3/4 (%)
	Gr 1	Gr 2	Gr 3	Gr 4	
Hematologic toxicity					
Leukocytopenia	30	29	5	0	6.0
Neutropenia	11	24	3	0	3.6
Anemia	55	18	6	1	8.3
Thrombocytopenia	36	22	12	0	14.3
Non-hematologic toxicity					
Anorexia	45	16	3	0	3.6
Nausea	40	9	3	0	3.6
Vomiting	11	6	0	0	0
Fatigue	59	11	3	0	3.6
Diarrhea	3	1	0	0	0
Constipation	20	0	0	0	0
Hypoalbuminemia	38	41	1	0	1.2
Elevated serum total bilirubin	28	33	4	1	6.0
Elevated serum aspartate aminotransferase	20	26	31	2	39.3
Elevated serum alanine aminotransferase	37	30	4	1	6.0
Elevated serum alkaline phosphatase	53	15	1	0	1.2
Elevated serum creatinine	12	1	0	0	0

Gr, grade.

after intra-arterial administration of cisplatin, but most were transient and manageable with appropriate medical treatment, such as antiemetic drug administration and intravenous hydration. There was no serious renal toxicity. Four patients

died within 30 days of the last treatment session: two of disease progression, one of acute coronary syndrome, showing no causal relationship with the treatment, and the remaining one due to known pulmonary artery tumor embolism.

DISCUSSION

In the current study, the response rate to TAI using cisplatin was only 3.6% in patients with TACE-refractory HCC. Moreover, the median progression-free survival of only 1.7 months was extremely disappointing. The efficacy of TAI using cisplatin for advanced HCC limited to TACE-refractory tumors was much worse than that reported from a previous Phase II study in patients with advanced HCC (response rate, 33.8%) (25). One possible explanation for this discrepancy in the response rate may be the differences in the characteristics of the enrolled patients between the two studies. Most patients in the previous Phase II trial were TACE-naïve, whereas only patients with TACE-refractory disease were included in the current study. In our previous study (30), TAI using epirubicin was reported to have unfavorable efficacy in a subset of patients with TACE-refractory HCC (response rate, 5%). When HCC is treated by TACE and/or becomes resistant to TACE, it might acquire resistance to cytotoxic agents, such as cisplatin or epirubicin. Furthermore, to select suitable candidates for this treatment, the predictive factors for disease control and survival for more than 12 months were also investigated, but could not be clarified (data not shown). Therefore, TAI using cisplatin or epirubicin cannot be recommended at present for this patient population in clinical practice.

Recently, systemic chemotherapy has become an important treatment modality for advanced HCC, because two RCTs (the SHARP trial and the Asia-pacific trial) of sorafenib versus placebo demonstrated significantly improved time-to-progression and overall survival in the drug-treated group, although sorafenib yielded a far-from-satisfactory response rate of only 2.3–3.3% (33,34). On the basis of the results of these RCTs, sorafenib is acknowledged as a standard agent for systemic chemotherapy in patients with advanced HCC. The efficacy of sorafenib for advanced HCC refractory to TACE has not yet been clarified, but in both of the aforementioned studies, the results of exploratory subgroup analyses in patients treated previously by TACE were reported. In the subset of patients with a previous history of treatment by TACE in the SHARP trial, the disease control rate (DCR) was significantly greater in the patients who were treated with sorafenib (44.2%) than in those who had received placebo (34.4%) (35). In addition, a trend towards a beneficial effect of sorafenib was also observed in relation to the median overall survival in this subpopulation of patients {11.9 vs. 9.9 months [hazard ratio (HR), 0.75; 95% CI, 0.49–1.14]}. In the Asia-pacific trial, 41% of the enrolled patients had a previous history of undergoing TACE. The

DCR for sorafenib (24.6%) in these patients was higher than that for placebo (9.1%) (36). Moreover, a tendency [HR for death was 0.84 (95% CI, 0.52–1.36)] towards favorable overall survival was also noted in the HCC patients with a previous history of TACE treated with sorafenib when compared with that in the same subpopulation of patients who received placebo. Sorafenib appeared to benefit patients with advanced HCC, regardless of whether or not they had previously been treated by TACE. Thus, molecular-targeted agents, including sorafenib, which exhibit mechanisms of action different from those of cytotoxic agents, may be superior for the treatment of HCC refractory to TACE. Therefore, patients with TACE-refractory HCC are receiving new molecular-targeted agents in clinical trials, and sorafenib is used as the standard agent for the treatment of advanced HCC in clinical practice.

In the current study, the most common Grade 3 and 4 adverse events were elevated AST, thrombocytopenia and anemia, which frequently also reflected the underlying cirrhosis. In terms of the gastrointestinal toxicities, only 4% of the patients experienced Grade 3 anorexia and nausea, and the symptoms resolved within a few days. Thus, the gastrointestinal toxicities were mild and manageable in the current study. There was no need for dose reduction or discontinuation of cisplatin on account of development of toxicities, except in one patient each with Grade 2 elevation of the serum creatinine and Grade 2 fatigue. Thus, advanced HCC patients showed good overall tolerability to TAI using cisplatin, which has also been reported to show favorable efficacy in these patients (25); in our study confined to TACE-refractory patients, however, the treatment showed only modest antitumor activity. TAI using cisplatin may therefore be easy to administer in combination with some molecular-targeted agents, such as sorafenib, since its toxicity is generally mild and its toxicologic profile is distinct from that of sorafenib.

In conclusion, TAI using cisplatin appeared to have only modest activity against TACE-refractory HCC, although this treatment was feasible and well tolerated. Further development of novel treatments is necessary to improve the prognosis of patients with TACE-refractory HCC.

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Conflict of interest statement

None declared.

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