ACKNOWLEDGMENTS

The authors thank Ms. Asami Yoshimoto for her help in the preparation of this manuscript and Krystal Johnston, MD, and Randi Hooten of MED Institute for their editorial assistance.

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Phase I/II Study of Radiologic Hepatic Arterial Infusion of Fluorouracil Plus Systemic Irinotecan for Unresectable Hepatic Metastases from Colorectal Cancer: Japan Clinical Oncology Group Trial 0208-DI

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ABSTRACT

Purpose: Treatment of patients who have metastatic colorectal cancer (CRC) by using a combination of hepatic arterial infusion chemotherapy (HAIC) and systemic chemotherapy has resulted in promising clinical outcomes. Additionally, image-guided HAIC is reported to be less invasive and distribute drugs more accurately than surgical HAIC. The purpose of this study was to assess the combination of image-guided delivery of fluorouracil through HAIC and systemic irinotecan in a multicenter phase I/II study.

Materials and Methods: Twenty-five patients with unresectable liver metastases from CRC were fitted with hepatic arterial catheter and port systems by using image-guided methods. Intraarterial fluorouracil (1,000 mg/m^2) was administered on days 1, 8, and 15 of each treatment cycle. The dose of systemic irinotecan on days 1 and 15 was escalated from 75 mg/m^2.

Results: No dose-limiting toxicity was encountered during phase I, and the recommended dose of irinotecan was set at 150 mg/m^2. Grade 3 or higher adverse events included hyperglycemia (15%), elevated γ-glutamyl transpeptidase levels (15%), and neutropenia (9%). The response rate and median survival time were 72% and 49.8 months (95% CI, 27.5–78.1 mo), respectively.

Conclusions: The combination of image-guided delivery of fluorouracil through HAIC and systemic irinotecan yielded favorable safety, response rate, and survival results. This combination should be evaluated in a large study.

ABBREVIATIONS

AE = adverse event, CRC = colorectal cancer, DLT = dose-limiting toxicity, DSA = digital subtraction angiography, HAIC = hepatic arterial infusion chemotherapy, MTD = maximum tolerated dose, OS = overall survival, RD = recommended dose, WBC = white blood cell

Modern chemotherapy with the use of active agents, such as irinotecan, oxaliplatin, and molecular-targeted therapies, has significantly prolonged the survival of patients with metastatic colorectal cancer (CRC) (1,2). However, achieving complete response and long-term survival is still rare, even with intensive therapy with combinations of these agents.

Although hepatic arterial infusion chemotherapy (HAIC) with fluorinated pyrimidines has demonstrated high local response rates for CRC liver metastases, 10 of 11 randomized

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This study was funded by the Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan.

None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2012; 23:1261–1267

http://dx.doi.org/10.1016/j.jvir.2012.06.031

Table 1. Eligibility Criteria

Inclusion criteria

1. Histologically documented colorectal cancer
2. Unresectable liver-limited metastases as determined by imaging studies
3. Previous resection of primary tumor with D1 or D2 lymph node dissection
4. No previous chemotherapy except adjuvant chemotherapy with fluoropyrimidines completed > 3 mo before study
5. At least one measurable tumor in the liver per RECIST (version 1.0)
6. Between 20 and 70 y of age
7. ECOG performance status of 0–2
8. Adequate hematological, hepatic, renal, and cardiac functions
9. Written informed consent

Exclusion criteria

1. Massive ascites or pleural effusion
2. Active gastrointestinal bleeding
3. Active infection
4. Watery diarrhea
5. Severe comorbid conditions
6. Other untreated cancers
7. Previous abdominal radiotherapy
8. Positive serum hepatitis B antigen or hepatitis C antibody
9. Allergy to iodinated contrast material
10. Severe mental disorder
11. Previous catheter placement into the hepatic artery
12. Pregnancy or nursing

ECOG = Eastern Cooperative Oncology Group, RECIST = Response Criteria in Solid Tumors.

controlled trials published before 2006 did not find any survival benefit of HAIC greater than that of systemic chemotherapy (3–13). Metaanalyses of HAIC studies have also demonstrated that HAIC does not improve survival in patients with CRC (14–16). Consequently, HAIC is not generally considered a first-line treatment or a component of standard treatment regimens.

Laparotomy was employed for HAIC catheter and pump placement in all previous randomized controlled trials of HAIC in Western countries. In Japan, on the contrary, a percutaneous technique for hepatic arterial catheter and port placement was developed in the 1980s and was established in the 1990s as an image-guided interventional radiologic procedure, with drug distribution evaluated by using contrast-enhanced computed tomography (CT) via the indwelling catheter–port system (17–20). The advantages of this technique are that it is minimally invasive and provides accurate periodic evaluation of drug delivery. In addition, HAIC treatment outcomes with this technique are favorable; phase II studies (17,21–23) of intermittent HAIC with fluorouracil in patients with CRC liver metastases with or without extrahepatic metastasis had median survival times of 18.6–26 months. HAIC treatment success requires monitoring of drug distribution to ensure that the administered drug is delivered directly to all liver tumors without reaching extrahepatic organs (20).

Kemeny et al (24) reported a phase I study of HAIC with floxuridine and dexamethasone combined with systemic irinotecan that was or was not followed with cryosurgery. The study demonstrated a response rate of 74% and a median survival time of 17 months in patients who did not undergo cryosurgery. In their study, however, surgical laparotomy was used for implantation instead of a radiologic intervention (24), and the drug and administration schedules were different from those of Japanese phase II studies. Thus, we conducted a multicenter phase I/II study to assess the feasibility, safety, and preliminary efficacy of image-guided delivery of fluorouracil through HAIC combined with systemic irinotecan.

MATERIALS AND METHODS

Patients

Inclusion and exclusion criteria are listed in Table 1. A Consolidated Standards of Reporting Trials diagram of this study is shown in Figure 1. The study protocol was approved by the institutional review boards of all participating institutions. All patients provided written informed consent. This study was registered to UMIN-CTR (UMIN C000000051, 2005/08/08).

Treatment

Placement of Intraarterial Catheter and Port System. A catheter and port system was implanted within 2 weeks of enrollment in the study. Details of the procedure are described elsewhere (19,25). In brief, percutaneous implantation of a catheter and port system was performed under local anesthesia by using an interventional radiologic technique. Before each cycle of chemotherapy, drug delivery was evaluated by digital subtraction angiography (DSA) and CT angiography through the implanted catheter and port system (Fig 2).

Chemotherapy Administration. After implantation of the catheter and port system, chemotherapy was started when the patient's laboratory values were as follows: white blood cell (WBC) count of at least 4,000/mm^3 and no greater than 12,000/mm^3, platelet count of at least 100,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels no greater than three times the upper limit of normal, bilirubin level no greater than 1.5 mg/dL, and serum creatinine level no greater than 1.5 mg/dL. Patients received concurrent systemic chemotherapy and HAIC in 4-week cycles, and the treatment protocol was considered to be complete after five cycles of this regimen. In each cycle, 1,000 mg/m^2 of fluorouracil in saline solution plus 100 mg of hydrocortisone were administered on days 1, 8,

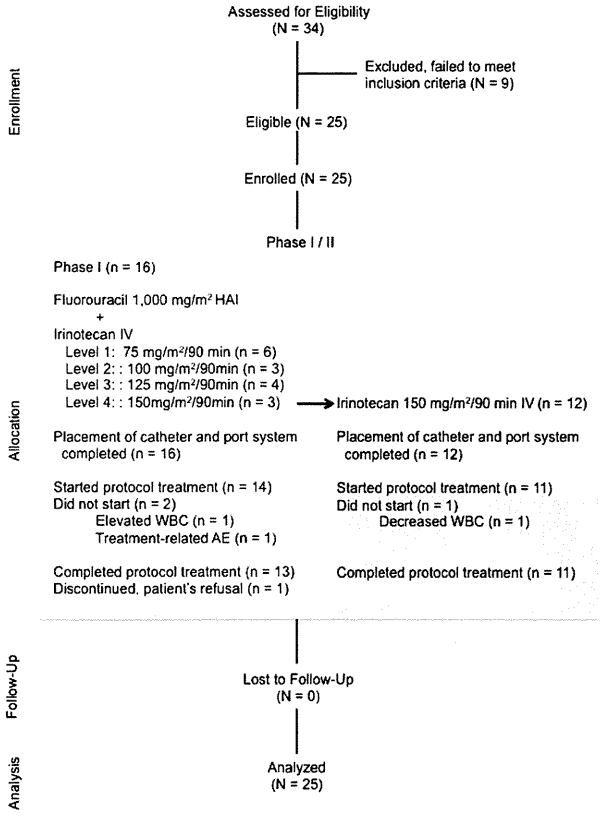

Figure 1. Consolidated Standards of Reporting Trials diagram. HAI = hepatic arterial infusion. (Available in color online at *www.jvir.org.*)

and 15 by continuous 5-hour infusion via a disposable balloon pump system. This dose was determined based on a previous phase I/II study of HAIC with fluorouracil (23). On days 1 and 15, following HAIC, irinotecan diluted in 5% glucose was administered via a 90-minute intravenous drip. The irinotecan doses planned for phase I of the trial were 75, 100, 125, and 150 mg/m^2. After the maximum tolerated dose (MTD) was determined, the study was advanced to phase II.

Patient and Tumor Evaluations

Pretreatment evaluations included medical history, physical examination, and laboratory examinations. Laboratory examinations included evaluation of complete blood counts, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and carcinoembryonic antigen. Baseline evaluation of tumors was performed by contrast-enhanced CT scans of the chest and abdomen. During the course of treatment, each patient was assessed weekly for toxicity, including laboratory determination of complete blood counts, and blood chemistry. CT examination was planned before treatment and after one, three, and five cycles of treatment. Patient responses to treatment were evaluated by three radiologists based on Response Evaluation Criteria In Solid Tumors, version 1.0. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Study Design and Statistical Analysis

This trial was designed as a phase I/II study. The primary endpoints of phase I were to identify dose-limiting toxicities (DLTs), MTD, and the recommended dose (RD) of systemic irinotecan when combined with HAIC that uses a fixed dose of fluorouracil. DLTs in phase I were defined as any grade 4 neutropenia or thrombocytopenia or any nonhematologic toxicity of grade 3 or more severe. We treated patients in cohorts of three to six. The first cohort received the lowest dose (ie, dose level 1) of irinotecan, and doses were escalated in a stepwise fashion. If DLTs were observed in less than one third of the cohort members, subsequent patients were treated at the next dose level. If more than one third of cohort members developed DLTs, the preceding dose level was identified as the MTD.

Based on the results of previous studies, 12 patients were needed in this study with a null proportion of 30%–45% and an alternative proportion of 74% to achieve 80% power, given that the one-sided significance level was 10% (24).

Secondary endpoints of the study included HAIC initiation rate, overall response rate, response rate in the liver, and toxicity. Survival analysis was performed by using the Kaplan–Meier method. Demographics and baseline variables were summarized by using descriptive statistics. Statistical significance was set at 0.05, and differences between groups were examined by using two-tailed *t* tests. We used SPSS software (version 17; SPSS, Chicago, Illinois) to perform all statistical analyses.

RESULTS

Patient Demographics

Twenty-five patients from five participating institutions were enrolled between November 2003 and March 2008. Patient characteristics are listed in Table 2. Synchronous liver metastases were seen in 84% of the patients, and 92% of the patients had not received previous adjuvant chemotherapy.

Initiation of HAIC and Systemic Chemotherapy

A catheter and port system was successfully placed in all 25 patients. Catheters were inserted via the left subclavian artery in all patients. Treatment consisting of HAIC and systemic chemotherapy was initiated according to the study protocol in 22 patients (88%; Fig 1). Treatment was not started in three patients as a result of elevated WBC count (n = 1), decreased WBC count (n = 1), and cerebral infarction that was presumably caused by catheter placement (n = 1). The elevated WBC count observed in one patient at dose level 1 and the decreased WBC count

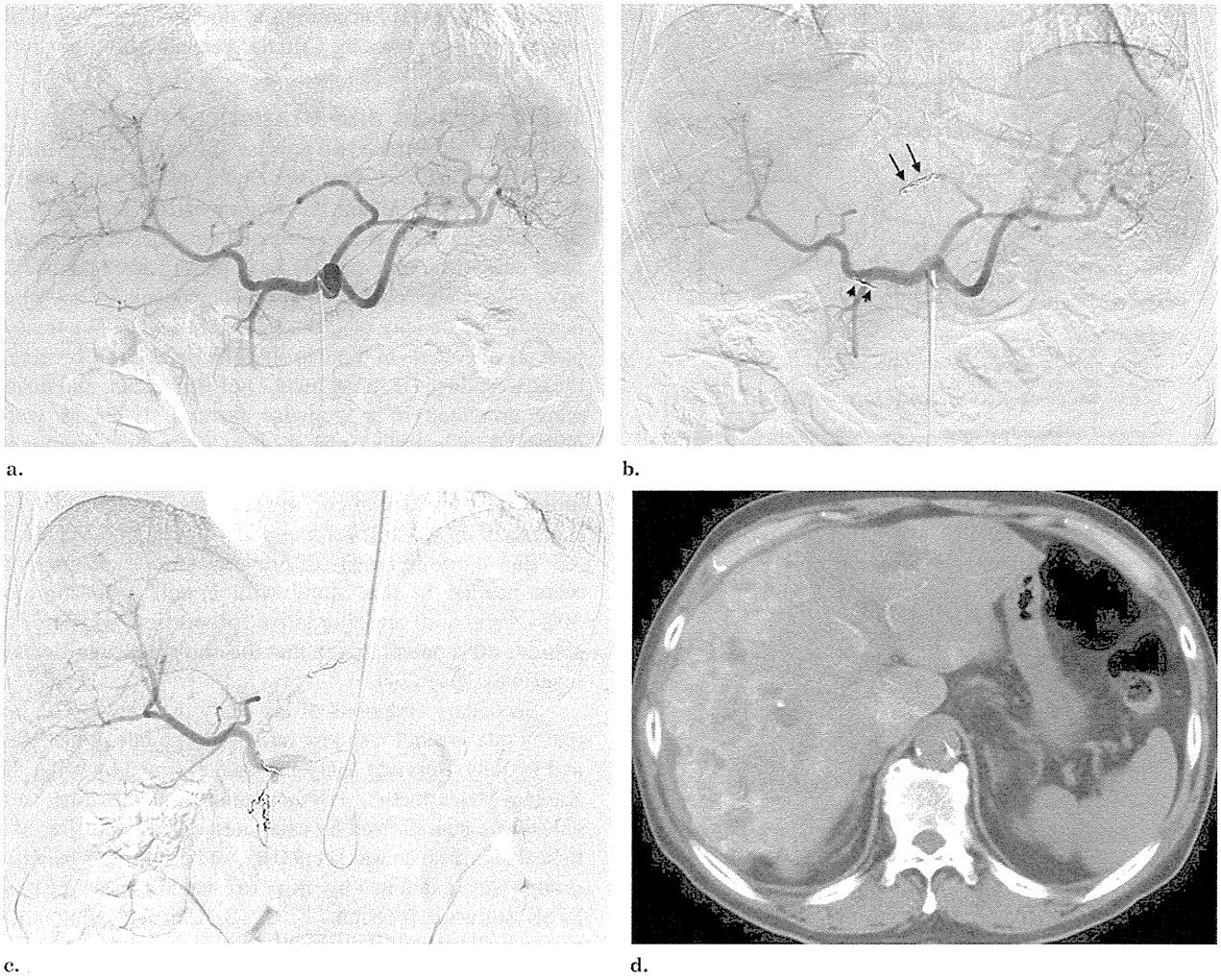

Figure 2. Image-guided insertion of catheter and port system for HAIC. **(a)** DSA of the celiac artery. The left hepatic artery is arising from left gastric artery (ie, replaced left hepatic artery). **(b)** DSA after embolization of the replaced left hepatic artery (long arrows) and right gastric artery (short arrows). The left hepatic artery is visualized from the collateral vessels. **(c)** DSA via the implanted port. The indwelling catheter is implanted via the left subclavian artery. **(d)** CT angiography via the implanted port. Adequate drug distribution is confirmed with enhancement of hepatic metastases by contrast material injected through the implanted port.

observed in one patient at dose level 4 were likely related to the primary disease process, because no clinical findings of infection were found. These two patients were removed from the study and treated by HAIC alone. Details of the patient who developed cerebral infarction are described in the Safety section. The HAIC initiation rate was 96%, including the two patients who were later removed from the study.

Dose-escalation Findings

In phase I, one of six patients developed DLT at dose level 1 (Fig 1). Of the 14 patients who started the treatment protocol, 13 patients completed five cycles. Because no DLT was encountered at dose levels 2–4, we were unable to determine the MTD of irinotecan. Dose level 4 (150 mg/m^2) was selected as the RD for phase II of the study.

Safety

There were no treatment-related deaths in this study. The incidence of grade 2 or higher adverse events (AEs) occurring during chemotherapy is shown in Table 3. In 106 cycles of protocol treatment, the following grade 3 or higher AEs occurred: leukopenia (2%), neutropenia (9%), elevated γ-glutamyl transpeptidase level (15%), hyperglycemia (15%), and hypokalemia (1%). The only grade 4 AE was neutropenia (2%).

Before the initiation of chemotherapy, one patient (4%) developed central nervous system ischemia. One day after placement of the catheter and port system, the patient developed hemiparesis, and magnetic resonance imaging confirmed multiple cerebral infarctions. The patient subsequently had moderate hemiparesis, but no other neurologic deficits. The indwelling catheter was thought to have caused the cerebral infarctions.

Table 2. Patient Characteristics (N = 25)

Characteristic	Value
Age (y)	
Median	63
Range	45–70
Sex	
Male	21 (84)
Female	4 (16)
ECOG performance status	
0	24 (96)
1	1 (4)
Location of primary tumor	
Colon	13 (52)
Rectum	12 (48)
Differentiation	
Well	7 (28)
Moderate	15 (60)
Poor	3 (12)
Synchronous	
Yes	21 (84)
No	4 (16)
Liver involvement	
< 30%	22 (88)
30%–60%	3 (12)
> 60%	0
Previous adjuvant chemotherapy	
Yes	2 (8)
No	23 (92)

Values in parentheses are percentages. ECOG = Eastern Cooperative Oncology Group.

Table 3. Per-patient Incidence of Grade 2 or Higher Adverse Events in All Cycles of Chemotherapy (N = 106)

Adverse Event	Grade 2	Grade 3	Grade 4
Nausea	3 (3)	0	0
Diarrhea	8 (8)	0	0
Stomatitis	1 (1)	0	0
Fatigue	3 (3)	0	0
Alopecia	12 (11)	0	0
Vertigo	0	1 (1)	0
Glycosuria	2 (2)	0	0
Cystitis	2 (2)	0	0
Leukopenia	21 (20)	2 (2)	0
Neutropenia	15 (14)	7 (7)	2 (2)
Anemia	10 (9)	0	0
Thrombocytopenia	2 (2)	0	0
Hyperbilirubinemia	1 (1)	0	0
GGT	11 (10)	16 (15)	0
ALP	3 (3)	0	0
Hyperglycemia	26 (25)	16 (15)	0
Hypokalemia	0	1 (1)	0

Values in parentheses are percentages. ALP = alkaline phosphatase, GGT = γ-glutamyl transpeptidase.

Response

A total of 25 patients were included in the response analyses. The overall response in the liver was 72%, and included four complete responses (16%) and 14 partial responses (56%). Four patients (16%) exhibited stable disease in the liver, and the responses of three patients (12%) could not be evaluated because the treatment protocol was not initiated. During the course of treatment, no patients developed any observable extrahepatic metastases. Therefore, the overall response rate was 72%.

Survival

Survival analysis was conducted based on all 25 patients (Fig 3). With a median follow-up period of 55.0 months (range, 22.8–87.7 mo), the median overall survival (OS) time was 49.8 months (95% CI, 27.5–78.1 mo).

DISCUSSION

The present study is a prospective trial to evaluate image-guided HAIC combined with systemic chemotherapy for patients with unresectable hepatic metastases from CRC. Our results demonstrate that this treatment may be effective and safe as an initial therapy, as 23 of the 25 patients in the study had not undergone previous chemotherapy. Twenty-one of these 23 patients were enrolled in the study after surgery to remove the primary tumor. Other noteworthy characteristics of the patients in this trial include good performance status (24 patients with a performance status of 0) and moderate tumor involvement in the liver (22 patients with < 30% involvement). To summarize, the characteristics of this patient cohort were resectable primary tumor, synchronous and unresectable liver metastases of moderate intrahepatic extent, good performance status, and limited previous chemotherapy.

We determined the feasibility and the safety of image-guided HAIC combined with systemic irinotecan. Generally, AEs caused by fluorouracil are well tolerated, and bone marrow suppression is not significant. Given that systemic irinotecan has a different toxicity profile than fluorouracil, and the intraarterial effects of fluorouracil were minimal in the present study, it could be surmised that the RD of irinotecan in this study should be the same as the standard RD of 150 mg/m^2 used in Japanese patients. However, modification of the usual treatment schedule of weekly fluorouracil HAIC to a schedule that included a 1-week treatment-free interval in the fourth week of each treatment cycle may account for the minimal hematologic toxicity we observed and the undetermined MTD (23). During phase II of this trial, grade 3 AEs were observed in 21 of 60 treatment cycles (35%), and no grade 4 AEs occurred. Furthermore, all patients, except one who did not meet the criteria for the initiation of chemotherapy, completed the planned five cycles of treatment. Therefore, this

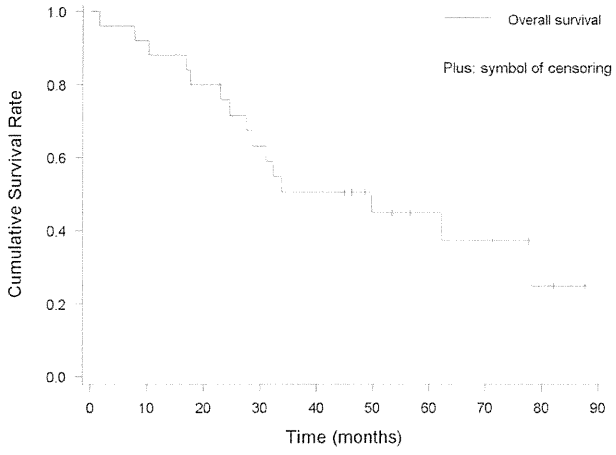

Figure 3. Graph of OS. The median OS time is 49.8 months (95% CI, 27.5–78.1 mo).

study demonstrated that image-guided HAIC with fluorouracil combined with systemic irinotecan (150 mg/m^2) is feasible and safe.

Hyperglycemia was a notable AE in this study. Hyperglycemia occurred in 56% of the 106 treatment cycles. The incidence of hyperglycemia in phase I was almost the same as in phase II. As there have been no reports of hyperglycemia as a result of irinotecan therapy, and intraarterial hydrocortisone (100 mg) was administered with fluorouracil on days 1, 8, and 15 to reduce vascular endothelial injury, this intraarterial hydrocortisone may have influenced the occurrence of hyperglycemia. There is some possibility that intraarterial direct administration of fluorouracil to the liver leads to deterioration of the glucose tolerance of the liver. Hyperglycemia does not directly alter the short-term patient prognosis, but it may become more important if longer survival is achieved with this treatment.

The HAIC initiation rate in the present study is comparable to rates seen in previous studies of image-guided HAIC. Tanaka et al (26) reported a technical success rate of 99.8% among 426 patients undergoing image-guided HAIC. Deschamps et al (27) reported a technical success rate of 94% among 93 patients. Moreover, Ganeshan et al (25) mentioned in their review of HAIC that interventional radiology played a vital role in establishing vascular access and assessing outcomes. On the contrary, the technical success rates of surgical HAIC, a technique widely employed in published randomized controlled trials, are not included in the reports of these trials or result in lower HAIC initiation rates than seen with image-guided HAIC. Kerr et al (10) reported an HAIC initiation rate of 68% following the surgical procedure used in their randomized study comparing HAIC with systemic chemotherapy. In the present small, prospective study, the HAIC initiation rate was 96%. This suggests that image-guided catheter placement is suitable for the initiation of HAIC.

In the present study, one patient developed cerebral infarction after catheter implantation. There have been several reports of cerebral ischemia as a complication of catheter implantation via the subclavian artery, and the incidence of this complication is approximately 5% (28,29). This complication should therefore be recognized as a severe AE caused by radiologic catheter placement via the subclavian artery, and other access routes such as the femoral or hypoepigastric artery should be considered.

The liver response rate of 72% we observed is similar to those of other studies of image-guided deliver of fluorouracil with the same infusion protocol through HAIC (17,21,22). This indicates that the addition of systemic irinotecan might not affect tumor response in the liver. However, previous studies have demonstrated an incidence of extrahepatic metastases of approximately 70% when patients were treated with HAIC alone. In the present study, no extrahepatic metastases were observed during the study. Therefore, systemic irinotecan may have reduced the occurrence of extrahepatic metastases. Because more than 90% of the fluorouracil administered via the hepatic artery is reported to pass through the liver and enter systemic circulation (30), irinotecan combined with fluorouracil may have prevented extrahepatic metastases in the present study.

It is notable that the median OS of the present study exceeded 4 years. The large proportion of patients with good PS may be a prominent factor in this result. Standard first- and second-line systemic chemotherapies have demonstrated a median survival of 18–24 months (31–34). Concerning the combination of HAIC with systemic chemotherapy, Kemeny et al (35) reported an OS of 36 months with fluorodeoxyuridine HAIC plus systemic oxaliplatin and irinotecan, and an OS of 22 months with fluorodeoxyuridine HAIC plus systemic oxaliplatin, fluorouracil, and leucovorin. Ducreux et al (36) reported an OS of 27 months with HAIC of oxaliplatin plus systemic irinotecan and fluorouracil. Therefore, HAIC combined with systemic chemotherapy may prolong the survival of patients with unresectable liver metastases from CRC.

The present study has several limitations. First, it was a phase I/II study involving a small number of patients. Second, we did not record postprotocol treatment. Therefore, OS may have been influenced by modern systemic chemotherapy with fluorouracil, leucovorin, oxaliplatin, irinotecan, and molecular-targeting agents. However, the OS observed in the present study is still a promising result. Thus, accurate HAIC that uses CT angiography for appropriate drug distribution in combination with systemic chemotherapy may lead to improved patient outcomes.

The present study demonstrates the feasibility of HAIC as an interventional procedure and that HAIC of fluorouracil combined with systemic irinotecan at 150 mg/m^2 is well tolerated. Also, the OS exceeding 4 years was a promising result, although it may have been affected by the treatments after the protocol. In conclusion, this combination chemotherapy should be evaluated in a larger study.

ACKNOWLEDGMENTS

The authors thank Haruhiko Fukuda, MD, for contributions to the study design.

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CLINICAL STUDY

Safety and Efficacy of Primary Metallic Biliary Stent Placement with Tract Embolization in Patients with Massive Ascites: A Retrospective Analysis of 16 Patients

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ABSTRACT

Purpose: To evaluate the safety and efficacy of primary metallic biliary stent placement with tract embolization in patients with massive ascites.

Materials and Methods: Sixteen patients with malignant biliary obstruction and massive ascites (age range, 44–79 y; median age, 59 y) were treated with primary percutaneous stent placement with tract embolization. These patients were unsuitable candidates for endoscopic intervention. Etiologies of biliary obstruction were gastric cancer with hilar nodal metastases (n = 9), pancreatic carcinoma (n = 5), cholangiocarcinoma (n = 1), and gallbladder carcinoma (n = 1). Eight patients had nonhilar lesions and the remaining eight had hilar lesions. Percutaneous accesses to the biliary system and stent placements were performed in a one-step procedure, and catheters were removed with tract embolization with metallic coils.

Results: Stent placement and tract embolization were successful in all patients, without external drainage catheters left in place. Significant reduction of serum bilirubin level was observed in 14 patients (87.5%). No bile peritonitis or intraperitoneal hemorrhage occurred. Major complications included postprocedural cholangitis (12.5%), bloody bowel discharge (6.2%), and right pleural effusion (25.0%). One patient who died 19 days after intervention was deemed to represent a procedure-related mortality. During the survival period (range, 19–175 d; median, 66 d), stent occlusion was noted in two patients at 6 and 159 days after the procedure. Primary stent patency was achieved in 14 patients (87.5%).

Conclusions: Primary biliary stent placement with tract embolization is technically safe and offers an effective palliative treatment option for patients with malignant biliary obstruction and massive ascites when endoscopic intervention is not possible.

ABBREVIATION

PTBD = percutaneous transhepatic biliary drainage

Most patients with malignant biliary obstruction have advanced-stage cancers with dismal prognoses (1). Percutaneous transhepatic biliary drainage (PTBD) and metallic stent placement are established methods to manage malignant biliary obstruction (2–4) when endoscopic intervention is not possible.

The disadvantage of PTBD is its association with hemorrhage, bile leakage, and catheter dislodgment, with reported incidences of less than 5% each (5–8). Especially in patients with massive ascites, PTBD is thought to be relatively contraindicated because of the high risk of intraabdominal bleeding and peritonitis caused by bile leakage, which is believed to be secondary to the presence of a tube passing through ascites (9). As a result, selection of the treatment approach can be difficult in patients with malignant obstructive jaundice and massive ascites who are unsuitable candidates for endoscopic intervention.

Some studies have demonstrated that transhepatic tract

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None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2012; 23:521–527

DOI: 10.1016/j.jvir.2012.01.073

Table 1. Disease and Treatment Details of Patients Undergoing One-Step Biliary Stent Placement with Transhepatic Tract Embolization

Pt. No.	Age (y)/ Sex	Primary Tumor	Biliary Obstruction	Degree of Biliary Dilation	Puncture Site/No.*	Stents	Paracentesis
1	57/ F	PC	Nonhilar	Moderate	Right/1	2	No
2	59/ M	PC	Nonhilar	Moderate	Right/1	1	Yes
3	72/ M	PC	Nonhilar	Severe	Right/1	1	Yes
4	74/ F	PC	Nonhilar	Mild	Left/1	2	No
5	57/ M	GC	Nonhilar	Moderate	Right/1	1	No
6	65/ M	GC	Nonhilar	Mild	Right/1	1	Yes
7	74/ F	GC	Nonhilar	Moderate	Right/1	1	Yes
8	50/ M	GBC	Nonhilar	Moderate	Right/1	1	No
9	60/ M	GC	Hilar (Bismuth I)	Severe	Left/1	2	No
10	66/ M	GC	Hilar (Bismuth I)	Moderate	Left/1	1	No
11	58/ M	GC	Hilar (Bismuth II)	Moderate	Left/1	4	No
12	52/ M	GC	Hilar (Bismuth III)	Moderate	Right/1	1	Yes
13	68/ F	GC	Hilar (Bismuth III)	Moderate	Right/2	3	No
14	44/ M	PC	Hilar (Bismuth III)	Moderate	Right/2	3	No
15	79/ M	CC	Hilar (Bismuth III)	Severe	Right/1	1	No
16	56/ M	GC	Hilar (Bismuth IV)	Moderate	Right/3	3	No

Note.— CC = cholangiocarcinoma, GBC = gallbladder carcinoma, GC = gastric cancer, PC = pancreatic carcinoma.
* Puncture number refers to the number of accesses into the biliary system.

embolization can prevent the complications associated with percutaneous intervention (10–15). Stent placement in a one-step procedure could immediately resolve biliary obstruction, shortening the duration of placement of the temporary drainage catheter (4,16–18). In addition, percutaneous biliary metallic stent placement with tract embolization performed in a single session might be a favorable method to manage biliary obstruction in patients with massive ascites who are not suitable candidates for endoscopic intervention or in whom endoscopic treatment has failed.

The purpose of the present study was to evaluate the safety and efficacy of primary metallic biliary stent placement with tract embolization in patients with massive ascites.

MATERIALS AND METHODS

Patient Population

This retrospective study was conducted in accordance with the principles of the amended Declaration of Helsinki, and with the approval of the institutional review board. Between July 2005 and June 2010, 16 patients with malignant biliary obstruction and massive ascites, in whom conventional endoscopic drainage failed or could not be performed because of altered anatomy after surgery, were treated with primary percutaneous expandable metallic stent placement. The patient population included 12 men and four women with a mean age of 62 years (median, 59 y; range, 44–79 y; Table 1).

Etiologies of malignant biliary obstruction were gastric cancer with nodal metastases (n = 9), pancreatic carcinoma (n = 5), cholangiocarcinoma (n = 1), and gallbladder carcinoma (n = 1). The diagnosis of biliary obstruction was confirmed by computed tomography (CT) and/or ultrasonography (US; Fig 1a). Eight patients had lesions involving the middle and distal common bile duct, and eight had proximal bile duct (ie, hilar) lesions. The latter were classified according to Bismuth classification as follows: type I, n = 2; type II, n = 1; type III, n = 4; and type IV, n = 1 (Table 1). All 16 patients had massive ascites caused by peritoneal dissemination and/or advanced disease, and five patients had liver metastases. Massive ascites was defined as a large amount of fluid in the paracolic regions and around the liver at the proposed puncture site, and resulted in a tense abdomen determined with imaging and physical examination (9,19). Cytologic examination of the ascites was performed in 12 of 16 patients, and a malignant cytologic result was revealed in nine patients.

In 11 of the 16 patients, endoscopic intervention was attempted, but resulted in failure because of gastroduodenal invasion by the primary disease (n = 8) or rigidity of the papilla of Vater (n = 3). In the remaining five patients, the endoscopic approach was not attempted because of previous surgery with Roux-en-Y conversion.

Procedures

Written informed consent was obtained from all patients before the procedures. All procedures were performed under local anesthesia with 1% lidocaine and conscious sedation with midazolam and pentazocine or fentanyl. Intravenous broad-spectrum antibiotic prophylaxis was routinely administered 6 hours before the procedure in all patients

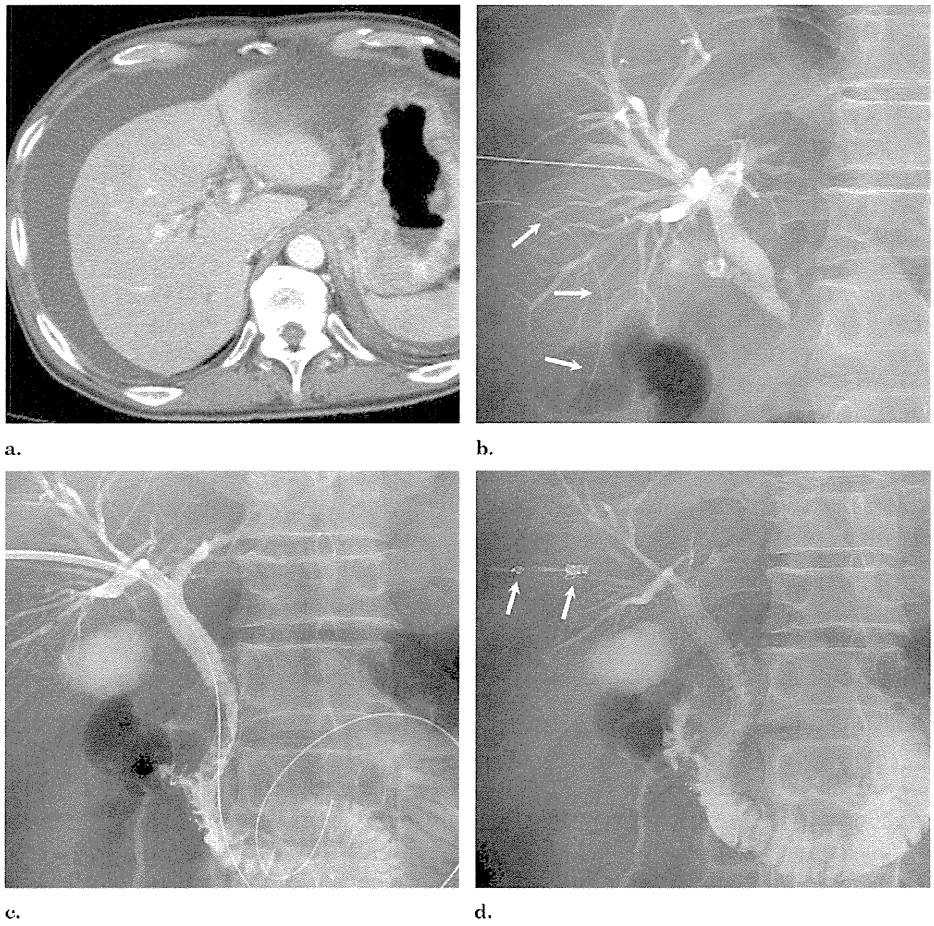


Figure 1. Gastric cancer with nodal metastasis in a 65-year-old man (patient 6; Table 1). **(a)** Contrast-enhanced CT before stent placement shows dilated intrahepatic biliary ducts and massive ascites. **(b)** Percutaneous transhepatic cholangiography reveals tight stricture at the distal common bile duct. Note that a 6-F tube was placed around the liver surface (arrows). **(c)** Cholangiography performed after stent placement shows good expansion of the stent and good flow of contrast material through the stent. **(d)** Embolization of the transhepatic tract was performed with metallic coils (arrows).

and continued for as long as 5 days after the procedure. Percutaneous puncture, insertion of the catheter into the intrahepatic biliary duct, and stent placement were performed in a single session without leaving an external drainage catheter. No patients had suspected cholangitis before the procedure, as we performed stent placement only for patients without combined infection. In five of the 16 patients, 6-F catheters were placed around the liver surface to monitor for intraperitoneal hemorrhage during the procedure before PTBD.

The appropriate intrahepatic bile duct was punctured with a 21-gauze needle (Top, Tokyo, Japan) under US guidance, and percutaneous transhepatic cholangiography was then performed to confirm obstruction of the bile duct (Fig 1b). After placement of a 6.5-F catheter (Seeking catheter; Hanako, Saitama, Japan) and a 0.035-inch angled hydrophilic guide wire (Radifocus Guide Wire M; Terumo, Tokyo, Japan) past the obstruction and into the duodenum, the overall length of the obstruction was confirmed with injection of contrast material. The guide wire was exchanged for a 0.035-inch guide wire (Amplatz Extra-Stiff Guide Wire; William Cook Europe, Bjaeverskov, Denmark), an introducer sheath (Create Medic, Yokohama, Japan) was inserted to increase the diameter of the tract, and the expandable metallic stent was then placed. Uncovered stents were placed through 7-F sheaths, and covered stents were placed through 10-F sheaths. Covered stents were mainly used in patients with aggressive pancreatic cancer based on operator preference. Seven patients who had common bile duct or Bismuth type I obstructions were each treated with a single stent. There were three patients in whom it was difficult to span the distance with a single stent (Table 1). In the six patients with Bismuth type II, III, and IV obstructions, attempts were made to minimize the number of punctures to prevent bile leakage or intraperitoneal hemorrhage as much as possible and to place the minimum number of stents required to drain at least 50% of the liver volume (3). The stents placed in the common bile duct extended 1 cm beyond the papilla of Vater in all patients. All placed stents were fully expanded with predilation (n =

Table 2. Outcomes of Patients Undergoing One-Step Biliary Stent Placement with Transhepatic Tract Embolization

Pt. No.	Clinical Success	Total Bilirubin (mg/dL)		Complications	Stent Occlusion (d)	Survival (d)	Cause of Death
		Before	After				
1	Yes	4.5	0.7	None	NA	61	Progression
2	Yes	5.4	2.7	None	NA	74	Progression
3	Yes	10.8	0.9	None	NA	39	Progression
4	Yes	1.1	0.7	None	NA	86	Progression
5	Yes	4.8	0.7	Right pleural effusion	NA	153	Progression
6	Yes	13.4	2.3	None	NA	66	Progression
7	No	6.4	17.4	Cholangitis	NA	19	Complication
8	Yes	2.7	0.5	Right pleural effusion	159	175	Progression
9	Yes	12.7	3.5	Bloody bowel discharge	NA	43	Progression
10	Yes	5.1	0.3	Self-limiting hemobilia	NA	169	Progression
11	Yes	7.3	3.4	Cholangitis	NA	33	Progression
12	Yes	8.8	0.8	None	NA	56	Progression
13	Yes	7.1	0.7	Right pleural effusion	NA	93	Progression
14	Yes	4.1	1.6	Right pleural effusion	NA	128	Progression
15	Yes	4.3	0.8	None	NA	66	Progression
16	No	8.7	16.4	None	NA	24	Progression

Note.—NA = not applicable.

12) or postdilation (n = 8) with 6–10-mm balloon catheters (Synergy [Boston Scientific, Natick, Massachusetts] or Powerflex [Cordis/Johnson and Johnson, Oosteinde, The Netherlands]).

After stent placement, the introducer sheath was replaced by a 6.5-F catheter, confirming good flow of contrast material through the biliary system (Fig 1c). The biliary access point and distal end of the transhepatic tract were carefully determined by injecting contrast material. Tract embolization was performed by advancing and tightly packing one to three 0.035-inch metallic coils (5 mm × 5 cm, 4 mm × 3 cm, 3 mm × 4 cm; MReye embolization coil; William Cook Europe) through a 6.5-F catheter. The coils were pushed by using a 0.035-inch wire, and the 6.5-F catheter was gently removed (Fig 1d).

Study Endpoints and Definitions

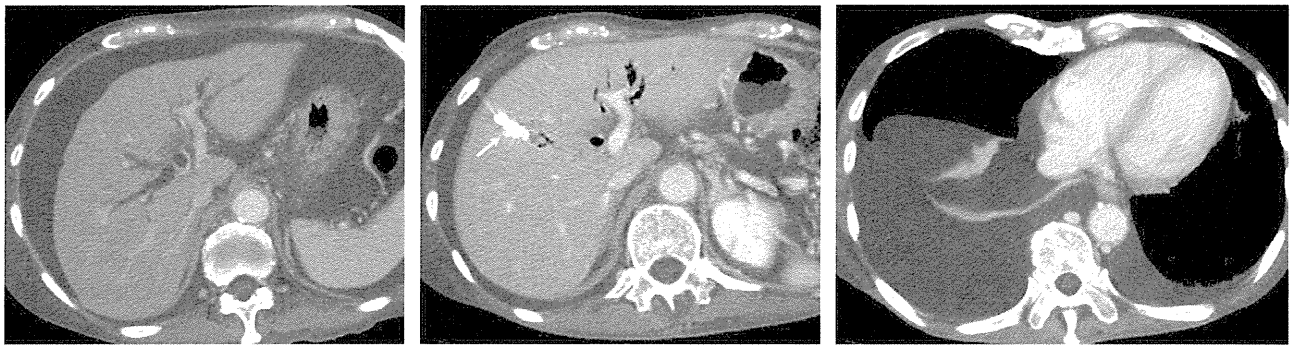
Technical success, clinical success, complications, stent patency, and duration of survival were retrospectively assessed. Technical success was defined as percutaneous transhepatic stent placement in the expected position and successful embolization of the tract without an external drainage catheter left in place. Clinical success was defined as a decrease in serum total bilirubin levels within 30 days of stent placement compared with levels recorded before the procedure. All complications arising from the procedure were divided into major and minor categories according to the reporting standards of the Society of Interventional Radiology (20).

Follow-up, which consisted of clinical examination and laboratory testing, including serum total bilirubin, serum liver enzyme levels, and complete blood count, was performed as needed until the time of death. US examination was performed to assess postprocedural biloma, ascites, and pleural effusion. When total serum bilirubin levels were increased and stent occlusion was suspected, CT or US examination was performed to confirm stent malfunction by dilation of the intrahepatic bile ducts. Stent patency was judged based on the absence of increased total serum bilirubin levels or the absence of dilation of intrahepatic bile ducts on CT or US examination even if total serum bilirubin level was increased. If there was no evidence of stent malfunction during the patient's life, the stent patency period was considered to be equal to the survival period.

RESULTS

Technical Success

Stent placement and tract embolization were successful in all patients without leaving an external drainage catheter, and the technical success rate was 100% (Table 2). All 16 patients received stent placement via the left (n = 4) or right (n = 12) hepatic lobe approach. Two patients received multiple stent placements through two puncture sites on the right, and one patient received three punctures on the right. In each of the remaining 13 patients, stents were placed through one puncture site. One patient received bilateral stent placement through one puncture site on the right in a "T" configuration. Consequently, a total of 20 transhepatic tracts were embolized. A total of 28 expandable metallic stents were inserted according to availability and operator preference. A total of 21 uncovered stents (Zilver; William Cook Europe) were placed in 11 patients, and seven cov-



a. b. c.

Figure 2. Gastric cancer with nodal metastasis in a 57-year-old man (patient 5). **(a)** Contrast-enhanced CT before the procedure shows dilated intrahepatic biliary ducts and massive ascites. **(b)** Contrast-enhanced CT after the procedure revealed improvement of obstructive jaundice and decreased ascitic fluid. Note that the transhepatic tract was tightly packed with metallic coils (arrow). **(c)** Contrast-enhanced CT also showed significantly increased right pleural effusion.

ered stents (VIABIL; W.L. Gore and Associates, Flagstaff, Arizona) were placed in five patients in the common bile duct.

Clinical Success

Reduction of the total serum bilirubin level compared with the preprocedural level was achieved in 14 of 16 patients, yielding a clinical success rate of 87.5%. The mean total serum bilirubin level before the stent placement was 6.7 mg/dL ± 3.5 (SD) (median, 5.9 mg/dL; range, 1.1–13.4 mg/dL), and that after the stent placement was 3.3 mg/dL ± 5.4 (median, 0.9 mg/dL; range, 0.3–17.4 mg/dL). The mean total serum bilirubin levels after the procedure were significantly lower than those before the procedure ($P = .009$).

Clinical success could not be achieved despite the procedure in two patients (12.5%). In one patient who had a Bismuth type IV obstruction, an additional stent was inserted into another intrahepatic biliary duct 6 days after the initial procedure to achieve drainage of the entire liver; however, the patient died 24 days after the procedure without showing any decrease of serum bilirubin level as a result of hepatic insufficiency caused by multiple liver metastases. The other patient, who had a distal bile duct obstruction, died of cholangitis 19 days after the procedure.

Complications

Major complications occurred in seven patients (43.7%), and included postprocedural cholangitis with fever and leukocytosis treated by administration of antibiotic therapy in two patients (12.5%), bloody bowel discharge requiring blood transfusion in one patient (6.2%) who had undergone balloon dilation of a biliary stricture, and right pleural effusion in four patients (25.0%). In one patient who died of cholangitis 19 days after stent placement, the death was judged to be a procedure-related mortality. The patient had distal bile duct occlusion and also had distal intestinal obstruction caused by peritoneal dissemination, and developed reflux cholangitis complicated by sepsis after the procedure, resulting in death. All four patients in whom right pleural effusion occurred received stent placement via the right hepatic lobe approach without paracentesis during the procedure. CT examination after stent placement showed increased right pleural effusion and decreased ascites (Fig 2). The pleural effusions were treated successfully by percutaneous drainage and aspiration over a period of 3–5 days. A diagnostic pleural tap from the right chest did not reveal bile, and laboratory testing of pleural effusion did not show increased total bilirubin levels. No peritonitis caused by bile leakage or intraperitoneal hemorrhage occurred in any of the 16 patients.

A minor complication was seen in one patient (6.2%). Self-limited hemobilia was caused by balloon dilation of biliary stricture and confirmed by cholangiography during the procedure. The patient did not require blood transfusion.

Follow-up

Complete follow-up until death was carried out for all patients. The survival period after stent placement ranged from 19 to 175 days (median, 66 d; mean, 80.3 d ± 50.5). Two patients died within 30 days after the procedure: one accounting for the procedure-related mortality mentioned earlier and another who died 24 days after the procedure because of hepatic insufficiency resulting from multiple liver metastases. The remaining 14 patients died of disease progression.

Of the 14 patients who survived for longer than 30 days after stent placement, three patients (21.4%) showed increased total serum bilirubin levels 37, 46, and 151 days after the procedure. One of these three patients showed stent occlusion, which was confirmed by US examination 159 days after stent placement, and died 175 days after the procedure without any repeat intervention. In the other two patients, no stent occlusion was evident on CT and/or US examination, and the patients died of hepatic insufficiency caused by disease progression 33 and 66 days after stent

placement. Overall, primary stent patency was achieved in 14 of 16 patients (87.5%), and secondary patency was achieved in an additional patient, for a total patency rate of 93.7%.

DISCUSSION

This study demonstrates that tract embolization for percutaneous biliary metallic stent placement in patients with massive ascites is technically feasible and clinically effective, with a limited number of severe complications. These findings indicate that percutaneous biliary stent placement may be considered as a treatment option even in patients with massive ascites when the endoscopic approach is not feasible or has failed.

In this study, adequate stent placement to cover the stricture was successfully performed in all patients, and tract embolization with metallic coils was also successfully carried out in all patients. Our results also show no evidence of bile peritonitis, subcapsular biloma, or intraperitoneal hemorrhage. These findings suggest that tract embolization is quite useful for preventing bile leakage and bleeding into the peritoneal cavity even in patients with massive ascites, as described in some previously published studies (10–13). Conversely, Thornton et al (18) found that a few patients (5.6%) who received primary metallic biliary stent placement had symptoms of bile peritonitis after catheter removal. The discrepant findings may have come about because most of their patients did not undergo tract embolization (three of 52 patients received primary biliary stent placement), and it was not revealed whether these three patients developed bile peritonitis (18). Although Lammer et al (21) also reported simultaneous deposition of compressed gelatin sponge into the transhepatic tract in uncomplicated cases, they documented no precise number of patients who underwent tract embolization. Nevertheless, Thornton et al (18) speculated that immediate removal of the biliary access facilitated by tract embolization might be desirable, and this would have mandated a new biliary drainage procedure for patients with ascites. The present results clarify their speculation.

We used metallic coils to embolize transhepatic tracts because they can be delivered precisely and placed tightly in the appropriate location, although other embolic materials, including gelatin sponges (10), n-butyl cyanoacrylate (11,12,14), AMPLATZER Vascular Plugs (15), and metallic coils (13) have also been used. The use of gelatin sponge or n-butyl cyanoacrylate poses a risk of material migration into the biliary tree, possibly resulting in biliary obstruction, and incomplete embolization of the tract. The AMPLATZER Vascular Plug is reasonable to use in the transhepatic tract but is comparably expensive. In addition to complete tract embolization, optimization of bile flow by full expansion of the stents is crucial in the authors' opinion for the prevention of bile reflux; however, this could not be definitively proven by the present study.

By contrast, a significant right pleural effusion developed in four of 12 patients who were treated by a right hepatic lobe approach without paracentesis. We assume that transpleural puncture associated with the use of a right hepatic lobe approach leads to the leakage of ascites into the pleural cavity. This may have been prevented by a left hepatic approach or large-volume paracentesis before the procedure. In addition, we encountered one patient who died of postprocedure cholangitis. A possible reason is that all the patients in the present study had more advanced disease and were in poorer general condition than patients in other published reports, and this condition predisposed them to lethal complications. This possibility indicates that early infection potentially leads to death in such patients who have advanced disease.

The 87.5% clinical success rate of biliary stent placement in the present study is comparable to those of others (2–5,8). It should be noted that, despite successful drainage of the entire liver, one of two patients who showed clinical failure died of hepatic insufficiency caused by multiple liver metastases. This outcome highlights the fact that biliary intervention does not always lead to clinical improvement in patients with extremely advanced disease, even if adequate drainage can be achieved.

The median and mean survival durations after stent placement in the present study were 66 days and 80.3 days, respectively. This may be attributable to the poor clinical status of the patients in the study. These patients had extremely advanced malignancies, most of which not of hepatobiliary/pancreatic origin. These results are consistent with those reported by Thornton et al (18) and Meller et al (21), who reported poorer survival after biliary stent placement in non–hepatobiliary/pancreatic malignancies than in hepatobiliary/pancreatic malignancies. We consider that primary stent placement with tract embolization might have been beneficial for patients with ascites and a limited survival period, because it provides 100% catheter-free survival and eliminates lifestyle limitation and potential complications such as insertion-site pain, catheter dislodgment, and pericatheter leakage of bile or ascites related to the presence of an external drainage catheter (18). It would be difficult to assess the true stent patency rate because of the short observation of the limited survival period.

The present study has limitations. First, the study design was retrospective, and the sample size was small. However, we are aware of no published that have investigated the efficacy of primary percutaneous biliary stent placement in patients with massive ascites except for one case report (11). The second limitation was the lack of long-term follow-up as a result of the patients' short life expectancies, which limited assessment of long-term stent patency. Finally, no real evaluation of the tract for bile leakage was undertaken in any sort of systemic manner; only a diagnostic tap of ascites and patient-reported abdominal pain were assessed. Despite these limitations and the slightly higher rate of complications than in other studies, we believe percutaneous stent placement with tract embolization in a single session may be an important treatment

option for patients with obstructive jaundice that cannot relieved by endoscopic intervention, in addition to massive ascites.

In conclusion, we report that primary biliary stent placement with coil embolization of the tract is technically safe in patients with massive ascites. It offers an effective palliative treatment option for malignant biliary obstruction when endoscopic intervention is not possible.

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Int J Clin Oncol (2012) 17:301–305
DOI 10.1007/s10147-012-0446-0

REVIEW ARTICLE

Clinical trials of interventional oncology

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Received: 19 June 2012 / Published online: 27 July 2012

Abstract Interventional oncology has great potential to be a good treatment modality in the field of oncology, because its procedures are minimally invasive and fairly quick. However, except for a few procedures such as percutaneous radiofrequency ablation and trans-catheter arterial chemo-embolization that have been recognized as standard treatments for hepatocellular carcinoma, most procedures have not been established as the standard treatment modality due to the limited number of clinical trials with compelling evidence. There are several common problems when performing clinical trials of interventional oncology. The first is that the outcomes of clinical trials are greatly influenced by the level of technical skill of the physicians. The second is that equipment and devices vary widely in countries and regions, and they also influence the outcomes. The third is that the methodology of clinical trials for techniques such as interventional oncology has not yet been established. The fourth is the difficulty of setting appropriate endpoints; quality of life is suitable for evaluating interventional oncology in palliative care, but it is not easy to set as the endpoint. The fifth is the difficulty of employing a blinded design, because the procedure cannot be performed without the physician's awareness. Despite such difficult situations, many multi-institutional clinical trials of interventional oncology have been carried out in Japan, with some challenging results. Establishing evidence is critical to making interventional oncology the standard treatment. Interventional radiologists should know the importance of clinical trials, and should move ahead in this direction in a step-by-step manner.

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Keywords Interventional oncology · Interventional radiology · Clinical trial · Evidence

Introduction

Interventional radiology is a subspecialty of diagnostic radiology, in which percutaneous treatments are conducted under an image-guidance system without any open surgery. The term interventional radiology was proposed by Malgulis as "interventional diagnostic radiology" in 1967 [1], and the concept of "interventional radiology" was established by Wallace in 1976 [2]. This procedure is minimally invasive and fairly quick. Since 2000, as the term "interventional radiology" became acknowledged in the field of oncology, a new one, "interventional oncology" has been used. Although the term is well-known, there are only a few procedures recognized as standard treatment modalities in oncology due to the limited number of clinical trials with compelling evidence.

In this review article, the current situation, issues, and challenges of clinical trials in interventional oncology are introduced.

Current situation of clinical trials in interventional oncology

Percutaneous radiofrequency ablation (RFA) is one of the typical procedures in interventional oncology. A RFA needle is inserted percutaneously into tumors under image guidance, and kills the tumor cells by a thermal ablative mechanism. RFA has been established as the standard treatment modality for multi-nodular ($n \leq 3$) hepatocellular carcinoma less than 3 cm in diameter [3]. The main

registered clinical trials of RFA for liver tumors are listed in Table 1 [4, 5]. Twenty-four out of 32 are randomized controlled trials (RCTs); 14 RCTs evaluated RFA by comparing it with other treatment modalities such as surgery, and 10 RCTs evaluated additional treatments such as trans-catheter arterial chemo-embolization (TACE) combined with RFA. Most of the RCTs set challenging endpoints such as overall survival (OS) and/or progression-free survival (PFS). Clearly, most clinical trials in this field try to expand the indications of RFA or to replace other treatment modalities such as surgical resection. Since large numbers of patient enrollments are critical for such RCTs, most of clinical trials in this field have been carried out in China.

The registered clinical trials of RFA for lung and renal tumors are listed in Table 2 [4, 5]. The number of trials is much smaller than for liver tumors, because RFA has not yet been established as a standard treatment in these fields. Fortunately, phase I trials for both lung and renal tumors have been carried out in Japan. If phase II trials can provide promising results, it may be possible to move to phase III trials to evaluate RFA as the standard treatment modality. It is well known that surgical resection of renal tumors in patients with poor renal function is risky, and therefore RFA may replace surgical resection as the standard treatment for such selected patients. On the other hand, percutaneous cryoablation for renal tumors is available in practice at present. The indications of RFA should also be considered with that of cryoablation in the treatment for renal tumors. On the other hand, surgical treatments including thoracoscopic resection are firmly established as the standard treatment modality for small lung tumors. These surgical procedures can be performed with minimal invasion, and patients with poor pulmonary function not indicated for general anesthesia are also not good candidates for RFA. Therefore, establishing RFA as the standard treatment for lung tumors seems much more difficult than for renal tumor.

The main registered clinical trials of interventional oncology for palliative care are listed in Table 3 [4, 5]. In spite of advantages such as minimal invasiveness and short procedure time, there are few clinical trials of interventional oncology. One of the reasons may be the difficulty of performing clinical trials in this field. Despite the difficulty of measuring quality of life (QOL) of patients in the palliative stage, most trials use it as a primary endpoint. Japan is the most active country in this field, performing 12 out of 15 clinical trials. The main activity in this field is medical treatment such as administration of opioids, hence it is very challenging to establish RCTs of interventional oncology as a standard treatment.

There are many clinical trials of trans-catheter arterial treatments such as trans-catheter arterial chemo-emboli-

Table 1 Registered clinical trials of radiofrequency ablation (RFA) for liver tumors (from clinicaltrials.gov and UMIN-CTR) ($N = 32$)

Country		Disease		No. of patients		Study design		Details of RCTs		Primary endpoint of RCTs	
China	16	HCC	28	≤50	6	RCT	24	RFA vs. others	14	OS	14
USA	6	Metastasis	1	>50, ≤100	7	Phase II	3	RFA ± others	10	PFS	2
EU	4	HCC/Metastasis	1	<100, ≤200	13	Phase I, I/II	3			Others	8
Asia	3	Any neoplasm	1	<200	6	Observational	2				
Japan	2	Others	1								
Other	1										

Table 2 Registered clinical trials of RFA for lung and renal tumors (from clinicaltrials.gov and UMIN-CTR)

Country		Disease		No. of patients		Study design		Details		Primary endpoint	
USA	3	Lung tumor	7	≤50	5	Phase I, I/II	1	RFA alone	4	AE	2
Japan	2			>50, ≤100	2	Phase II	3	RFA c/w others	3	CR rate	2
China	1					Observational	3			PFS	2
Other	1									Other	1
USA	1	Renal tumor	3	≤50	2	Phase I/II	1	RFA alone	2	AE	1
Japan	1			>100	1	Phase II	1	RFA c/w others	1	CR rate	1
China	1					Observational	1			PFS	1

c/w comparing with, *AE* adverse events, *CR* complete response

Table 3 Registered clinical trials of interventional oncology for palliative care (from clinicaltrials.gov and UMIN-CTR)

Disease		Country		No. of patients		Study design		Intervention	Primary endpoint
Vena cava syndrome	3	Japan	2	≤50	3	Phase I/II	1	Stent	Safety
		Canada	1			RCT	1		QOL
						Observational	1		QOL
Persistent ascites	2	Japan	2	≤50	2	Phase I/II	1	Perito-neovenous shunt	Safety
						RCT	1		QOL
Colon stenosis		Japan	2	≤50	2	Phase II	1	Stent	QOL
		Company	1	>50, ≤100	1	RCT	1		QOL
						Observational	1		QOL
Broncheal stenosis		Canada	1	>50, ≤100	1	RCT	1	Stent	Patency
Painful bone tumor		Japan	2	≤50	2	Phase I/II	1	Cement injection	Safety
						RCT	1		QOL
Painful bone tumor		Japan	1	≤50	1	Phase I/II	1	RFA	Safety
Painful pelvic tumor		Japan	1	≤50	1	Phase I/II	1	RFA	Safety
Upper gastrointestinal obstruction		Japan	2	≤50	2	Phase II	1	PTEG	QOL
						RCT	1		QOL

PTEG percutaneous trans-esophageal gastric tubing

zation (TACE) and hepatic arterial infusion chemotherapy (HAIC) for liver tumors. TACE is established as the standard treatment modality for intermediate stage HCC, and the most important clinical question is the efficacy of the combination of TACE with molecular target agents such as solafenib. Trials to evaluate the superiority of such combinations require approximately 1000 cases, and therefore are carried out as pharmaceutical company oriented international RCTs with TACE ± molecular target agent design. However, details of TACE including selection of anti-cancer agents, selection of embolization materials, catheterization technique, TACE interval and imaging modalities employed vary in each trial. TACE is the standard treatment, but the details of TACE have not yet been standardized. Additionally, in most of these RCTs, overall survival (OS) is used for the primary endpoint. However, intermediate-stage HCC patients in whom TACE fails have the chance to receive other molecular target agents when the protocol is off, and such post-protocol treatments may influence their OS. Therefore, it is not easy to determine the true impact of TACE with molecular target agents on the prolongation of OS in this group of patients.

Issues of clinical trials in interventional oncology

There are several common problems when performing clinical trials in interventional oncology. It is important to understand these problems prior to making the appropriate evidence-based clinical decision in practice based on the results of clinical trials.

Level of skills

The essence of the treatment modality of interventional oncology is technical skill, although it may also sometimes depend upon various kinds of devices and drugs. Therefore, the technical skill directly influences the treatment outcome, which means that outcomes can vary in accordance with the technical skill of each study group even in the same procedure. Level of techniques can be seen in various fields of interventional oncology. For example, in clinical trials of HAIC for unresectable liver metastases from colorectal cancer, Kerr et al. [6] reported they could not start HAIC after port-catheter placement in 39 % of patients, while Tanaka et al. [7] reported that the success rate was 97 %. Additionally, there is a "learning curve" in technical procedures through experience. Even though the same physician performs the same procedure, the outcomes may well vary depending upon the number of cases experienced.

Variety of equipments and devices

The efficiency of equipment for image guidance such as ultrasonography, angiography and computed tomography greatly influences the outcomes of procedures in interventional oncology. However, this is quite varied in different countries and regions due to their economic situation. For example, CT-angio systems, which were developed in Japan and greatly influence the outcome of TACE for hepatocellular carcinoma [8], are routinely used in Japan, but are available in only a few institutions in Western countries. A micro-catheter, which is an indispensable

device for accurate super-selective TACE, is commonly used in some countries including Japan, but not used in other countries. On the other hand, microspheres for vascular embolization are commercially available in many countries, but have not yet been approved in Japan. In summary, the equipment and devices for interventional oncology are quite varied in different countries and regions.

Lack of methodology in clinical trial

The methodology of clinical trials in oncology has been developed to focus mainly on the development of anti-cancer agents. While the key concepts of clinical trials are the same in the field of interventional oncology, the design of clinical trials to evaluate safety in medical oncology cannot be adapted to interventional oncology. Commonly, in a phase I study to evaluate the safety of a newly developed agent, step-by-step dose escalation is used. However, the concept of dose escalation cannot be use in interventional oncology, because the procedure itself is being evaluated. Many new procedures have been developed in interventional oncology, but a clinical trial methodology to evaluate safety, the most important first step in introducing a newly developed procedure, is lacking and has not been established.

Difficulty of setting appropriate endpoints

Because all anti-tumor procedures in interventional oncology are loco-regional treatments, it is not easy to show a significant survival benefit such as OS. Of course, OS is one of the hardest endpoints, and loco-regional treatment should also show an advantage using such a hard endpoint. However, OS is sometimes influenced by additional treatments, and the advantages of loco-regional treatments on OS are minimized with additional factors. On the other hand, the result frequently observed when loco-regional treatment is effective is the improvement of symptoms, which is very important especially in palliative care. However, the evaluation of symptom improvement and quality of life is still difficult to use as a reliable hard endpoint. Therefore, most clinical trials of interventional oncology in palliative care must be performed with such unreliable endpoints.

Difficulty of employing blinded design

As with surgical treatments, interventional procedures cannot be performed without the physician's awareness. Therefore, it is usually impossible to use a blinded design for RCTs such as with or without procedures. Only when a part of the procedure is randomized, such as active drug injection versus placebo drug injection, can a double-blind design be applied for RCTs.

Table 4 Clinical trials of Japan Interventional Radiology in Oncology Study Group (JIVROSG)

JIVROSG-0201	Phase I/II of TTPVS for persistent ascites
JIVROSG-0202	Phase I/II of PVP for painful bone mets
JIVROSG-0203	Phase I/II of RFA for lung cancer
JIVROSG-0204	Phase I/II of RFA for painful intrapelvic tumor
JIVROSG-0205	Phase I/II of PTEG for upper GI obstruction
JIVROSG-0206	Phase I/II of stent therapy for colonic stenosis
JIVROSG-0208	Phase I/II of RFA for painful bone mets
JIVROSG-0301	Phase I/II of hepatic arterial GEM for cholangio carcinoma
JIVROSG-0302	Phase I/II of uterine artery embolization for uterine fibroid
JIVROSG-0401	Phase I/II of CDDP-TACE for HCC
JIVROSG-0402	Phase II of stent therapy for SVC/IVC syndrome
JIVROSG-0604	Phase II of EPI-Dox/Dox-Lipiodol-GS TACE for HCC (Korea–Japan)
JIVROSG-0606	Phase III of HAIC with FOLFOX for liver mets from CRC
JIVROSG-0701	Phase I/II of RFA for renal cancer
JIVROSG-0702	Phase II of RFA for lung cancer
JIVROSG-0703	Phase II of PVP for painful bone mets
JIVROSG-0704	Phase I/II of RFA for osteoid osteoma
JIVROSG-0803	Phase III of shunt for persistent ascites
JIVROSG-0804	Phase III of PVP for painful bone mets
JIVROSG-0805	Phase III of PTEG for upper GI obstruction
JIVROSG-0806	Phase III of stent therapy for colorectal stenosis
JIVROSG-0807	Phase III of stent therapy for SVC/IVC syndrome

TTPVS trans-jugular trans-hepatic peritoneovenous shunt, *PVP* percutaneous vertevroplasty, *GI* gastrointestinal, *GEM* gemcitabine, *CDDP* cisplatin, *SVC* superior venacava, *IVC* inferior venacava, *EPI* epirubicin, *Dox* doxorubicin, *GS* gelatin sponge, *HAIC* hepatic arterial infusion chemotherapy, *FOLFOX* combination chemotherapy with folinic acid, fluorouracil and oxaliplatin, *CRC* colorectal cancer

Clinical trials of interventional oncology in Japan

To establish evidence in interventional oncology, the Japan Interventional Radiology in Oncology Study Group (JIVROSG) was organized in 2002 with a grant from the Ministry of Health, Welfare and Labor. At present, JIVROSG is composed of certificated interventional radiologists from 90 institutions, and more than 20 clinical trials listed in Table 4 have been carried out. Through carrying out these trials, JIVROSG developed the "JIVROSG 3 × 3 method" as a new phase I study design for evaluating the safety of technical procedures, and has performed some phase I/II trials for newly developed procedures using this method [9, 10]. Additionally, phase III RCTs to evaluate procedures of interventional oncology in palliative care have been carried out since 2010. RCTs in palliative care are not easy, but if interventional oncology showed a significant advantage in these trials, it could become the

standard treatment in these fields. This is the primary challenge of interventional oncology for palliative care worldwide.

Conclusion

Interventional oncology has potential advantages as a better treatment in various fields of oncology because of its features. However, most procedures in interventional oncology have not been recognized as the standard treatment because of lack of firm evidence. Although there are issues in performing clinical trials of interventional oncology, establishment of evidence is critical to making interventional oncology the standard treatment in oncology. Interventional radiologists should know the importance of clinical trials, and should move ahead in this direction in a step-by-step manner.

Acknowledgment This review article was supported in part by a grant-in-aid for cancer research from the National Cancer Center in Japan.

Conflict of interest The author declares that he has no conflict of interest.

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