LMWH for the prevention of venous thromboembolism and its safety in oncologic patients undergoing interventional procedures.

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

References

1. Sofue K, Takeuchi Y, Arai Y, Sugimura K (2013) Life-threatening cerebral edema caused by acute occlusion of a superior vena cava stent. Cardiovasc Intervent Radiol 36:272–275. doi:10.1007/s00270-012-0421-1
2. Trousseau A (1865) Phlegmasia alba dolens. Lectures on clinical medicine, delivered at the Holte-Dieu, Paris 5:281–332
3. Blom JW, Doggen CJ, Osanto S, Rosendaal FR (2005) Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 293:715–722
4. Ganeshan A, Hon LQ, Warakaulle DR et al (2009) Superior vena caval stenting for SVC obstruction: current status. Eur J Radiol 71:343–349
5. Uberoi R (2006) Quality assurance guidelines for superior vena cava stenting in malignant disease. Cardiovasc Intervent Radiol 29:319–322
6. Lyman GH, Khorana AA, Kuderer NM et al (2013) Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 31:2189–2204
7. Warkentin TE, Levine MN, Hirsch J et al (1995) Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332:1330–1335

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CASE REPORT

Infusion of 50 % glucose solution to occlude an intrahepatic portosystemic venous shunt before percutaneous transhepatic portal embolization: report of a case

Keitaro Sofue · Yoshito Takeuchi · Kentaro Shibamoto · Koji Sugimoto · Kazuro Sugimura · Yasuaki Arai

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Abstract A 68-year-old man with cholangiocarcinoma underwent percutaneous transhepatic portal embolization to expand the indication for hepatic resection. Selective right posterior portography revealed an intrahepatic portosystemic venous shunt (IPSVS) connecting the segment VII branch to the right hepatic venous branch. An infusion of 50 % glucose solution was given to occlude the shunt. This is novel management for IPSVSs when they are numerous, small, or torturous, and makes the subsequent procedures simpler, shorter, and less expensive.

Keywords Percutaneous transhepatic portal embolization · Intrahepatic portovenous shunt · Glucose solution

Introduction

Percutaneous transhepatic portal embolization (PTPE) is performed to expand the indications for major hepatic resection. Various embolic agents are used to achieve this and include gelatin sponge, fibrin glue, polyvinyl alcohol particles, cyanoacrylate and ethiodized oil, and absolute ethanol [1, 2].

Intrahepatic portosystemic venous shunts (IPSVS) can be congenital or may develop secondary to portal hypertension or trauma [3, 4]. For patients with an IPSVS, the therapeutic effect of PTPE is insufficient because of overflow of the embolic agent into the systemic circulation, potentially resulting in non-targeted embolization of the pulmonary artery. In this situation, blood flow through the portosystemic shunt must be stopped. An IPSVS is usually embolized with microcoils or particles [3, 5]; however, this can be difficult when there are numerous shunts or the shunt is small or torturous.

We report a case of PTPE coexisting with an IPSVS which was successfully occluded with an infusion of 50 % glucose solution.

Case report

A 68-year-old man with cholangiocarcinoma underwent preoperative PVE to induce selective hypertrophy and expand the indication for extended right hepatic resection. Contrast-enhanced computed tomography of the abdomen did not reveal an anomalous portovenous shunt. The right anterior branch of portal vein was punctured percutaneously with a 21-gauze needle (Top, Tokyo, Japan) under ultrasonographic guidance. A 5-French (F) sheath (Introducer set; Medikit, Tokyo, Japan) was advanced into the portal vein using the Seldinger technique under fluoroscopic guidance. A reverse-curved 5-F balloon catheter with a tip hole (Selecon balloon catheter; Terumo-Clinical Supply, Gifu, Japan) was also inserted into the posterior branch of the portal vein.

Selective right posterior portography was done with balloon occlusion, revealing an IPSVS connecting the segment VII branch to the right hepatic venous branch (Fig. 1). We decided to embolize the portovenous shunt to prevent overflow of the embolic agent into the systemic

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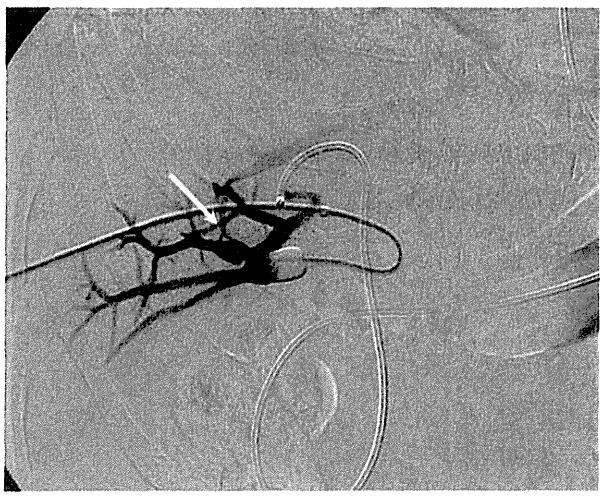

Fig. 1 Selective right posterior portogram with balloon occlusion revealed an intrahepatic portovenous shunt connecting the segment VII branches to the right hepatic venous branch (*arrow*)

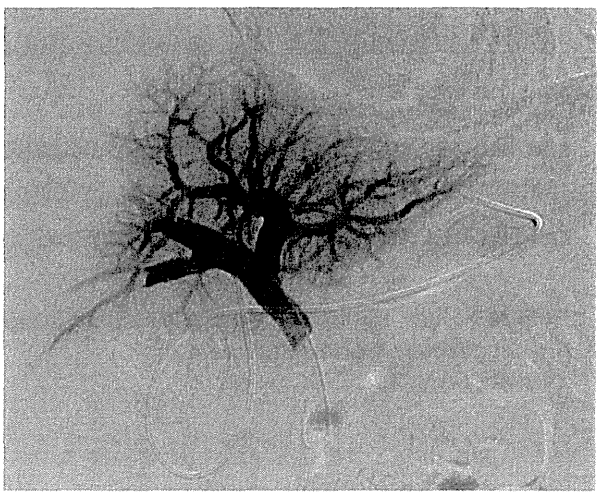

Fig. 3 Direct portogram obtained after embolization of right portal vein revealed no residual flow in the right portal venous branch or intrahepatic portovenous shunt

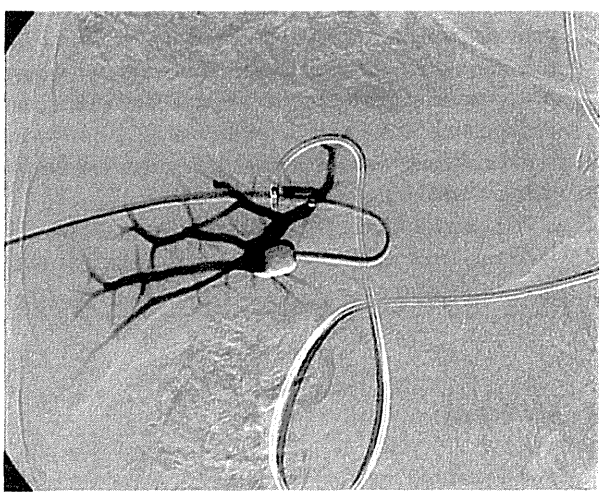

Fig. 2 Right posterior portogram with balloon occlusion after the infusion of 10 ml of 50 % glucose solution confirmed disappearance of the intrahepatic portovenous shunt

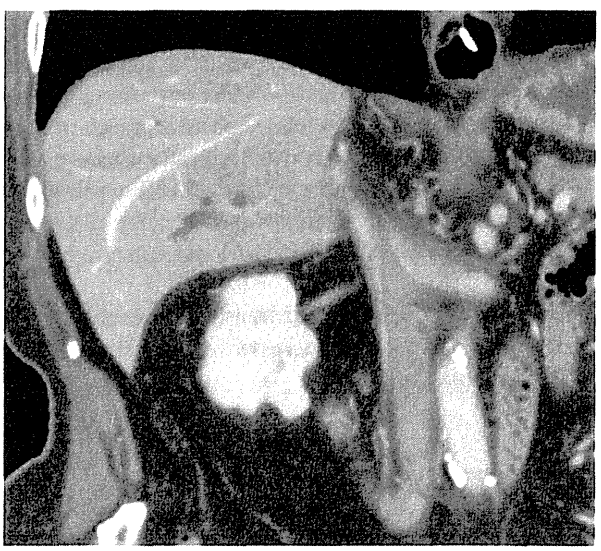

Fig. 4 Coronal image of contrast-enhanced computed tomography obtained 20 days after portal vein embolization shows sufficiently thrombosed right portal branches without right hepatic vein embolization

circulation and to occupy the right posterior branch of the portal vein with embolic agent exclusively.

First, we infused 10 ml of 50 % glucose solution from the catheter, keeping the balloon inflated. Repeated selective right posterior portography showed disappearance of the portovenous shunt (Fig. 2). We injected 5 ml of absolute ethanol to embolize the right posterior branch of the portal vein, and 6 ml of absolute ethanol with balloon occlusion to embolize the right anterior branch of the portal vein. Finally, post-embolization portography confirmed complete occlusion of the right portal branches (Fig. 3).

He was followed-up for 20 days after the procedure using computed tomography, and the left lobe of the liver became hypertrophic with a hypertrophy rate of 151.7 % without recanalization of right portal vein, right hepatic vein embolization, and unexpected pulmonary embolization (Fig. 4). He underwent extended right hepatectomy 24 days after the procedure, and his postoperative course was uneventful.

Discussion

Percutaneous transhepatic portal embolization (PTPE) is widely accepted as an effective method for inducing

atrophy of the embolized lobe to be resected and compensatory hypertrophy of the contralateral lobe [1, 2]. The technical considerations for PTPE are that the portal vein is securely occluded, stagnating the embolic agents such as liquid or microparticles, without recanalization and non-target embolization [1, 6].

An IPSVS is a rare vascular anomaly which communicates persistently between the portal vein and the hepatic vein [3]. Two theories have been proposed to explain the cause of IPSVSs: congenital origin, suggesting a persistent embryonic venous anastomosis; and acquired origin, suggesting the formation of a shunt following portal hypertension or trauma [3, 4]. Typical contrast-enhanced CT findings of IPSVS are a dilated portal branch directly communicating with the hepatic vein through a dilated venous aneurysm [7]. Treatment of IPSVSs should be considered for patients with symptoms of hepatic encephalopathy. However, the IPSVS must be occluded before the PTPE, because it may cause insufficient occlusion of the portal vein and unexpected embolization of the pulmonary artery due to overflow of the embolic agent through the shunt. The embolic agents used for IPSVS should be selected according to the shunt size and morphology. Coils, gelatin sponge, n-butyl cyanoacrylate, and an amplatzer vascular plug have all been used [3, 5, 8].

We decided to use 50 % glucose solution to occlude the small shunt in our patient. Previous reports proposed the embolic mechanism of 50 % glucose for patients with esophageal or gastric varices treated endoscopically, as the endothelial cells of the vessel are injured by its high osmolarity, blood flow stagnates, and thrombus formation [9, 10]. Several investigators have also reported the utility of hypertonic solution injected into the vessels directly during balloon-occluded retrograde transvenous obliteration and sclerotherapy of the varicose leg veins [11, 12]. The advantages of 50 % glucose are that it is easy to inject repeatedly without significant risk and it is less expensive than other embolic materials. We aimed to decrease the blood flow of the IPSVS, thereby allowing the injected absolute ethanol to occupy the portal vein sufficiently. This experiment was similar to that of the 50 % glucose solution infusion to occlude collateral vessels before the injection of ethanolamine oleate to treat gastric varices [11]. The shortcoming of 50 % glucose solution infusion would be that a large IPSVS is not occluded and remains after the injection, and embolization using coils or an amplatzer vascular plug may be required. An additional disadvantage is that injecting a large amount of the agent may induce hyperglycemia. Further experience or studies are warranted to clarify the embolic efficacy of 50 % glucose infusion for IPSVS, because this study is only case report and not fully supported theoretically.

In summary, we reported a case of percutaneous transhepatic portal embolization coexisting with an IPSVS, which was successfully occluded with an infusion of 50 % glucose solution. This is novel management for IPSVSs that are numerous, small, or torturous, and makes the accompanying procedures simpler, shorter, and less expensive, reducing the need for coils or an amplatzer vascular plug.

Conflict of interest Keitaro Sofue and his co-authors have no conflict of interest.

References

1. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. J Vasc Interv Radiol. 2005;16:779–90.
2. Wakabayashi H, Okada S, Maeba T, Maeta H. Development of a de novo tumorous necrotic lesion in the liver after transcatheter arterial embolization combined with iodized oil infusion: report of a case. Surg Today. 1996;26:49–52.
3. Chevallier P, Oddo F, Souci J, Diaine B, Padovani B. Macroscopic intrahepatic portosystemic venous shunt: review of the literature and reclassification. J Radiol. 2001;81:597–604.
4. Park JH, Cha SH, Han JK, Han MC. Intrahepatic portosystemic venous shunt. AJR Am J Roentgenol. 1990;155:527–8.
5. Lee YJ, Shin BS, Lee IH, Ohm JY, Lee BS, Ahn M, et al. Intrahepatic portosystemic venous shunt: successful embolization using the Amplatzer Vascular Plug II. Korean J Radiol. 2012;13:827–31.
6. Di Stefano DR, de Baere T, Denys A, Hakime A, Gorin G, Gillet M, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. Radiology. 2005;234:625–30.
7. Ito K, Fujita T, Shimizu A, Sasaki K, Tanabe M, Matsunaga N. Imaging findings of unusual intra- and extrahepatic portosystemic collaterals. Clin Radiol. 2009;64:200–7.
8. Yoshimatsu R, Takeuchi Y, Morishita H, Iida N, Okabe H, Yamagami T, et al. Successful embolisation of intrahepatic portosystemic venous shunt using coils and n-butyl cyanoacrylate through two approach routes. Br J Radiol. 2006;79:e162–5.
9. Chang KY, Wu CS, Chen PC. Prospective, randomized trial of hypertonic glucose water and sodium tetradecyl sulfate for gastric variceal bleeding in patients with advanced liver cirrhosis. Endoscopy. 1996;28:481–6.
10. Kuo MJ, Yeh HZ, Chen GH, Poon SK, Yang SS, Lien HC, et al. Improvement of tissue-adhesive obliteration of bleeding gastric varices using adjuvant hypertonic glucose injection: a prospective randomized trial. Endoscopy. 2007;39:487–91.
11. Yamagami T, Kato T, Hirota T, Yoshimatsu R, Matsumoto T, Nishimura T. Infusion of 50 % glucose solution before injection of ethanolamine oleate during balloon-occluded retrograde transvenous obliteration. Australas Radiol. 2007;51:334–8.
12. Le Baleur A, Bourgeois A, Gillot C, Pillot P, Bellagha I, Frileux C. Per-operative multi-sclerosis using 66 % glucose. Treatment of choice and best prevention of pigmentations of venous origin. Phlebologie. 1983;36:349–52.

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Flow confirmation study for central venous port in oncologic outpatient undergoing chemotherapy: Evaluation of suspected system-related mechanical complications

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ABSTRACT

Purpose: To evaluate the efficacy and outcome of a flow confirmation study (FCS) in oncologic outpatients undergoing chemotherapy suspected of a central venous port (CVP) system-related mechanical complication.

Materials and methods: A total of 66 patients (27 men, 39 women; mean age, 60 years) received FCS for the following reasons: prolonged infusion time during chemotherapy ($n=32$), inability to inject saline fluid ($n=15$), lateral neck and/or back pain ($n=6$), subcutaneous extravasation of anticancer drug ($n=5$), arm swelling ($n=4$), and inability to puncture the port ($n=4$). FCS consisted of examining the position of CVP, potential secondary shifts or fractures, and integrity of the system using contrast material through the port.

Results: Of the 66 patients, 43 had an abnormal finding uncovered by FCS. The most frequent abnormal findings was catheter kinking ($n=22$). Explantation and reimplantation of the CVP system was required in 21 of the 66 patients. Remaining 45 patients were able continue using the CVP system after the FCS without any system malfunction.

Conclusion: FCS was effective for evaluating CVP system-related mechanical complications and was useful for deciding whether CVP system explantation and reimplantation was required.

1. Introduction

The use of a central venous port (CVP) was first reported by Niederhuber et al. [1] and has since become an essential system for the management of outpatient chemotherapy for the treatment of malignant tumors, which consist mainly of continuous and repeated infusion regimens of anticancer drugs [2]. Recently, most CVPs have been inserted by interventional radiologists using local anesthesia and real-time ultrasound (US), or fluoroscopic guidance, as reported by Morris et al. [3]. The advantage of radiological CVP implantation is the higher rate of technical success, compared with the landmark technique [4,5]. However, there were no differences in the early or late occurrence of post-procedural complications among US guidance, the landmark technique, and surgical cut-down [5]. Therefore, post-procedural CVP system-related complications remain a problematic issue.

Complications following CVP implantation have been well described in several publications [6–11], and post-procedural CVP system-related complications can be approximately divided into thirds as follows: infectious, venous thrombotic, and mechanical complications [11]. Infectious complications, including local infections and catheter-related blood stream infections, are diagnosed based on clinical findings and laboratory cultures [5,10]. Venous thrombotic complications mainly manifest as arm or facial swelling, cyanosis, venous distension, and superficial venous collaterals [12]. Mechanical complications include catheter malposition, catheter occlusion, catheter fragmentation, port damage, and fibrin sheath formation. These complications lead to system malfunction, and system explantation and reimplantation may occasionally be required. On the other hand, other troubles, such as infusion pump dysfunction or human error, can also occur and such difficulties are occasionally difficult to distinguish from mechanical complications even if a double-check system is utilized during bedside examinations [13].

At our institution, when a CVP system-related mechanical complication is suspected, patients are examined using a flow confirmation study (FCS) performed using fluoroscopy or digital subtraction angiography (DSA) in an angiographic suite, and

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Table 1
Clinical characteristics of patients.

Parameter	Value
Age, year	
Mean ± SD	60 ± 13
Range	15–79
Sex	
Men:Women	27:39
Complaint leading to suspicion of CV-port dysfunction	
Prolonged infusion time during chemotherapy	32
Inability to inject saline fluid	15
Lateral neck and/or back pain	6
Subcutaneous extravasation of anticancer drug	5
Arm swelling	4
Inability to puncture the port	4
Duration of CV-port implantation until complaint, days	
Mean ± SD	255 ± 301
Range	7–1475

SD, standard deviation.

interventional radiologists are responsible for making a diagnosis and deciding whether a system explantation and reimplantation should be performed. Although there are quite a few reports discussing CVP complications as well as giving percentages [6–11], no studies have elucidated the percentage of mechanical complications and defining them using FCS in large clinical experience.

The purpose of this study was to evaluate the efficacy and outcome of an FCS in oncologic outpatients undergoing chemotherapy who are suspected of having a CVP system-related mechanical complication.

2. Materials and methods

2.1. Patient population

This study was conducted in accordance with the amended Helsinki Declaration, and institutional Review Board approval was obtained for this retrospective study. Between July 2007 and December 2010, the continuous infusion of anticancer drugs was performed via an implanted CVP on an outpatient basis in a total of 1546 oncologic patients. Chemotherapy was started in the outpatient chemotherapy room using a drip infusion of the anticancer drug via a CVP after a physician and a nurse had checked the function of the CVP by flushing 10 mL of a saline solution through a specific puncture needle.

In 66 of the 1546 patients (4.3%), a CVP system-related mechanical complication was suspected and an FCS was subsequently performed by interventional radiologists. These 66 patients were analyzed and enrolled in the present retrospective study. The patient population included 27 men and 39 women with a mean age of 60 years (range, 15–79 years). The underlying cancers in these 66 patients were colorectal cancer in 41, gastric cancer in eight, ovarian cancer in four, esophageal cancer in three, osteosarcoma in three, pancreatic cancer in two, Ewing's sarcoma in two, non-Hodgkin's lymphoma in one, and an unknown primary origin in two. A CVP system-related mechanical complication was suspected in these patients for the following reasons: prolonged infusion time during chemotherapy ($n = 32$), inability to inject saline fluid ($n = 15$), lateral neck and/or back pain ($n = 6$), subcutaneous extravasation of anticancer drug ($n = 5$), arm swelling ($n = 4$), and inability to puncture the port ($n = 4$). The period between CVP implantation and the initial suspicion of a system-related mechanical complication varied from 7 to 1475 days (mean, 254 days) (Table 1).

In all 1546 patients, the CVP was implanted via the left subclavian vein ($n = 1083$), the right subclavian vein ($n = 427$), or the right internal jugular vein ($n = 36$) by interventional radiologists using US and fluoroscopic guidance; the protocol that was used

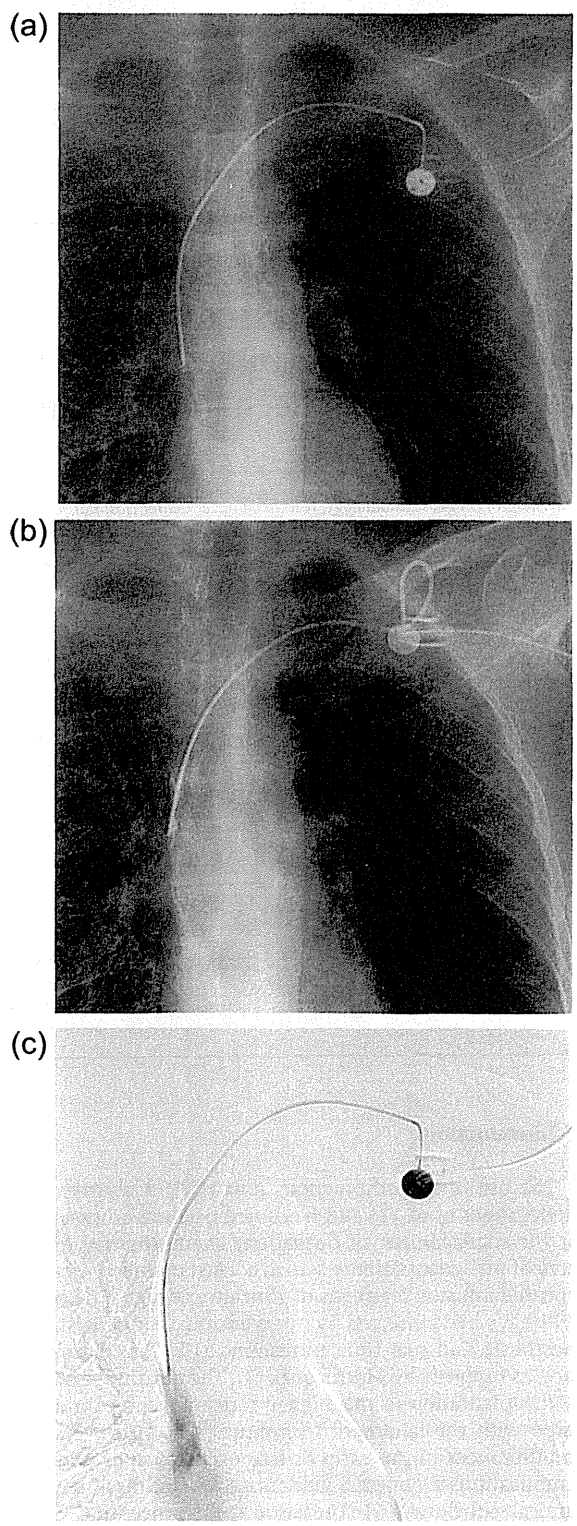


Fig. 1. Normal flow confirmation study findings in a 20-year-old woman with osteosarcoma. (a) Chest fluoroscopy reveals the adjusted catheter course and tip. (b) Chest fluoroscopy while the patient had raised her left arm shows a significant secondary shift of the catheter course and tip but did not indicate secondary catheter malfunction. (c) Digital subtraction angiography with the manual injection of contrast material through the port reveals excellent flow through the CVP system and no CVP system-related mechanical complications.

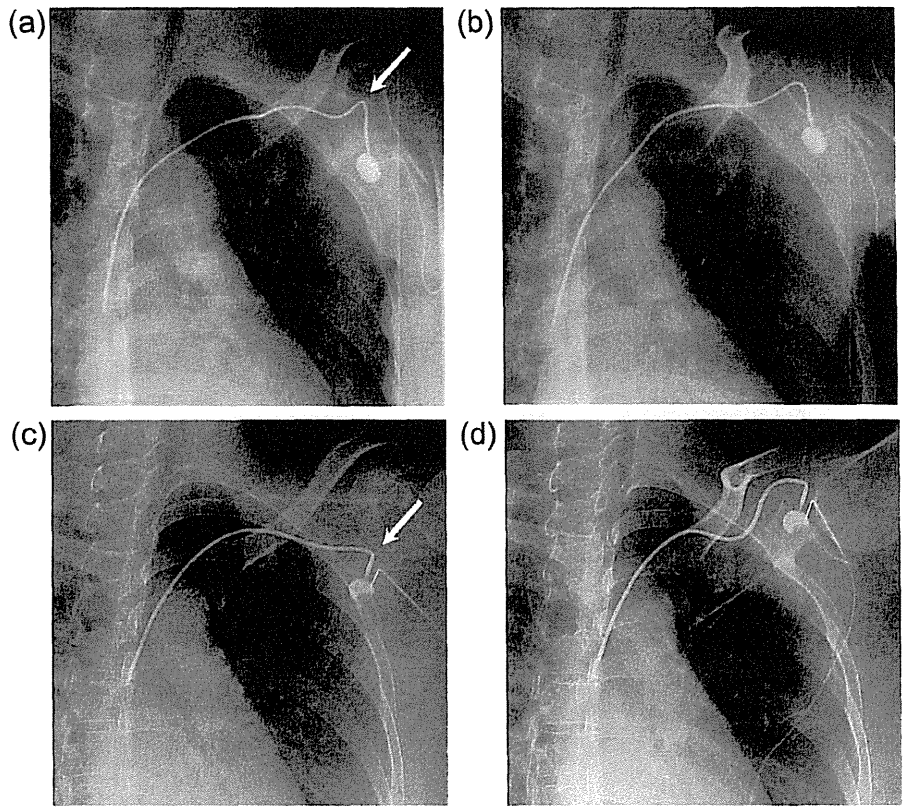


Fig. 2. Temporary catheter kinking in a 55-year-old woman with colon cancer (a), (b), and permanent catheter kinking in a 48-year-old woman with colon cancer (c), (d). Saline could not be injected in these patients, and a CVP malfunction was suspected. (a) Chest fluoroscopy after the injection of contrast material shows catheter kinking in a subcutaneous space (arrow). (b) The kinking was relieved when the patient raised her arm and was manually revised from the body surface. (c) Chest fluoroscopy after the injection of contrast material also revealed catheter kinking in a subcutaneous space (arrow). (d) The kinking was not relieved regardless of the patient's breathing and arm position, and the kink could not be revised from the body surface. The CVP system was explanted and reimplanted one day after the FCS.

was essentially identical to a previously described one [14]. The CVP consisted of a 6-Fr IV catheter and Septum ports from Orca CV kits (Sumitomo Bakelite, Tokyo, Japan) in 1278 patients, an 8-Fr Groshong catheter and MRI ports (Bard Inc., Salt Lake City, UT, USA) in 242 patients, and a 6-Fr Anthron PU catheter (Toray Medical, Tokyo, Japan) and CELSITE ports (B. Braun Medical Inc., Bethlehem, PA, USA) in 26 patients.

2.2. Flow confirmation study

FCS was performed in an angiographic suite (AXIOM Artis dta; Siemens Medical Solutions, Erlangen, Germany) using fluoroscopy and DSA after obtaining written informed consent from all the patients prior to the procedures. Fluoroscopy was first performed to confirm that the catheter and port were located in their original positions while the patient was lying in a supine position (Fig. 1a); significant secondary shifts or kinking of the catheter were then examined while the patient took a deep breath and raised his or her arm (Fig. 1b). Catheter kinking was categorized as temporary or permanent. The former is a kink that was positional and/or variable with breathing cycle and did not require explantation and reimplantation, while permanent is a fixed finding requiring replacement of port.

Finally, the possible occlusion or injury of the catheter or port, and fibrin sheath formation were examined using fluoroscopy or DSA with the manual injection of 10 ml of contrast material (Iopamiron 370; Bayer Schering Pharma, Osaka, Japan) through the port (Fig. 1c). The selective angiograms were obtained using a field of view that is closely collimated around the CVP system. The tube was positioned below the table and the input screen of the image intensifier was almost in contact with the patient skin. The acquisition was made with a frame rate of six frames per second and two second delay to obtain multiple masks for subtraction with breath-holding. Image acquisition was stopped when opacification of the CVP system and superior vena cava became apparent. The catheter or port injury is defined that a contrast material leaked through the catheter or port.

2.3. Follow-up

Based on the FCS results, the interventional radiologists determined whether the CVP system should be reimplanted. After the FCS, the patients in whom CVP explantation was determined unnecessary were followed until death or until they were lost to follow-up. The deadline for data acquisition was December 31, 2011.

3. Results

Fourty-three (65.2%) of the patients had abnormal findings: permanent catheter kinking ($n=11$) (Fig. 2a and b), temporary catheter kinking ($n=11$) (Fig. 2c and d), fibrin sheath formation around the catheter ($n=6$; Fig. 3a), inappropriate catheterization ($n=3$), venous stenosis or occlusion ($n=3$; Fig. 3b), catheter malposition into the azygos vein ($n=2$; Fig. 3c), catheter occlusion ($n=2$), and catheter injury (Fig. 3d), catheter fragmentation (Fig. 3e), catheter

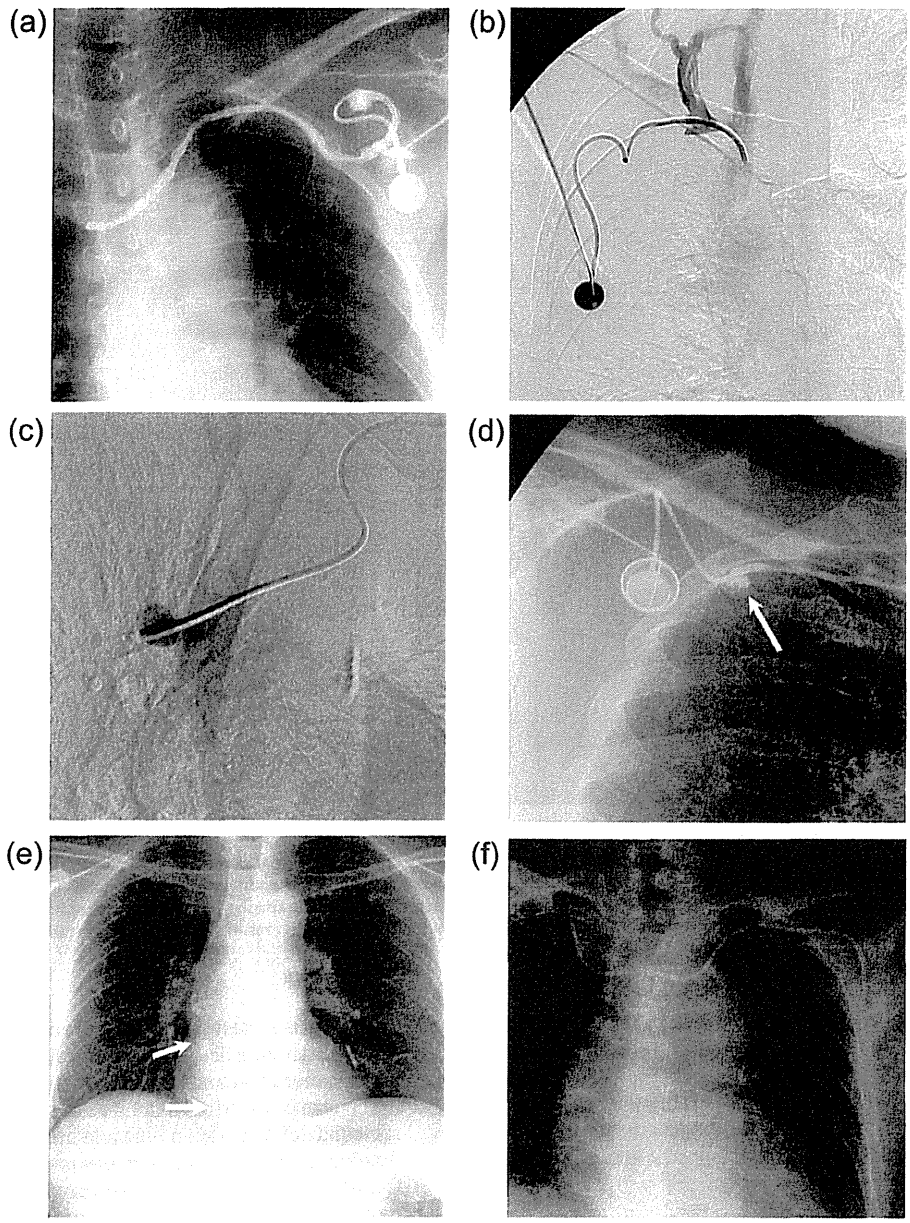


Fig. 3. Abnormal flow confirmation study findings. (a) A 71-year-old woman with gastric cancer complained of a prolonged infusion time during chemotherapy. Chest fluoroscopy after the injection of contrast material revealed fibrin sheath formation around the catheter. The CVP system was explanted and reimplanted six days after the FCS. (b) A 55-year-old man with esophageal cancer presented with right arm swelling. Digital subtraction angiography with manually injected contrast material through the port showed severe stenosis of the subclavian vein and the development of collateral circulation. Note that an abnormal catheter loop and retraction is evident, and the catheter tip is located too high in the SVC. (c) A 75-year-old man with colon cancer complained of a prolonged infusion time during chemotherapy. Digital subtraction angiography with manually injected contrast material through the port revealed catheter malposition into the azygos vein. This malposition was corrected spontaneously. (d) A 66-year-old man with colon cancer complained of the subcutaneous extravasation of the anticancer drug. Chest fluoroscopy after the injection of contrast material showed catheter injury in the clavicle and first rib region (arrow). The CVP system was explanted and reimplanted on the day of the FCS. (e) A 52-year-old woman with pancreas cancer presented with the subcutaneous extravasation of the anticancer drug. Chest fluoroscopy revealed a pinch-off catheter fragmentation (arrows). The embolized catheter was successfully retrieved using a loop snare guidewire, and the CVP system was reimplanted one day after the FCS. (f) A 73-year-old man with colon cancer presented with right lateral neck pain during chemotherapy. Chest fluoroscopy revealed catheter malposition into the right internal jugular vein. The CVP system was explanted and reimplanted six days after the FCS, as this malposition had led to secondary venous thrombosis.

malposition into the internal jugular vein (Fig. 3f), manually reparable port reversal, and manually irreparable port reversal ($n = 1$ each). The relations between the incidence of suspected CVP system malfunction and the FCS findings are summarized in Table 2. In the remaining 23 (34.8%) of the 66 patients, an FCS did not reveal any abnormal findings. The cause of the complaints in these patients was judged to be non-CVP system-related troubles, and follow-up observation was obtained resulting in continuing to use the CVP system without any system malfunction thereafter with a range of 89–946 days.

In one of two patients, a catheter occlusion was successfully relieved by strongly flushing the catheter with saline. Catheter malposition to the azygos vein spontaneously corrected itself in two patients. In four of the six patients with fibrin sheath formation

Table 2
Incidence of complaints leading to a suspicion of CV-port dysfunction and flow confirmation study findings.

Complaints leading to a suspicion of CV-port dysfunction (number)	Flow confirmation study	
	Abnormal findings	Number
Prolonged infusion time during chemotherapy (32)		
	Temporary catheter kinking	9
	Permanent catheter kinking	**5**
	Fibrin sheath formation	**1+3**
	Catheter malposition into azygos vein	2
	No abnormal findings	12
Inability to inject saline fluid (15)		
	Permanent catheter kinking	**6**
	Temporary catheter kinking	2
	Catheter occlusion	**1+1**
	Fibrin sheath formation	**1**
	No abnormal findings	4
Lateral neck and/or back pain (6)		
	Catheter malposition into IJV	**1**
	Venous occlusion	**1**
	Inappropriate catheterization	1
	No abnormal findings	3
Subcutaneous extravasation of anticancer drug (5)		
	Inappropriate catheterization	2
	Catheter injury	**1**
	Catheter fragmentation	**1**
	Fibrin sheath formation	**1**
Arm swelling (4)		
	Venous occlusion	**1+1**
	No abnormal findings	2
Inability to puncture the port (4)		
	Manually irreparable port reversal	**1**
	Manually reparable port reversal	1
	No abnormal findings	2

IJV, internal jugular vein.
Bold type means the number of CV-port dysfunction requiring system explantation and reimplantation.

around the catheter, thrombolytic infusion of urokinase through the port was performed, and CVP was able to use after the thrombolysis in three of the four patients.

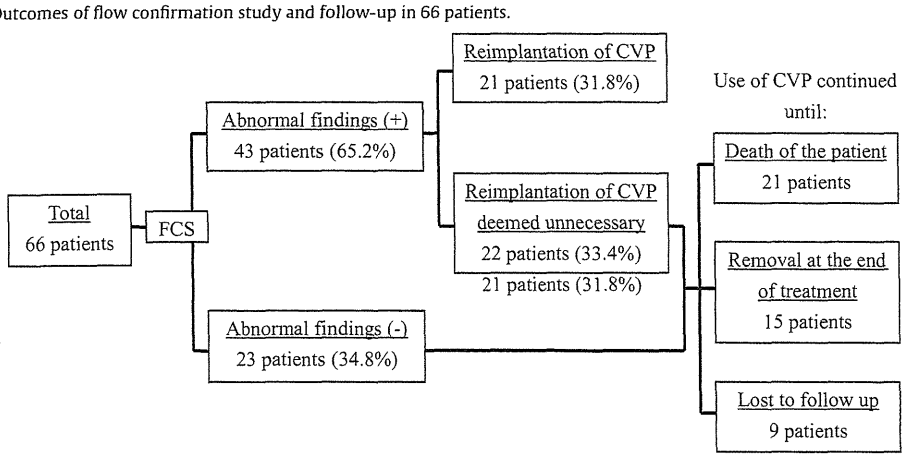
Explantation and reimplantation of the CVP system was required in 21 (31.8%) of the 66 patients for the following reasons: permanent catheter kinking ($n = 11$), fibrin sheath formation ($n = 3$), venous occlusion ($n = 2$), catheter occlusion ($n = 1$), catheter injury ($n = 1$), catheter fragmentation ($n = 1$), catheter malposition into the internal jugular vein ($n = 1$), and manually irreparable port reversal ($n = 1$). Because catheter malposition into the internal jugular vein led to secondary venous thrombosis, the CVP system was explanted and was reimplanted after thrombolytic therapy using warfarin for 28 days. The mean duration from the confirmation of a problem to system explantation and reimplantation was 12 days (range, 0–63 days). The remaining 45 patients (68.2%) were able continue using the CVP system after the FCS without any system malfunction until the death ($n = 21$), removal of CVP at end of therapy ($n = 15$), or the loss of follow-up ($n = 9$), with a range of 30–946 days (mean, 485 days) (Table 3).

4. Discussion

For the diagnosis of CVP system-related mechanical complications, chest radiography can evaluate the accurate positioning or course of the catheter, enabling malposition, fragmentation, or kinking of the catheter to be diagnosed. However, several mechanical complications cannot be diagnosed using chest radiography alone, including secondary catheter malposition or kinking, minor catheter injury, catheter occlusion, and fibrin sheath formation [9]. We hypothesized that FCS enables examination of all potential mechanical complications and their management by real-time fluoroscopy and the injection of a contrast material through the port.

The present study demonstrated that CVP system-related mechanical complications could be detected during an FCS in 65.2% of all the patients in whom a CVP malfunction was suspected, and reimplantation of the CVP system was required in only 31.8% of the patients. A prolonged infusion time and the inability to inject saline fluid were the most common complaints, and they mainly resulted from catheter kinking, catheter occlusion, and fibrin sheath formation, which required interventions including thrombolytic infusion, catheter stripping, and reimplantation of the CVP system [9,11,15–17]. These complaints have also been reported for situations where the tip of the catheter is in contact with the vein wall or the catheter is temporarily kinked [9,15]. Under these

Table 3
Outcomes of flow confirmation study and follow-up in 66 patients.



circumstances, having the patient change the position of his or her arm or head or having him or her perform deep breathing may correct the problem, and an FCS can thus prevent redundant interventions. These findings indicate that not all patients who are suspected of having a malfunctioning CVP develop CVP system-related mechanical complications, and only half of the patients in whom an FCS produces abnormal findings require system reimplantation.

In this study, 34.8% of the patients did not have abnormal FCS findings. We suspect that non-CVP system-related malfunction including infusion pump dysfunction or human error may have caused the complaints [8,13]. Moreover, these patients may have experienced venous thrombotic complications, since such complications can occur around the catheter and are independent of CVP functioning, resulting in normal FCS findings [15,18]. In cases of arm swelling, both venography and FCS may be required to fully evaluate the existence and extent of venous occlusion, because FCS provides information only regarding the catheter tip and the downstream vein.

On the other hand, 45 (68.2%) of all the patients in whom no abnormal FCS findings were observed or in whom reimplantation of the CVP system was deemed unnecessary despite the presence of abnormal FCS findings were able to continue using the CVP without any system malfunctions during the follow-up period. These findings indicate that FCS is reliable in predicting CVP functionality.

The current study had some limitations. First, the study design was retrospective in nature, and the study had a small sample size. Furthermore, 9 of 66 patients were lost to follow up, which may have affected the results of this study. Second, the CVPs were mainly implanted via a left subclavian vein. Subclavian vein access has been used as a secondary option using US guidance by interventional radiologists, and left-sided access may increase the incidence of significant secondary shifts in the catheter course [19]. These unusual accesses for the central vein may have affected the rate of post-interventional CVP system-related complications.

Interventional radiologists have the great advantage of expertise with imaging and catheterization technology. Oncologic patients who receive chemotherapy using CVP should benefit from the skills of these experts not only for CVP implantation, but for the diagnosis and management of post-procedural CVP system-related complications.

In conclusion, FCS was effective for evaluating post-procedural CVP system-related mechanical complications and for distinguishing non-CVP system-related complications in oncologic outpatients undergoing chemotherapy. Moreover, FCS was useful for deciding whether CVP system explantation and reimplantation was required. FCS should be performed by interventional radiologists in an angiographic suite for all patients who are suspected of having a CVP system-related mechanical complication.

References

[1] Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery 1982;92:706–12.

[2] Biffi R, de Braud F, Orsi F, et al. Totally implantable central venous access ports for long-term chemotherapy. A prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. Annals of Oncology 1998;9:767–73.

[3] Morris SL, Jaques PF, Mauro MA. Radiology-assisted placement of implantable subcutaneous infusion ports for long-term venous access. Radiology 1992;184:149–51.

[4] Randolph AG, Cook DJ, Gonzales CA, et al. Ultrasound guidance for placement of central venous catheters: a metaanalysis of the literature. Critical Care Medicine 1996;24:2053–8.

[5] Biffi R, Orsi F, Pozzi S, et al. Best choice of central venous insertion site for the prevention of catheter-related complications in adult patients who need cancer therapy: a randomized trial. Annals of Oncology 2009;20:935–40.

[6] Openshaw KL, Picus D, Hicks ME, Darcy MD, Vesely TM, Picus J. Interventional radiologic placement of Hohn central venous catheters: results and complications in 100 consecutive patients. Journal of Vascular and Interventional Radiology 1994;5:111–5.

[7] Vardy J, Engelhardt K, Cox K, et al. Long-term outcome of radiological-guided insertion of implanted central venous access port devices (CVAPD) for the delivery of chemotherapy in cancer patients: institutional experience and review of the literature. British Journal of Cancer 2004;91:1045–9.

[8] Inaba Y, Yamaura H, Sato Y, et al. Central venous access port-related complications in outpatient chemotherapy for colorectal cancer. Japanese Journal of Clinical Oncology 2007;37:951–4.

[9] Marcy PY. Central venous access: techniques and indications in oncology. European Radiology 2008;18:2333–44.

[10] Teichgräber UK, Kausche S, Nagel SN, Gebauer B. Outcome analysis in 3160 implantations of radiologically guided placements of totally implantable central venous port systems. European Radiology 2011;21:1224–32.

[11] Bessoud B, de Baere T, Kuoch V, et al. Experience at a single institution with endovascular treatment of mechanical complications caused by implanted central venous access devices in pediatric and adult patients. American Journal of Roentgenology 2003;180:527–32.

[12] Kovacevich DS, Papke LF. Guidelines for the prevention of intravascular catheter-related infections, Centers for Disease Control and Prevention. Nutrition in Clinical Practice 2003;18:95–6.

[13] Ahlin C, Klang-Soderkvist B, Brundin S, Hellstrom B, Pettersson K, Johansson E. Implementation of a written protocol for management of central venous access devices: a theoretical and practical education, including bedside examinations. Journal of Infusion Nursing 2006;29:253–9.

[14] Sakamoto N, Arai Y, Takeuchi Y, Takahashi M, Tsurusaki M, Sugimura K. Ultrasound-guided radiological placement of central venous port via the subclavian vein: a retrospective analysis of 500 cases at a single institute. Cardiovascular and Interventional Radiology 2010;33:989–94.

[15] Denny Jr DF. Placement and management of long-term central venous access catheters and ports. American Journal of Roentgenology 1993;161:385–93.

[16] Santilli J. Fibrin sheaths and central venous catheter occlusions: diagnosis and management. Techniques in Vascular and Interventional Radiology 2002;5:89–94.

[17] Gebauer B, Teichgräber UK, Podrabsky P, Werk M, Hänninen EL, Felix R. Radiological interventions for correction of central venous port catheter migrations. Cardiovascular and Interventional Radiology 2007;30:668–74.

[18] Yukisawa S, Fujiwara Y, Yamamoto Y, et al. Upper-extremity deep vein thrombosis related to central venous port systems implanted in cancer patients. British Journal of Radiology 2010;83:850–3.

[19] Puel V, Caudry M, Le Metayer P, et al. Superior vena cava thrombosis related to catheter malposition in cancer chemotherapy given through implanted ports. Cancer 1993;72:2248–52.

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ORIGINAL ARTICLE

A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis

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Abstract
Purpose The objective of this study was to evaluate the response rate, survival, and adverse effects of hepatic arterial infusion chemotherapy (HAIC) using cisplatin in patients with advanced hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT).
Methods Twenty-five patients of advanced HCC with PVTT in the main or first branch, having no prior history of chemotherapy, measurable lesions, adequate liver and renal function, and adequate bone marrow reserve, were enrolled. Cisplatin was administered at the dose of 65 mg/m^2 via the proper hepatic artery. Treatment was repeated every 4–6 weeks for a maximum of six courses until the appearance of evidence of tumor progression or unacceptable toxicity.
Results The median number of treatments was 3 (range 1–6). Among the 25 enrolled patients, complete response was achieved in 1 (4 %) patient and partial response in 6 (24 %), corresponding to a response rate of 28 % (95 % CI 12–49 %). The median progression-free and overall survival times and the 1-, 2-, and 3-year survival rates in the enrolled patients were 3.6 and 7.6 months and 40.3, 36.0, 20 %, respectively. Four of the seven patients who showed complete or partial response survived for more than 3 years. The main grade 3/4 non-hematological adverse events of this treatment were elevation of the serum aspartate aminotransferase (44 %) and alanine aminotransferase (24 %).
Conclusion HAIC with cisplatin exerts moderate activity with mild toxicity in advanced HCC patients with PVTT. Especially, markedly prolonged survival can be expected in patients who respond to this treatment.

Keywords Hepatocellular carcinoma · Hepatic arterial infusion chemotherapy · Tumor thrombosis · Cisplatin · Clinical trial

Abbreviations

HCC	Hepatocellular carcinoma
PVTT	Portal vein tumor thrombosis
HAIC	Hepatic arterial infusion chemotherapy
AFP	Alpha-fetoprotein
PIVKA II	Protein induced by vitamin K absence or antagonist-II
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase

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Introduction

For advanced hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT), chemotherapy remains one of the most important treatment modalities [1–4]. Sorafenib, an oral multikinase inhibitor targeting Raf kinase and receptor tyrosine kinases, has been acknowledged as the standard agent for advanced HCC [5, 6]. However, it has yielded rather unsatisfactory results in terms of the response and survival in patients with advanced HCC [7, 8]. Hepatic arterial infusion chemotherapy (HAIC), which can increase the local concentration of anticancer drugs with reduced systemic distribution, may be expected to exert better antitumor efficacy and lesser toxicity [9, 10]. Although promising results of HAIC have been reported for advanced HCC with PVTT [11–20], no chemotherapeutic agent or regimen has yet been shown to confer a survival benefit sufficient for adoption as standard therapy.

Cisplatin, which is a heavy metal (platinum) ion complex compound that exerts cytotoxicity by binding to double-stranded DNA, is widely used as one of the chemotherapeutic agents in transcatheter arterial embolization [21–23]. Cisplatin in the form of a fine powder suitable for hepatic artery infusion (IA-call®, Nippon Kayaku Co., Ltd.) has been developed in Japan. Since the solubility of this agent is 2.86 times higher than that of standard cisplatin, the injection time can be shortened. In a phase II trial, administration of this agent by intra-arterial injection over 20–40 min at the dose of 65 mg/m^2 in repeated doses at 4- to 6-week intervals was shown to yield favorable results (response rate 33.8 %) [24]. However, the efficacy of this regimen for advanced HCC with PVTT has not yet been fully evaluated. Therefore, we conducted a multicenter phase II trial to evaluate the efficacy and safety of HAIC with cisplatin in HCC patients with PVTT in the main and/or first branch.

Patients and methods

Eligibility

Patients eligible for study entry had advanced HCC with PVTT. The eligibility criteria were as follows: HCC confirmed by histological examination or liver tumor with a radiological hallmark of HCC and elevation of the serum α-fetoprotein (AFP) levels to ≥400 ng/mL; tumor thrombosis in the main and/or first portal vein; unsuitable candidate for surgical resection; age 20 years or over; Eastern Cooperative Oncology Group performance status of 0–2; measurable disease; interval of 4 weeks or over between the last treatment and the present therapy, and no influence of previous treatments; adequate hematological function (hemoglobin ≥9.0 g/dL, leukocytes ≥3,000/mm^3, and platelets ≥50,000/mm^3), adequate hepatic function [Child-Pugh classification of A or B, serum total bilirubin ≤2.0 mg/dL, and serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤150 U/L], adequate renal function (serum creatinine ≤1.1 mg/dL); availability of written informed consent.

The exclusion criteria were as follows: prior chemotherapy with cisplatin for HCC, prior radiotherapy, transcatheter arterial chemoembolization or intra-arterial chemotherapy for PVTT, refractory pleural effusion or ascites, no distant metastases, allergic reaction to iodine contrast medium, severe renal, heart or mental disease, active infection, excluding hepatitis B or C viral infection, active concomitant malignancy, pregnant and lactating females; females of childbearing age unless using effective contraception.

The pretreatment evaluation consisted of a complete history and physical examination and baseline assessments of organ function. In addition, dynamic computed tomography of the abdomen and chest radiography were performed for pretreatment staging to assess the local extent of the tumor and exclude the presence of distant metastasis. The number of tumors and tumor distribution were examined by computed tomography and/or angiography. This phase II study was conducted with the approval of each institutional review board and conducted in accordance with the Declaration of Helsinki.

Treatment procedure

Following conventional visceral angiography, HAIC was performed by introducing a angiographic catheter into the proper, right or left hepatic artery, or another feeding artery, and injection of cisplatin at the dose of 65 mg/m^2 over 20–40 min by Seldinger's technique, not using implanted port system for hepatic arterial infusion chemotherapy. Until the appearance of evidence of tumor progression and/or unacceptable toxicity, the treatment was repeated every 4–6 weeks for a maximum of six cycles. Neither lipiodol nor gelatin sponge was allowed in the protocol treatments. Antiemetic prophylaxis with a 5-HT3 antagonist (granisetron 1 mg) plus dexamethasone 8 mg was used at the attending physician's discretion. Patients received adequate hydration and/or diuretics 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. The cisplatin dose was reduced in case of grade 4 hematological adverse events or serious events had developed during the previous cycle. Patients who were refractory to this treatment regimen were allowed to

receive other anticancer treatments at the attending physician's discretion.

Response and toxicity assessment

The antitumor effect was assessed by intravenous contrast enhanced computed tomography or magnetic resonance imaging every 4–6 weeks. Responses were evaluated according to the WHO criteria [25]. The best overall response was recorded for each patient. The duration of response was defined as the interval from the onset of partial response until the first evidence of disease progression or death. Basic laboratory tests, including a complete blood count with differential leukocyte count, and serum chemistry were performed at least once every 2 weeks during this treatment. The treatment-related adverse events were assessed using the Common Terminology Criteria for Adverse Events, v2.0. Serum levels of AFP and protein induced by vitamin K absence or antagonist-II (PIVKA II) were measured every 4–6 weeks. In patients with a pretreatment AFP level of $\geq$100 ng/mL and of PIVKAII of $\geq$100 mAU/mL, the AFP and PIVKAII responses were assessed; a positive response was defined as a >50 % reduction from the pretreatment level. Progression-free survival was defined as the time from the date of initial treatment to the first documentation of progression or death. Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up. The progression-free survival and overall survival curves were calculated by the Kaplan–Meier method.

Statistical considerations

The primary endpoint of this trial was the response rate, and the secondary endpoints were adverse events, progression-free survival, and overall survival. The number of patients enrolled was planned using a two-step design [26] based on an expected response rate of 30 %, a response rate corresponding to no activity of 10 %, α error of 10 %, and β error of 10 %. An interim analysis was planned after 15 patients had been enrolled. If zero or one of the first 15 patients showed a partial response or complete response, the study was to be ended. If a response was detected in more than one of the first 15 patients studied, an additional 10 patients were to be enrolled in a second stage of accrual for more precise estimation of the actual response rate. If a response was detected in more than five of the 25 patients studied, this treatment was considered to be effective. This population was defined as including any patients who received at least one course of study medication. The trial was registered at UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000488).

Results

Patient characteristics

Twenty-five patients were enrolled in this trial between January 2005 and April 2007 at 3 institutions in Japan, because four patients showed partial response among the first 15 patients in the interim analysis. The characteristics of all the 25 patients are shown in Table 1. There were 20 males and five females, with a median age of 67 (range 47–79) years. Hepatitis B surface antigen and hepatitis C virus antibody were positive in 4 patients (16 %) and 15 patients (60 %), respectively. There were 17 (68 %) patients and 8 (32 %) patients with Child-Pugh class A and B, respectively. Portal vein invasion was noted in the main vein and the first branch in 19 patients (76 %) and 6 (24 %) patients, respectively.

A total of 83 courses were given, with a median of three courses (range 1–6) per patient. The median dose of cisplatin per treatment was 100 mg (range 85–130 mg). The reasons for treatment discontinuation were completion of treatment (6 courses) in 5 patients (20 %), disease progression in 16 patients (64 %), rupture of esophageal varices in 1 patient (4 %), hepatic failure in 1 patient (4 %), and accidental perforation of the colon in 1 patient (4 %). As subsequent treatments, 15 patients did not receive any treatments and the remaining 10 patients received further treatment: HAIC with epirubicin (4 patients), HAIC with interferon plus 5-fluorouracil (5-FU) (1 patient), HAIC with cisplatin (2 patients who had shown disease progression after the termination of 6 cycles of HAIC with cisplatin), and transcatheter arterial chemoembolization with epirubicin (2 patients).

Treatment efficacy

Of the 25 patients, 24 were evaluable for response; the remaining one patient (4 %) could not be evaluated because of early discontinuation of this protocol treatment. One patient (4 %) showed complete response, and 6 (24 %) showed partial response, corresponding to an overall response rate of 28 % (95 % CI 12–49 %); the mean duration of the response was 7.9 months (range 1.4–19.5 months). Eleven patients (44 %) showed stable disease and 5 patients (20 %) showed progressive disease. During the treatment, the serum AFP level decreased by more than 50 % in 7 (44 %) of the 16 patients with a pretreatment level of $\geq$100 U/mL, and the serum PIVKA II level decreased by more than 50 % in 15 (68 %) of the 22 patients with a pretreatment level of $\geq$100 mAU/mL.

At the time of the analysis, 21 patients developed tumor progression; among the remaining 4 patients, the tumor progression status could not be confirmed in 3 patients (on

Table 1 Patient characteristics ($n = 25$)

Characteristics	Number of patients	%
Age (years)		
Median	67	
Range	47–79	
Sex		
Male	20	80
Female	5	20
Eastern Cooperative Oncology Group performance status		
0	21	84
1	4	16
Hepatitis B surface antigen		
Positive	4	16
Hepatitis C antibody		
Positive	15	60
Child-Pugh classification		
A	17	68
B	8	32
Prior treatments		
Present	13	52
Resection	4	16
Local ablation	5	20
TACE	10	40
Portal vein invasion		
Main	19	76
First branch	6	24
Tumor distribution		
Unilateral	8	32
Bilateral	17	68
Ascites		
Present	6	24
Alpha-fetoprotein (ng/mL)		
Median	1,075	
Range	11.3–386,300	
PIVKAII (mAU/mL)		
Median	1,600	
Range	18–423,350	

TACE transcatheter arterial chemoembolization, *PIVKAII* protein induced by vitamin K absence or antagonist-II

account of death due to hepatic failure (1 patient), variceal rupture (1 patient), or accidental perforation of the colon (1 patient)), and one patient remains alive without tumor progression. The median progression-free survival was 3.6 months. All patients were included in the survival assessment. Of the 25 patients, 21 died. The causes of death were tumor progression (18 patients), hepatic failure (1 patient), rupture of esophageal varices (1 patient), and accidental perforation of the colon (1 patient). The median survival time and 1-, 2-, and 3-year survival rates of the patients were 7.1 months and 36, 20, and 20 %, respectively (Fig. 1). The median survival time was 45.4 months in the patients who showed complete or partial response, and four of these patients survived for more than 3 years; on the other hand, the median survival time in the patients who showed stable or progressive disease was 5.8 months.

Adverse events

The adverse events occurring in the patients enrolled in this study are summarized in Table 2. The adverse events represent the maximum grade occurring in the patients during the entire course of therapy. Grade 3–4 leukocytopenia, neutropenia, and thrombocytopenia occurred in 5 (20 %), 2 (8 %), and 4 (16 %) of the patients, respectively; however, they were all transient and recovered fully without treatment. The major non-hematological adverse events were elevations of the serum AST and ALT levels. Grade 3–4 AST and ALT elevations were observed in 11 (44 %) and 6 (24 %) of the patients, respectively. However, the levels returned to the initial levels within one month without any additional treatment. No cumulative adverse events were seen in this patient series. One patient developed perforation of the colon on day 37 after the commencement of the first cycle; however, this was judged as an accidental event not causally related to the treatment. There were no other serious non-hematological adverse events.

Discussion

HAIC is widely undertaken in Japan for patients with advanced HCC who are not suitable candidates for

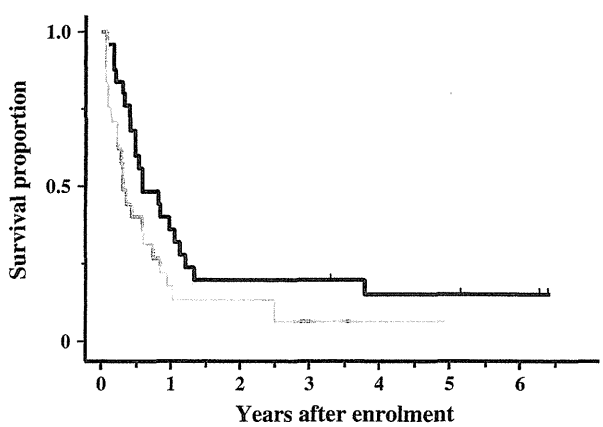

Fig. 1 Overall survival (*black line*) and progression-free survival (*gray line*) curves of the 25 patients of advanced hepatocellular carcinoma with tumor thrombosis in the main and/or first branch of the portal vein treated by hepatic arterial infusion chemotherapy using cisplatin. *Tick marks* indicate censored cases

Table 2 Adverse events

	Grade				
	1	2	3	4	3–4 (%)
Hemoglobin	6	7	0	0	0
Leukocytes	7	9	5	0	20
Neutrophils	6	7	2	0	8
Platelets	6	6	4	0	16
Nausea	10	5	0	0	0
Vomiting	9	1	0	0	0
Anorexia	13	6	0	0	0
Fatigue	8	3	0	0	0
Fever	3	0	0	0	0
Diarrhea	0	0	0	0	0
Abdominal pain	2	0	0	0	0
Weight loss	2	1	0	0	0
Total bilirubin	10	5	0	0	0
Hypoalbuminemia	6	7	0	0	0
AST	1	3	10	1	44
ALT	3	5	5	1	24
Alkaline phosphatase	3	0	0	0	0
Creatinine	3	2	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase

resection, local ablative therapies, or transcatheter arterial chemoembolization, such as those with complicating PVTT [3, 4]. HAIC is usually administered using one of the following three well-reported regimens: cisplatin alone [11, 24], 5-FU plus cisplatin [12–15], and 5-FU plus interferon [16–20]. The efficacies of these regimens for HCC patients with PVTT are shown in Table 3 [11–20]. The reported response rates and disease control rates are approximately 20–40 % and 50–80 %, respectively, and the reported median survival is in the range of 7–12 months. However, optimum regimen for patients of advanced HCC with PVTT still remains controversial. Recently, a randomized phase II trial comparing 5-FU and interferon with best salvage therapy (BST), such as 5-FU plus cisplatin or cisplatin alone, has been reported [27]. Although the response rate was quite similar in both groups, the patients treated with 5-FU and interferon seemed to show inferior disease control and overall survival rates as compared to those treated by BST. Thus, the optimal regimen for HAIC has not yet been clarified. Transarterial radioembolization with yttrium-90 microspheres is one of the good options for HCC with PVTT, and the treatment efficacy has been reported to be favorable (Table 3) [28, 29]. However, this treatment has not been established as standard therapy, because the survival benefit has not been clarified by randomized trials.

In this study, cisplatin was selected as the trial chemotherapeutic agent for HAIC, because it is widely used in Japan, it can be administered by short infusion, and it requires no indwelling reservoir system for hepatic arterial infusion, unlike 5-FU plus cisplatin or 5-FU plus interferon. The response and disease control rates to HAIC with cisplatin in this study were 28 and 76 %, respectively, and the median overall survival time was 7.1 months. These results are comparable to previous reports (Table 3). Besides, in the patients who achieved complete or partial response, the median survival time was 45.4 months and four of them survived for more than 3 years. In previous reports also, the prognoses in the responders to HAIC were extremely favorable [11–13, 15–17, 19]. Thus, HAIC sometimes causes favorable tumor shrinkage, and a markedly prolonged survival time can be expected in such patients. If the tumor response to HAIC can be predicted prior to the start of the treatment, more appropriate selection of suitable candidates for HAIC may be possible. Therefore, identification of reliable markers to predict a favorable response to HAIC is warranted.

In comparison with systemic administration of anticancer agents, HAIC allows high local concentrations of anticancer drugs to be achieved, with reduced systemic distribution, thereby increasing the activity of the anticancer drug and reducing the likelihood of systemic adverse effects. With regard to the toxicity, the toxicity of HAIC with cisplatin was very mild. The main grade 3–4 adverse events were leukocytopenia (27 %), neutropenia (47 %), increased AST (40 %), and increased ALT (20 %). These adverse events were transient and reversed without any specific treatments. Furthermore, no cumulative or serious adverse events were seen in this study. Therefore, this treatment was considered to be well tolerated and even patients with Child-Pugh B could be included as candidates for this treatment.

HAIC is considered as one of the valid treatment options for advanced HCC, because it has been shown to exert a favorable effect with mild toxicities in advanced HCC patients with PVTT. However, it has not been acknowledged as a standard therapy for advanced HCC, because no chemotherapeutic agent or regimen has yet been shown to confer a survival benefit sufficient for adoption as a standard therapy [1–4]. On the other hand, sorafenib has been acknowledged as a standard agent for the treatment of patients with advanced HCC, including HCC with vascular invasion and extrahepatic metastases, because two pivotal phase III trials comparing sorafenib versus placebo have shown the survival benefit afforded by sorafenib [7, 8]. Sorafenib has a limited tumor shrinkage effect, but is capable of prolonging the time-to-progression and the overall survival. In the comparison of the efficacy between HAIC with cisplatin and sorafenib (Table 3), the efficacy of cisplatin seemed to be equivalent to that of sorafenib [7, 30]; therefore, cisplatin may be one of the promising

Table 3 Treatment efficacy of hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis

Regimen	*n*	RR (%)	DCR (%)	Median TTP/PFS (months)	Median OS (months)	1-year OS (%)	2-year OS (%)	3-year OS (%)	Median OS for responder (months)	References
Yttrium 90 (Child-Pugh A)	35	50	NA	5.6	10.4	NA	NA	NA	NA	Salem et al. [28]
Yttrium 90 (Child-Pugh B)	57	28	NA	5.9	5.6	NA	NA	NA	NA	Salem et al. [28]
Yttrium 90	76	NA	NA	NA	10.0	NA	NA	NA	NA	Sangro et al. [29]
Sorafenib[a]	108	NA	38.9	4.1	8.1	NA	NA	NA	NA	Bruix et al. [7]
Sorafenib[a]	44	NA	24	NA	4.4	NA	NA	NA	NA	Kang et al. [30]
5-FU/Cisplatin	48	48	77	NA	10.2	45.0	31.0	25.0	31.6	Ando et al. [12]
5-FU/Cisplatin	38	8	66	NA	6.0	21.0	NA	NA	NA	Cheong et al. [14]
5-FU/Cisplatin	18	33	72	NA	NA	28.0	NA	NA	15.0	Lai et al. [13]
5-FU/Cisplatin	52	39	65	4.1	15.9	53.3	34.8	26.1	40.7	Ueshima et al. [15]
5-FU/IFNα	55	44	51	5.2	11.8	48.9	28.6	16.4	24.4	Ota et al. [16]
5-FU/IFNα	116	52	54	NA	NA	34.0	18.0	NA	59 % (2 years)	Obi et al. [17]
5-FU/IFNα	31	29	55	5.8	7.5	29.0	5.6	NA	NA	Uka et al. [18]
5-FU/IFNα	102	39	47	2.0	9.0	36.8	21.2	10.8	25.0	Nagano et al. [19]
5-FU/IFNα	57	25	58	3.3	10.5	NA	NA	NA	NA	Yamashita et al. [20]
Cisplatin	24	21	25	NA	7.0	38.0	16.0	NA	37.3	Kondo et al. [11]
Current study (Cisplatin)	25	27	72	3.6	7.1	36	20	20	45.4	Ikeda

RR response rate, *DCR* disease control rate, *TTP* time to progression, *PFS* progression-free survival, *OS* overall survival, *5FU* 5-fluorouracil, *IFN* interferon, *NA* not available

[a] The study included the patients with macrovascular invasion

regimens for advanced HCC with PVTT. In addition, sorafenib and cisplatin have different toxicity profiles, except for causing liver dysfunction. Sorafenib and cisplatin have been reported to exert a synergistic effect against liver cancer in preclinical research [31, 32], and some clinical trials of combined regimens of sorafenib and cisplatin have been performed in patients with gastric cancer [33], nasopharyngeal carcinoma [34], and lung cancer [35]. Therefore, combined use of the two drugs may yield superior results. Furthermore, a randomized controlled trial comparing sorafenib plus HAIC with sorafenib could clarify the additional effect of HAIC and establish HAIC as a standard treatment for advanced HCC. Therefore, a phase I trial of sorafenib plus HAIC with cisplatin has already been conducted, and a randomized phase II trial of sorafenib plus HAIC with cisplatin versus sorafenib alone (UMIN000005703) is ongoing.

This study involved some limitations. First, the number of enrolled patients was not so high, and the results should be interpreted with some caution. Secondly, 10 patients received chemoembolization as prior therapy. This might lead to resistance to HAIC with cisplatin. Finally, as this was a single-arm phase II trial, the survival benefit of HAIC with cisplatin could not be clarified. All of these limitations argue for the conduct of a randomized trial to further compare this treatment with standard therapy in advanced HCC patients with PVTT.

In conclusion, HAIC with cisplatin exerts moderate activity with mild toxicity in HCC patients with PVTT. Especially, markedly prolonged survival can be expected in patients who respond to this treatment. At present, a randomized controlled trial of HAIC using a combination of cisplatin and sorafenib is under way.

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Conflict of interest None.

References

1. El-Serag HB (2011) Hepatocellular carcinoma. N Engl J Med 365:1118–1127
2. Forner A, Llovet JM, Bruix J (2012) Hepatocellular carcinoma. Lancet 379:1245–1255
3. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M (2011) Management of hepatocellular carcinoma in Japan: consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 29:339–364
4. Yamashita T, Kaneko S (2012) Treatment strategies for hepatocellular carcinoma in Japan. Hepatol Res. doi:10.1111/j.1872-034X.2012.01029.x

5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378–390
6. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25–34
7. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM (2012) Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 57:821–829
8. Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Yang TS, Tak WY, Pan H, Yu S, Xu J, Fang F, Zou J, Lentini G, Voliotis D, Kang YK (2012) Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. Eur J Cancer 48:1452–1465
9. Ensminger WD, Gyves JW (1983) Regional chemotherapy of neoplastic diseases. Pharmacol Ther 21:277–293
10. Tzoracoleftherakis EE, Spiliotis JD, Kyriakopoulou T, Kakkos SK (1999) Intra-arterial versus systemic chemotherapy for non-operable hepatocellular carcinoma. Hepatogastroenterology 46:1122–1125
11. Kondo M, Morimoto M, Numata K, Nozaki A, Tanaka K (2011) Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Jpn J Clin Oncol 41:69–75
12. Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, Sumie S, Yano Y, Okuda K, Sata M (2002) Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 95:588–595
13. Lai YC, Shih CY, Jeng CM, Yang SS, Hu JT, Sung YC, Liu HT, Hou SM, Wu CH, Chen TK (2003) Hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 9:2666–2670
14. Cheong JY, Lee KM, Cho SW, Won JH, Kim JK, Wang HJ, Hahm KB, Kim JH (2005) Survival benefits of intra-arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with portal vein tumor thrombosis. Hepatol Res 32:127–133
15. Ueshima K, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, Kitai S, Ishikawa E, Yada N, Inoue T, Hagiwara S, Minami Y, Chung H (2010) Hepatic arterial infusion chemotherapy using low-dose 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma. Oncology 78(Suppl 1):148–153
16. Ota H, Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T, Nakamura M, Damdinsuren B, Wada H, Marubashi S, Miyamoto A, Dono K, Umeshita K, Nakamori S, Wakasa K, Monden M (2005) Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. Br J Cancer 93:557–564
17. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, Teratani T, Shiina S, Omata M (2006) Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer 106:1990–1997
18. Uka K, Aikata H, Takaki S, Miki D, Kawaoka T, Jeong SC, Takahashi S, Toyota N, Ito K, Chayama K (2007) Pretreatment predictor of response, time to progression, and survival to intra-arterial 5-fluorouracil/interferon combination therapy in patients with advanced hepatocellular carcinoma. J Gastroenterol 42:845–853
19. Nagano H, Wada H, Kobayashi S, Marubashi S, Eguchi H, Tanemura M, Tomimaru Y, Osuga K, Umeshita K, Doki Y, Mori M (2011) Long-term outcome of combined interferon-α and 5-fluorouracil treatment for advanced hepatocellular carcinoma with major portal vein thrombosis. Oncology 80:63–69
20. Yamashita T, Arai K, Sunagozaka H, Ueda T, Terashima T, Yamashita T, Mizukoshi E, Sakai A, Nakamoto Y, Honda M, Kaneko S (2011) Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma. Oncology 81:281–290
21. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (1995) A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 332:1294–1296
22. Pelletier G, Ducreux M, Gay F, Luboinski M, Hagège H, Dao T, Van Steenbergen W, Buffet C, Rougier P, Adler M, Pignon JP, Roche A (1998) Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. J Hepatol 29:129–134
23. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J (2002) Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35:1164–1171
24. Yoshikawa M, Ono N, Yodono H, Ichida T, Nakamura H (2008) Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. Hepatol Res 38:474–483
25. World Health Organization (1979) WHO handbook for reporting results of cancer treatment, vol 48. World Health Organization, Geneva
26. Simon R (1987) How large should a phase II trial of a new drug be? Cancer Treat Rep 71:1079–1085
27. Monden M, Sakon M, Sakata Y, Ueda Y, Hashimura E, FAIT Research Group (2012) 5-fluorouracil arterial infusion + interferon therapy for highly advanced hepatocellular carcinoma: a multicenter, randomized, phase II study. Hepatol Res 42:150–165
28. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L (2010) Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 138:52–64
29. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, Van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Iñarrairaegui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfar H, Jakobs TF, Lastoria S, European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY) (2011) Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology 54:868–878
30. Kang YK, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Burock K, Zou J, Voliotis D, Cheng AL (2008) Sorafenib is effective in patients from the Asia-Pacific region with hepatocellular carcinoma (HCC): subgroup analysis of effect of macroscopic vascular invasion, extrahepatic spread, and ECOG performance status on outcome. Hepatology 48(suppl 1):976A (abstr 1505)

31. Chen FS, Cui YZ, Luo RC, Wu J, Zhang H (2008) Coadministration of sorafenib and cisplatin inhibits proliferation of hepatocellular carcinoma HepG2 cells in vitro. Nan Fang Yi Ke Da Xue Xue Bao 28:1684–1687
32. Eicher C, Dewerth A, Thomale J, Ellerkamp V, Hildenbrand S, Warmann SW, Fuchs J, Armeanu-Ebinger S (2013) Effect of sorafenib combined with cytostatic agents on hepatoblastoma cell lines and xenografts. Br J Cancer 108:334–341
33. Sun W, Powell M, O'Dwyer PJ, Catalano P, Ansari RH, Benson AB 3rd (2010) Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. J Clin Oncol 28:2947–2951
34. Xue C, Huang Y, Huang PY, Yu QT, Pan JJ, Liu LZ, Song XQ, Lin SJ, Wu JX, Zhang JW, Zhao HY, Xu F, Liu JL, Hu ZH, Zhao LP, Zhao YY, Wu X, Zhang J, Ma YX, Zhang L (2013) Phase II study of sorafenib in combination with cisplatin and 5-fluorouracil to treat recurrent or metastatic nasopharyngeal carcinoma. Ann Oncol 24:1055–1061
35. Paz-Ares LG, Biesma B, Heigener D, von Pawel J, Eisen T, Bennouna J, Zhang L, Liao M, Sun Y, Gans S, Syrigos K, Le Marie E, Gottfried M, Vansteenkiste J, Alberola V, Strauss UP, Montegriffo E, Ong TJ, Santoro A, NSCLC [non-small-cell lung cancer] Research Experience Utilizing Sorafenib (NExUS) Investigators Study Group (2012) Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol 30:3084–3092

Phase II Study of Percutaneous Transesophageal Gastrotubing for Patients with Malignant Gastrointestinal Obstruction; JIVROSG-0205

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ABSTRACT

Purpose: This multicenter, prospective study was conducted to evaluate the efficacy of percutaneous transesophageal gastrotubing (PTEG) as an esophagostomy procedure for bowel decompression in patients with malignant bowel obstruction.

Materials and Methods: The study subjects were patients with malignant bowel obstruction treated with a nasogastric tube (NGT). After receiving PTEG, efficacy evaluations were conducted, with NGT designated as the control state. The procedure was considered effective only when discomfort in the nasopharynx was improved for at least 2 weeks. Safety was evaluated by using National Cancer Institute Common Toxicity Criteria, version 2.0. PTEG was performed by using a PTEG kit.

Results: From February 2003 to December 2005, 33 patients were enrolled. The technical success rate was 100%, and the procedure was considered effective in 30 of 33 cases. The three cases in which the procedure was ineffective could not be evaluated as a result of deterioration of general status or early death. The one recorded complication was a tracheoesophageal fistula that caused grade 2 aspiration pneumonia.

Conclusions: PTEG is an effective technique to relieve discomfort in the nasopharynx caused by NGT in patients with terminal malignant tumors. PTEG should be considered an efficacious method for bowel decompression in patients who are ineligible for surgical procedures, percutaneous gastrostomy, or percutaneous enterostomy.

ABBREVIATIONS

NGT = nasogastric tube, QOL = quality of life, PTEG = percutaneous transesophageal gastrotubing, RFB = rupture-free balloon

Gastrointestinal obstruction caused by constriction of the upper gastrointestinal tract by malignant tumor or carcinomatous peritonitis is a common symptom in terminal cancer, reportedly occurring in 5%–42% of patients. Vomiting caused by a malignant gastrointestinal tract obstruction is typically treated with a nasogastric tube (NGT) or small-bowel intubation. However, this condition has a bad prognosis, and transnasal decompression can add to the patient's distress and reduce quality of life (QOL) (1).

Gastric bypass or colostomy procedures may be performed as surgical treatment; however, these procedures are not possible for all patients because of the invasiveness of laparotomy or the general condition or prognosis of the patient (1,2). Pharmacotherapy may be given as supportive care, and a somatostatin analogue (ie, octreotide) has recently been often reported as useful (1–3). Unfortunately, because the half-life of octreotide is only 1.5 hours, continuous subcutaneous injection is needed.

As another method, percutaneous gastrostomy or percutaneous enterostomy can be performed for decompression (1,2,4,5), and metallic stents are sometimes inserted as a substitute for a gastric bypass or colostomy procedure (1,2). However, patients may sometimes show accumulation of ascitic fluid, carcinomatous peritonitis, or other pathologic conditions following gastrectomy

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that may lead to peritonitis as a result of leakage from the puncture site or tumor infiltration from the puncture route.

The current reality is that, for patients with a gastrointestinal constriction caused by a malignant tumor, no standard treatment exists that does not severely reduce QOL. The establishment of minimally invasive treatment methods for such patients to achieve bowel decompression without reducing QOL is therefore an essential challenge in palliative medicine for patients with cancer.

In 1994, Oishi et al (6) developed a method called percutaneous transesophageal gastrotubing (PTEG) that involves percutaneous insertion of a tube through the cervical esophagus so the patient feels little discomfort after tube placement. PTEG is receiving attention as a promising treatment for patients with malignant bowel obstruction accompanying constriction of the upper gastrointestinal tract or for patients with carcinomatous peritonitis caused by a malignant tumor with a poor prognosis (6). To our knowledge, no prospective clinical studies have been performed on PTEG to date, and clinical assessments have yet to be established. The present multicenter, prospective study was therefore conducted to evaluate the safety and clinical efficacy of PTEG for patients with terminal cancer with malignant bowel obstruction, such as constriction of the upper gastrointestinal tract or carcinomatous peritonitis caused by a malignant tumor.

MATERIALS AND METHODS

Study Design and Endpoints

The study design used was a nonrandomized, multicenter, phase II trial. This study was approved by the Japanese Society of Interventional Radiology and the ethics committees of each of the participating institutions, and was registered at the University Hospital Medical Information Network Clinical Trials Registry (study ID C000000249). The primary endpoint was clinical efficacy, and the secondary endpoints were the frequency of adverse events and the feasibility of the procedure.

Patient Eligibility

Inclusion criteria consisted of the following: (i) placement of an NGT or ileus tube as a result of malignant bowel obstruction, such as constriction of the upper gastrointestinal tract or carcinomatous peritonitis, with no improvement of symptoms expected; (ii) no obvious pathologic conditions in or around the cervical esophagus; (iii) adequate bone marrow, liver, renal, and cardiac function (ie, platelet count $\geq$ 50,000/mm^3, prothrombin time $\geq$ 50%, total serum bilirubin level $\leq$ 3.0 mg/dL, serum creatinine level $\leq$ 2.0 mg/dL, no obvious heart failure); (iv) Eastern Cooperative Oncology Group performance status of 0–3; (v) expected survival of more than 4 weeks; and (vi) written informed consent from the patient.

Exclusion criteria consisted of the following: (i) presence of a tracheal fistula from a tracheotomy, (ii) malignant bowel obstruction in which the lesion located most orally was no higher than the transverse colon, (iii) pregnancy or possible pregnancy, and (iv) previous or scheduled local therapy for the neck region (surgical treatment on the region from the mandible to the clavicle, radiation therapy to soft tissue in the region from the mandible to the clavicle, radiation therapy to the neck, or intravenous hyperalimentation in the jugular vein or via a supraclavicular approach).

Technique for PTEG

The PTEG was created as Ohishi et al (6) and Mackey et al (8) described (6–8) with the use of a PTEG kit (Sumitomo Bakelite, Tokyo, Japan; **Figs 1–6**) and the following procedures. (i) A rupture-free balloon (RFB) was inserted through the nose and positioned in the cervical esophagus. (ii) The RFB was inflated with approximately 10–15 mL of 4× diluted water-soluble contrast medium (Urografin; Bayer Yakuhin, Osaka, Japan), and then the thyroid gland, carotid artery, and trachea were separated, and the RFB was detected just under the skin (**Figs 2, 3**). (iii) The RFB was punctured percutaneously under ultrasound (US) guidance, and a guide wire was inserted into the RFB through the needle (**Fig 4a**). (iv) The puncture site was dilated by using a dilator with a sheath (**Fig 4b**), and then an indwelling tube was appropriately inserted into the esophagus (**Fig 5**).

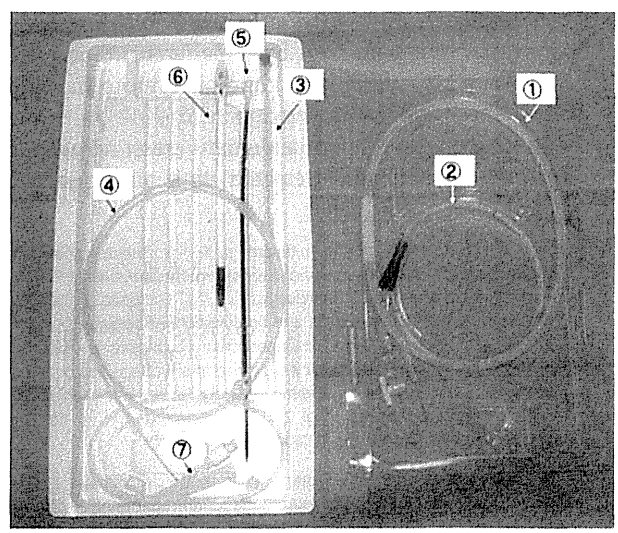

Figure 1. PTEG kit including straight-type guide wire (*1*), RFB (*2*), 18-gauge puncture needle with sheath (*3*), J-type guide wire (*4*), 8-F dilator (*5*), 16-F peel-away sheath (*6*), and indwelling tube with balloon (*7*). (Available in color online at *www.jvir.org*.)