Cardiovasc Intervent Radiol (2010) 33:1153–1158
DOI 10.1007/s00270-009-9779-0

CLINICAL INVESTIGATION

Clinical Application of a New Indwelling Catheter with a Side-Hole and Spirally Arranged Shape-Memory Alloy for Hepatic Arterial Infusion Chemotherapy

Kunihiro Yagihashi · Kenji Takizawa · Yukihisa Ogawa · Kyoko Okamoto · Misako Yoshimatsu · Atsuko Fujikawa · Hiroshi Shimamoto · Yasuo Nakajima

Received: 26 April 2009 / Accepted: 3 December 2009 / Published online: 22 December 2009

Abstract A new indwelling catheter, G-spiral (GSP), was developed for hepatic arterial infusion chemotherapy (HAIC) by way of an implanted catheter-port system (CPS). Here we evaluated its physical properties and the outcomes of its clinical use. The GSP vessel-fixing power and its ability to follow a guidewire were determined with a vascular in vitro model, and Student *t* test was used to determine statistical significance ($P < 0.05$). A retrospective analysis was performed to evaluate the technical success rate and to identify the clinical complications associated with radiologic CPS implantation with GSP in 65 patients with unresectable hepatic tumors. The mean vessel-fixing power of the GSP (14.4 g) significantly differed from that of a GSP with a cut shape-memory alloy (3.3 g). The mean resistance to following the guidewire displayed by the GSP (88.5 g) was significantly less than that for a 5F W-spiral (106.3 g) or 4F Cobra-type angiographic catheter (117.8 g). The CPS was placed successfully in 64 of 65 cases (98.5%). Hepatic artery occlusion was observed in one case. Occlusion, cracking, and infection of CPS were observed in one, two, and one case, respectively. The GSP is a highly useful indwelling catheter that can be used for HAIC.

K. Yagihashi (✉) · K. Takizawa · Y. Ogawa · K. Okamoto · M. Yoshimatsu · A. Fujikawa · H. Shimamoto · Y. Nakajima
Department of Radiology, St. Marianna University School of Medicine, Kanagawa 216-8511, Japan
e-mail: k2yagihashi@marianna-u.ac.jp

Keywords Interventional radiology · Liver tumor · Catheter-port system · Chemotherapy · Side-hole catheter

Introduction

For unresectable hepatic malignant tumors, hepatic arterial infusion chemotherapy (HAIC) with a subcutaneously implanted port is widely performed [1, 2]. As interventional techniques have progressed, radiologic percutaneous implantation of a catheter-port system (CPS) has become common in lieu of the indwelling method using surgical laparotomy [1–9]. However, there remain some important problems related to HAIC, including hepatic artery occlusion, catheter dislodgement, and vascular injury (occlusion, pseudoaneurysm, penetration). Such serious complications can cause temporary or permanent HAIC interruption [3–6, 8, 9].

To decrease incidence of the above-mentioned complications, a fixed catheter method, called the gastroduodenal artery (GDA)-coil fixation method (GDA method) was developed [4–6, 9]. Furthermore, to prevent catheter dislodgement, the W-spiral catheter (WSP), which has a shape-memory alloy (SMAL) for vessel fixation, was developed. However, the WSP reportedly can cause pseudoaneurysm and vascular penetration by mechanical injury of the vessels due to SMAL positioning at the catheter tip [10, 11]. To avoid SMAL-related vascular injury and to decrease technical burdens (such as side-hole creation and manual length adjustment from the tip to the side-hole), we designed the G-spiral catheter (GSP) [12]. In the present study, we investigated whether GSP was appropriate for use as an indwelling catheter for HAIC using a vascular in vitro model and retrospective analysis of HAIC patient clinical use.

Materials and Methods

Structure of the GSP

The GSP was designed to be anatomically adapted for the indwelled GDA. It required no alterations such as are common in conventional indwelling catheters, e.g., side-hole creation or manual length adjustment from the tip to the side-hole. The main features of the GSP include a side-hole with a platinum marker and a SMAL. The GSP measured 80 cm in length, with a shaft of 5F in the proximal 60 cm and 4F in the distal 20 cm. The 2.5 cm-long SMAL was placed 3 cm proximal from the tip. The short- and long-type GSPs displayed distances of 3 and 5 cm, respectively, from the SMAL to the side-hole. The platinum marker was positioned at each end of the SMAL and 0.3 cm distal to the side-hole. The catheter surface was coated with nonthrombogenic polyvinylpyrrolidone (PVP) (Fig. 1A, B).

In Vitro Analyses of the GSP

From December 2004 to February 2005, we determined the fixing-power sustainability and insertion resistance according to previously reported methods [13, 14], using an in vitro vascular model constructed of a water-filled tube (37°C) made of flexible polyvinyl chloride (outer diameter 6 mm and inner diameter 4.5 mm) (Fig. 2). The catheter was heated to 37°C, inserted into the vascular model, and the maximum static friction was measured while the GSP was removed at a rate of 700 mm/min by an actuator (Linier Motor, LU2B20SA-1; Oriental Motor, Tokyo, Japan) using an expression strain gauge load transducer (Load Cell; Nippon Tokushu Sokki, Tokyo, Japan). The

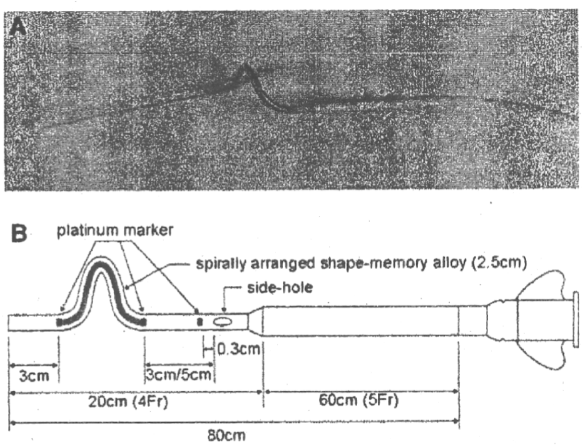

Fig. 1 Configuration of the GSP. Photo of the catheter tip (**A**) and schematic drawing of the GSP (**B**). A spirally arranged SMAL was placed 3 cm from the tip

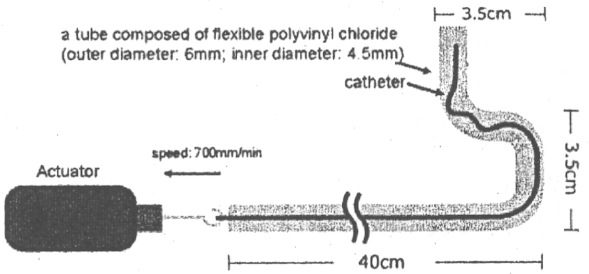

Fig. 2 Schematic of the model used to measure the frictional resistance of the catheter

data were compared with those of a 5F WSP (5-WSP; Piolax Medical Devices, Yokohama, Japan), a 3.3F WSP (3.3-WSP; Piolax), a GSP in which the SMAL was cut, and a 5-WSP in which the SMAL was cut.

A 0.035" guidewire (Radifocus; Terumo, Tokyo, Japan) was inserted into a similar vascular model to measure the maximum load when the catheter followed the guidewire. The data were compared with that of a 5-WSP and a 4F Cobra-type angiographic catheter (4-Cobra; Terumo). All measurements were performed 10 times. Student t test was performed with JMP software (SAS, Cary, NC), and statistical significance was defined at $P < 0.05$.

Patients

Subjects

From July 2005 to December 2007, 65 patients with unresectable hepatic tumors (41 men and 24 women; mean age 64.7 years [range 42–84]) underwent HAIC with GSP indwelling. Forty-five patients had metastatic liver tumors; of these the primary diseases included cancers of the colorectal region (28 cases), breast (four cases), gastric region (three cases), pancreas (two cases), bile duct (two cases), uterine cervical region (one case), uterine endometrial region (one case), ovary (one case), gallbladder (one case), pheochromocytoma (one case), and gastrointestinal stromal tumor (one case). Twenty patients had hepatocellular carcinomas.

Eligibility criteria to undergo HAIC included the following: a life expectancy >2 months, performance status ≤2 according to Eastern Cooperative Oncology Group Criteria [15], adequate bone marrow reserve with ≥3,000/ml white blood cells and ≥80,000/ml platelets, no renal dysfunction (creatinine level <1.25 times the normal upper limit), and a sufficiently maintained hepatic function (total bilirubin level <3.0 mg). Patients provided informed consent before the procedure. This retrospective study was approved by the Institutional Review Board of our hospital.

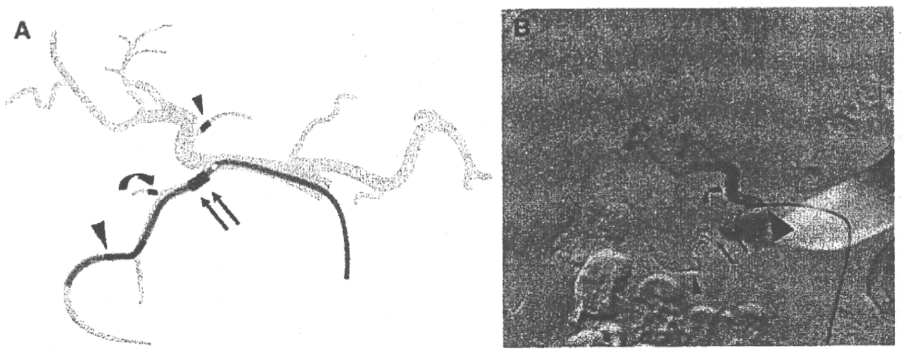

Fig. 3 The GDA method. **A** Schematic of the GDA method. The GSP is inserted in the hepatic artery with the catheter side-hole placed in the CHA and the distal shaft fixed within the gastroduodenal artery using microcoils (*arrows*). The catheter tip lumen (*large arrowhead*), right gastric artery (*small arrowhead*), and posterior superior pancreaticoduodenal artery (*curved arrow*) are occluded using microcoils. **B** Arteriogram of a 65-year-old man with liver metastases from colon cancer. Image taken by way of the implanted CPS shows that the GSP is implanted in the hepatic artery with the side-hole (*large arrowhead*) located in the CHA and distal catheter shaft fixed within the gastroduodenal artery using microcoils (*arrows*). The catheter tip lumen (*small arrowhead*) and right gastric artery (*curved arrow*) are occluded using microcoils

Technical Procedure of CPS Implantation

All procedures were performed in the angiography room. As a rule, catheter placement was performed according to the GDA method. The procedure was performed by an interventional radiology (IR) supervisor, with 14–28 years of experience, in the Radiology Department and an IR doctor with 7–10 years of experience.

With the patient under local anesthesia, an introducer sheath was inserted by way of the right common femoral artery, and celiac and superior mesenteric arteriographs were obtained using a 4F hook-shaped angiographic catheter to ascertain the vascular anatomy. To unify hepatic arterial flow as needed, the replaced right and accessory left hepatic arteries were embolized using microcoils (Tornado; Cook, Bloomington, IN), and the right gastric artery was embolized to prevent extrahepatic chemotherapeutic agent perfusion. After angiography and blood flow alteration, the lengths of the GDA and the common hepatic artery (CHA) were measured on the monitor, and the suitable GSP type was selected for the side-hole to be positioned in the CHA.

A 0.035" guidewire (Radifocus [Terumo] or Surf [Piolax]) was advanced to the right gastroepiploic artery (RGEA). While holding the guidewire in place, the angiographic catheter and introducer sheath were removed, and the GSP was inserted over the guidewire and advanced into the RGEA. The position was adjusted so that the SMAL was positioned near the transition point from the GDA to RGEA, corresponding to the bifurcation of the anterior superior pancreaticoduodenal artery (ASPDA). When removing the guidewire, the side-hole was confirmed to be positioned on the CHA. Next, a microcatheter was advanced into the GSP using coaxial technique, and the end-hole of GSP was embolized with a microcoil (Tornado; Cook). The microcatheter was advanced through the side-hole to the GDA. The GDA was then embolized by the microcoils placed around the GSP to ensure fixation to the vessel wall and discontinuation of blood flow to the GDA (Fig. 3A, B). Finally, the indwelling catheter was connected to a port and was embedded into the subcutaneous space at the lower abdominal wall.

In cases of stenosis or GDA absence caused by previous surgery or tumor invasion, the GSP was indwelled in the peripheral branch of hepatic artery (intrahepatic peripheral artery [IHA] method) (Fig. 4). In cases of CHA stenosis, the GSP was indwelled in the splenic artery (SPA) so that the side-hole was positioned in the celiac trunk after (where needed) coil embolization of the left gastric artery. Coil embolization of the proximal part of the SPA around the GSP was also performed (SPA method) (Fig. 5). The CPS was filled with heparinized saline solution (1000 u/ml) after implantation, and HAIC was started within 1 week.

Evaluation of the Clinical Utility of GSP

To evaluate the clinical utility of GSP, we investigated the following during the procedure and the observation period: technical success rate (percentage of completed CPS implantations), hepatic artery patency, and occurrence of complications, such as vascular injury (stenosis, pseudoaneurysm, intimal damage) or CPS issues (dislodgement, cracking, kinking, port breakage, inversion, infection). Hepatic artery patency and complications were evaluated every 1–4 months with digital subtraction angiography by way of the CPS. Especially in cases with progressive disease or HAIC-related symptoms, the drug distribution was

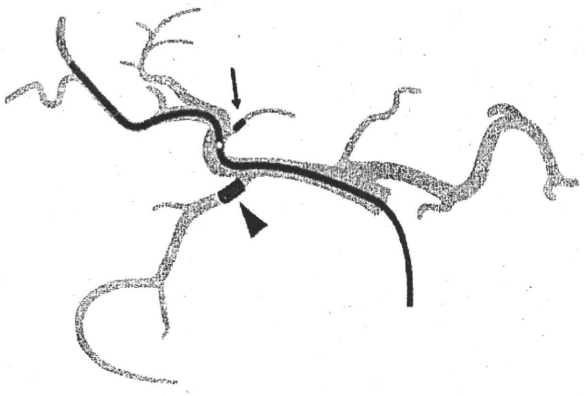

Fig. 4 Schematic of the IHA method. The GSP is advanced into the peripheral hepatic artery, with the side-hole placed in the proper hepatic artery. The right gastric artery (*arrow*) and gastroduodenal artery (*arrowhead*) are embolized with microcoils

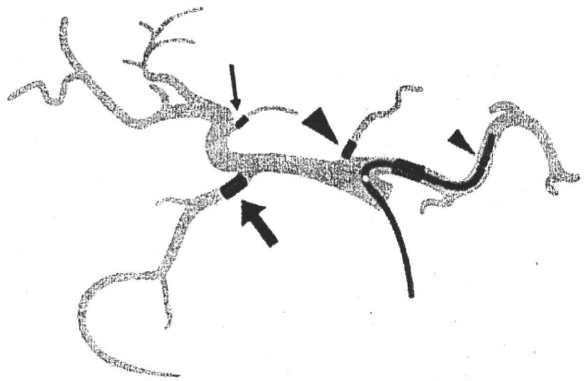

Fig. 5 Schematic of the SPA method. The GSP is advanced into the SPA, with the side-hole placed in the celiac trunk. The right gastric artery (*small arrow*), left gastric artery (*large arrowhead*), and gastroduodenal artery (*large arrow*) are embolized with microcoils. The catheter tip lumen is occluded using microcoils (*small arrowhead*)

evaluated using computed tomography angiography (CTA) by way of the CPS.

Results

In Vitro Analyses of the GSP

Mean ± SD of catheter removal resistance was 14.4 ± 0.9 g for the GSP and 3.3 ± 0.37 g for the GSP in which the SMAL had been cut ($P < 0.001$). Removal resistance of the 5-WSP was 31.1 ± 1.9 g and that of the 5-WSP in which the SMAL had been cut was 3.1 ± 0.3 g ($P < 0.001$). Removal resistance of the GSP was approximately 1.3 times higher than that of the 3.3-WSP (11.0 ± 1.1 g; $P = 0.043$).

Mean ± SD of GSP resistance in following the guidewire was 88.5 ± 5.42 g, which was less than those of the 5-WSP (106.3 ± 4.69 g, $P = 0.023$) or the 4-Cobra (117.8 ± 6.22 g, $P = 0.006$).

Technical Clinical Success Rate

CPS implantation was successful in 64 of 65 cases (98%), and there were no complications during the procedure. In the one unsuccessful case, marked hepatic artery narrowing was observed due to previous HAIC, and the scheduled HAIC was cancelled. The indwelling methods used included GDA (51 cases), IHA (11 cases), and SPA (two cases). A short-type GSP was used in 60 cases, GDA for 49 cases, IHA for 10 cases, and SPA for one case. A long-type was used in four cases, with GDA for two cases and IHA and SPA for one case each. Patient characteristics and the indwelling methods are listed in Table 1.

Hepatic Artery Patency

Of the 48 patients observed after CPS implantation, hepatic arterial occlusion was observed in only one patient (2%) during the observation period (mean 295 days [range 41–826]).

Complications

There were no complications during the indwelling procedure. Hepatic arterial stenoses were seen in five cases (10.4%). In four of these five cases, the peripheral branch of the right hepatic arteries was stenosed; in the remaining one case, the left hepatic artery was stenosed. The mean time since implantation in these cases was 303.9 days (range 118–477), and the mean number of infusion chemotherapy administrations was 22.4 times (range 15–39). Vascular

Table 1 Patient characteristics, GSP type, and catheter-placement methods

Characteristics	Catheter-placement method		
	GDA ($n = 51$)	IHA ($n = 11$)	SPA ($n = 2$)
Sex			
Male	33	6	0
Female	18	5	2
Primary or metastatic liver tumor			
Primary	18	2	0
Metastatic	33	9	2
Type of GSP			
Short	49	10	1
Long	2	1	1

injuries, such as pseudoaneurysm, penetration, and dissection, were not observed during the observation period. No catheter dislodgement or other HAIC-interrupting issue was observed. Only one case (2%) displayed CPS obstruction at 50 days after catheter implantation. A crack in the indwelling catheter was observed near the port in two cases (4%) at 120 and 134 days after catheter implantation. Infection of CPS occurred in one case (2%) at 247 days after implantation. There were no complications in cases with either the IHA or SPA method.

Discussion

Our study results show that GSP enables efficient catheter replacement because of ease in following the guidewire and prevention of catheter dislodgement by the SMAL. Catheter placement for HAIC using a GSP had a high technical success rate and a relatively low complication frequency.

The fixed catheter tip method for HAIC decreases the incidence of hepatic arterial occlusion and catheter dislocation compared with the conventional method, in which an end-hole catheter is inserted into the hepatic artery [4, 9]. However, because the fixed catheter tip method is technically difficult, expertise is required to perform it. Thus, the GSP was invented to decrease the technical burdens and complications [12].

Mean removal resistance of the 5-WSP was the highest of the catheters tested, possibly because of its thicker catheter wall and stronger SMAL power. However, the 5-WSP carries a risk of vascular injury [10] and displays a higher resistance to following the guidewire. Removal resistance of the GSP was 14.4 ± 0.9 g; there were no cases of catheter dislodgement; and the catheter appeared to properly fix to the vessel. The mean ± SD of the resistance of the GSP following the guidewire was 88.5 ± 5.42 g, which was significantly lower than that of the 5-WSP (106.3 ± 4.69 g) or the 4-Cobra (117.8 ± 6.22 g). This result is possibly derived from the fact that the GSP tip is straight, and its surface is coated with PVP. These results show that GSP insertion is easier than that of the other catheter types.

In the GSP, the side-hole with the platinum marker was positioned 8.5 cm proximal to the tip (4.25 cm from the SMAL center) for the short-type and 10.5 cm proximal to the tip (6.25 cm from the SMAL center) for the long-type. There are few references in which the length of the GDA was measured [16, 17], and reported mean lengths range from 3.8 cm (range 2.2–6) [16] to 5.7 cm (range 3.5–7.5) [17]. Our measurements of CHA and GDA lengths in 50 consecutive cases on abdominal CTA using the workstation (Ziostation; Ziosoft, Tokyo, Japan) showed that the average lengths of CHA and GDA were 3.73 cm (range 1.48–7.59) and 3.72 cm (range 1.16–6.72), respectively (unpublished observations). Based on anatomic distance, the short-type GSP—for which the GDA length was <4.25 cm and total length of the CHA and GDA was >4.25 cm—was applicable in 43 cases (86%). The long-type GSP—in which the length of the GDA was <6.25 cm and the total length of CHA and GDA was >6.25 cm—was applicable in five cases (10%). There were two cases for which neither the short- nor long-type GSP could be used, indicating that the GDA method using GSP might not be applicable in all cases.

The technical key for using GSP is to appropriately place the SMAL near the transition from the GDA to RGEA, corresponding to the bifurcation of the ASPDA. The GSP was designed to fit the curve of this transition area. Because the pancreas is fixed to the retroperitoneum, the GDA mobility is presumably low, although the RGEA in the gastrocolic ligament is mobile. This is why such a strong stability of the implanted GSP could be obtained [12]. According to previous reports, the technical success rate of the fixed catheter tip method using other indwelling catheters ranges from 97–100% [3, 4, 8], which is almost the same as that obtained in the present study. The reported frequency of dislodgement is 2.8–5% [3–6, 8, 9], and the reported frequency of hepatic arterial occlusion is 3.3–18% [3–6, 8, 9]. In our study, no dislodgement was observed, and the occurrence of hepatic arterial occlusion was 2%. Because of the SMAL, the stability of the GSP was probably reinforced by the coils that were filled around the GSP for GDA embolization. Thus, the GSP effectively prevented catheter dislodgement. Hepatic arterial occlusion and hepatic arterial stenoses were seen in one and five cases, respectively, at the peripheral branches. No stenoses or occlusions were seen at the CHA or the proper hepatic artery. These vascular changes were thus thought to be caused by drug-induced vascular damage [18].

We used the GSP for the IHA or the SPA method in 11 and two cases, respectively. The indwelling procedures were successful and the clinical outcomes were satisfactory, warranting further analysis of GSP as a possible catheter choice for these methods.

Our experimental and clinical results indicate that the GSP enables efficient catheter replacement because of ease in following the guidewire. The GSP also effectively prevents indwelling catheter dislodgement because of adequate vessel fixing power. Catheter placement for HAIC using the GSP had a high technical success rate and a comparatively low frequency of complications. Thus, GSP is a potentially suitable catheter for HAIC because it delivers increased convenience without compromising safety.

Acknowledgment We thank Machi Suka MD, PhD for advice on statistical analysis.

References

1. Lorenz M, Muller HH (2000) Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with non-resectable liver metastases from colorectal carcinoma. J Clin Oncol 18:243–254
2. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J (1994) Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. Lancet 344:1255–1260
3. Irie T (2001) Intraarterial chemotherapy of liver metastases: Implantation of a microcatheter-port system with use of modified fixed catheter tip technique. J Vasc Interv Radiol 12:1215–1218
4. Tanaka T, Arai Y, Inaba Y, Matsueda K, Aramaki T, Takeuchi Y et al (2003) Radiologic placement of side-hole catheter with tip fixation for hepatic arterial infusion chemotherapy. J Vasc Interv Radiol 14:63–68
5. Yamagami T, Iida S, Kato T, Tanaka O, Hirota T, Nakamura T et al (2002) Using n-butyl cyanoacrylate and the fixed-catheter-tip technique in percutaneous implantation of a port-catheter system in patients undergoing repeated hepatic arterial chemotherapy. AJR Am J Roentgenol 179:1611–1617
6. Yamagami T, Kato T, Iida S, Hirota T, Nishimura T (2005) Management of end hole in placement of port-catheter system for continuous hepatic arterial infusion chemotherapy using the fixed catheter tip method. AJR Am J Roentgenol 184:1332–1339
7. Seki H, Shiina M (2006) Placement of a long tapered side-hole catheter in the hepatic artery: technical advantages, catheter stability, and arterial patency. AJR Am J Roentgenol 187:1312–1320
8. Tajima T, Yoshimitsu K, Kuroiwa T, Ishibashi T, Irie H, Aibe H et al (2005) Percutaneous femoral catheter placement for long-term chemotherapy infusions: preliminary technical results. AJR Am J Roentgenol 184:906–914
9. Seki H, Ozaki T, Shiina M (2008) Side-hole catheter placement for hepatic arterial infusion chemotherapy in patients with liver metastases from colorectal cancer: long-term treatment and survival benefit. AJR Am J Roentgenol 190:111–120
10. Yoshioka T, Horikawa N, Takayama K, Nakatani T, Masui K, Kikuchi E et al (2003) Implantation of the intra-arterial port-catheter system using W spiral catheter in the peripheral hepatic arteries without fixation for treatment of malignant liver tumors: clinical experience. Intervent Radiol 18:282–286
11. Shimamura T, Sato R, Noguchi T, Sasaki K, Cho N (2009) Case of indwelling catheter dislocation into the duodenum during hepatic arterial infusion chemotherapy. Nippon Shokakibyo Gakkai Zasshi 106:383–388
12. Okamoto K, Takizawa K, Yagihashi K, Nakaji S, Sakaino S, Ogawa Y et al (2006) Initial experience using new W-spiral catheter (G-spiral) corresponding to 0.035 inch-GW for GDA-coil fixation method. Intervent Radiol 21:170–173
13. Sadaoka S (1999) Comparative study of the physical properties of microcatheters frequently used for abdominal IVR. Nippon Acta Radiol 59:867–876
14. Saeki M, HoshikawaY, Nakajima Y, Inaoka T (2003) Development of a wave-shaped hydrophilic-coated guidewire for long tube insertion: clinical application and sliding resistance test. Intervent Radiol 18:30–34
15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655
16. Kosinski C (1928) Quelques observationes sur le rameaux du tronc cæliaque et des artères mésentériques chez l'homme. C R Assoc Anat 23:241–260
17. Kimura Y, Kimura W, Hirai I, Sugawara S, Sakurai F (2005) Surgical anatomy for the arteries of the pancreas. Yamagata Med J 23:11–21
18. Takeuchi Y, Arai Y, Inaba Y, Ota T, Sueyoshi S, Yamagami T et al (1996) A new percutaneous catheterization "side holed catheter placement with fixation" for a long-term arterial chemotherapeutic infusion: its effectiveness to prevent hepatic arterial occlusion. J Jpn Soc Angiogr Interv Radiol 11:471–476

original article

Annals of Oncology 20: 1943–1947, 2009
doi:10.1093/annonc/mdp242
Published online 1 July 2009

Phase I/II clinical study of percutaneous vertebroplasty (PVP) as palliation for painful malignant vertebral compression fractures (PMVCF): JIVROSG-0202

T. Kobayashi[1]*, Y. Arai[2], Y. Takeuchi[2], Y. Nakajima[3], Y. Shioyama[4], M. Sone[5], N. Tanigawa[6], O. Matsui[7], M. Kadoya[8] & Y. Inaba[9] Japan Interventional Radiology in Oncology Study Group (JIVROSG)

[1]*Department of Diagnostic and Interventional Radiology, Ishikawa Prefectual Central Hospital, Ishikawa;* [2]*Department of Diagnostic Radiology Division, National Cancer Center Hospital, Tokyo;* [3]*Department of Radiology, St. Marianna University, Yokohama;* [4]*Department of Radiology, Dokkyo Medical University, Tochigi;* [5]*Department of Radiology, Iwate Medical University, Iwate;* [6]*Department of Radiology, Kansai Medical University, Isaka;* [7]*Department of Radiology, Kanazawa University, Ishikawa;* [8]*Department of Radiology, Shinshu University, Matsumoto and* [9]*Department of Diagnostic and Interventional Radiology, Aichi Cancer Center, Aichi, Japan*

Received 8 May 2008; revised 18 November 2008; revised 18 March 2009; accepted 26 March 2009

Background: The safety and efficacy of percutaneous vertebroplasty (PVP), a new treatment modality for painful malignant vertebral compression fractures (PMVCF) using interventional radiology techniques, were evaluated prospectively.
Materials and methods: After confirming the absence of safety issues in phase 1, a total of 33 cases were registered up to and including phase 2. Safety and efficacy were evaluated by National Cancer Institute—Common Toxicity Criteria version 2 and Visual Analogue Scale (VAS) at 1 week after PVP. Based on VAS score decreases, efficacy was classified into significantly effective (SE; ≥5 or reached 0–2), moderately effective (ME; 2–4), or ineffective (NE; <2 or increase).
Results: Procedures were completed in all 33 patients (42 vertebrae). Thirty days after PVP, two patients died of primary disease progression, but no major adverse reactions (>grade 2) were observed. Response rate was 70% (95% confidence interval 54% to 83%) [61% (n = 20) with SE, 9% (n = 3) with ME, and 30% (n = 10) with NE] and increased to 83% at week 4. Median time to response was 1 day (mean 2.4). Median pain-mitigated survival period was 73 days.
Conclusion: For PMVCF, PVP is a safe and effective treatment modality with immediate onset of action.
Key words: percutaneous vertebroplasty, interventional radiology, pain relief, vertebral metastasis, percutaneous cement plasty

introduction

The pain relief of painful malignant vertebral compression fractures (PMVCF) is one of the key elements for achieving better quality of life in patients under palliative care. The mainstay for pain relief is pharmacological therapy such as with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, and if patients are not responsive to these agents or have pain upon body movement, radiotherapy is administered. However, despite being a noninvasive therapeutic modality, radiotherapy is less than ideal because it requires 2–4 weeks to obtain a therapeutic effect and does not achieve complete pain relief in most cases [1, 2].

Since the report of percutaneous vertebroplasty (PVP) by Galibert et al. [3], in 1987, the technique has been widely reported [4–10]. These reports indicate that it is highly effective for prompt pain relief for metastatic vertebral tumors from any primary sites. On the other hand, severe, albeit rare, complications such as pulmonary embolism, cerebral infarction, cardiogenic shock, and spinal cord injury due to leakage of cement into the spinal canal have also been documented [11–13]. All these reports, however, have been retrospective in nature, and to our knowledge, no study has yet prospectively investigated the safety and therapeutic effect of this modality. Although it cannot be excluded that severe complications may very rarely occur, to minimize the frequency of reported complications, it is important to evaluate in a prospective study whether this procedure can be carried out safely when conducted by trained interventional radiologists for clearly defined indications.

Therefore, we undertook a phase I/II multi-institutional prospective study of PVP as Japan Interventional Radiology in Oncology Study Group (JIVROSG)-0202. In this study, we evaluated the safety and efficacy of PVP as a palliative intervention for patients with PMVCF.

materials and methods

patient selection

Patients were required to have an imaging [including radiography and computed tomography (CT)] diagnosis of changes in the thoracic or

Correspondence to: Dr T. Kobayashi, Department of Diagnostic and Interventional Radiology, Ishikawa Prefectual Central Hospital, Kuratsukihigashi 2-1, Kanazawa-shi, Ishikawa Prefecture, 920-8530, Japan. Tel: +81-76-237-8211; Fax: +81-76-238-2337; E-mail: kobaken@ipch.jp

lumbar vertebrae caused by malignant tumor metastases or multiple myeloma, limitation of daily activities due to pain from the lesions and/or the risk of compression fracture, and no exposure of the vertebral tumors to the vertebral canal (defined as vertebral canal surface showing no tumor invasion on CT or magnetic resonance imaging). In addition, the patients had to have an Eastern Cooperative Oncology Group performance status (PS) of zero to three, preserved major organ function (bone marrow, heart, liver, lung, and kidney), and an anticipated survival of at least 4 weeks. Patients were excluded if their pain grade of Visual Analogue Scale (VAS) [14] was ≤2, they could not maintain the position needed for treatment, they had a bleeding tendency with bleeding time ≥5 min, fever ≥38°C, cardiac failure requiring continuous drug therapy, history of major drug allergy such as anaphylactic shock to any drugs, so as to minimize the possibility of cardiac toxicity due to the bone cement preparation, and/or confirmed or possible pregnancy. In addition, patients were judged ineligible for this trial if the vertebral lesions harbored possible active inflammation (tuberculous or other infectious), if marked vertebral flattening was present (defined as the height of the affected vertebral body showing a mean value of one-third of that of the superior and inferior vertebral bodies), if five or more continuous vertebrae were affected precluding evaluation of the therapeutic effect or if in a single session four or more vertebrae required therapy.

Both the ethics committee of the Japanese Society of Interventional Radiology and each institutional review board approved the protocol of this study before patient entry. All patients provided written informed consent.

collaborative institutions

This study was conducted in 10 institutions comprising JIVROSG. Each of these institutions has at least one full-time interventional radiologist certified by the Japanese Society of Interventional Radiology (Table 1).

study end points

The primary end point of this study was to evaluate the safety of PVP, and the secondary end point was to evaluate the efficacy of PVP for pain relief as well as the incidence and grade of adverse events.

study design

This study was a multi-institutional, single-arm, open-label, noncomparative trial. The phase I part of this trial was conducted using the 3 × 3 method proposed by the JIVROSG. This method was applied as follows. To be able to quickly terminate the study if the incidence of adverse events associated with this modality exceeded one-third of the patients, three separate groups with three cases each were enrolled at 4-week intervals. If severe adverse events of the first group with three cases, according to the National Cancer Institute—Common Toxicity Criteria (NCI-CTC) version 2.0 [15] or equivalent adverse events, were limited to one or less of the first three cases, then the second group with three cases was added. When the number of adverse events in the combined first and second groups with six cases was two or less, then the third group with three cases was added. If the number of adverse events of the total nine cases of all three groups was three or less, then subsequently all cases up to the target number were enrolled without distinguishing them into three different groups. If the incidence of adverse events in each of the first, second and third groups exceeded the above-noted permissible limits, the advisability of trial continuation or possible termination was rediscussed.

Table 1. Collaborative institutions

National Cancer Center Hospital
Kyoto First Red Cross Hospital
St Marianna University
Ibaraki Prefectural Central Hospital
Kansai Medical University
Iwate Medical University
Kanazawa University
Shinshu University
Aichi Cancer Center
Tochigi Cancer Center Hospital

In the phase II part of this study, 24 cases were enrolled. Since the treatment administered in phases 1 and 2 was exactly the same, the primary and secondary end points of the cases registered in phase 1 were evaluated together with those of the cases of phase 2. So, the primary and secondary end points were evaluated in all 33 cases.

The observation period for adverse events was defined as the 1-month period following the completion of the procedure. Subsequently, the presence/absence of pain recurrence at the treated site, the period of pain relief (absence of recurrent pain at the treated site from before therapy to obtaining a decrease of VAS score to ≤2), and patient survival period were investigated. In the follow-up investigation, recurrence was defined as occurring on the day on which pain worse than that before therapy was noted, with the period up to this day defined as the pain-mitigated survival period.

statistical analysis

In the phase I part of this study, a cohort size of nine patients was considered to make it possible to quickly terminate the study if the incidence of adverse events associated with this modality exceeded one-third. During phase I through phase II, the study was designed to detect adverse events having an incidence of at least 10%, setting 80% power, 10% predicted rate, and 30% unacceptable rate. We anticipated a protocol dropout rate of 10%. Thus, the target accrual number of patients was calculated to be 33. All enrolled patients were included for the intention-to-treat analyses.

registration of cases

The registration period extended from February 2003 until May 2006. To enter a patient into the study, the investigator had to log on to a restricted Web site using the JIVROSG data center, enter patient indication/contraindication data, and register the case. After the executive office verified the suitability of the entered data and the presence/absence of any missing items, a registration number specific to that patient was issued and the case registration procedure completed. Subsequently, all communications were limited to these issued patient registration numbers. PVP was commenced within 1 week of this patient registration.

interventional procedures of PVP

The interventional procedures of PVP in this study were conducted as follows. After injection of 0.5 mg atropine sulfate and securing a venous access, the patient was placed prone on the table used for fluoroscopy or CT fluoroscopy, and an electrocardiogram apparatus and blood pressure monitor were attached. Following disinfection of the puncture site and injection of local anesthesia, an 11–14 ga metallic needle was inserted up to the site where the bone cement was to be injected under fluoroscopic or CT-fluoroscopic guidance (Figure 1A). Acrylic bone cement was prepared, and the use of bone cement mixed with up to 30% bactericidal barium was recommended if bone cement was injected under fluoroscopic guidance (Figure 1B). The injection was stopped when sufficient bone cement was judged to have been distributed, after which the needle was withdrawn (Figure 1C). When multiple (up to three) vertebrae were to be treated, these steps were repeated for each vertebra. The patient was kept at bed rest for 2 h after the procedure.

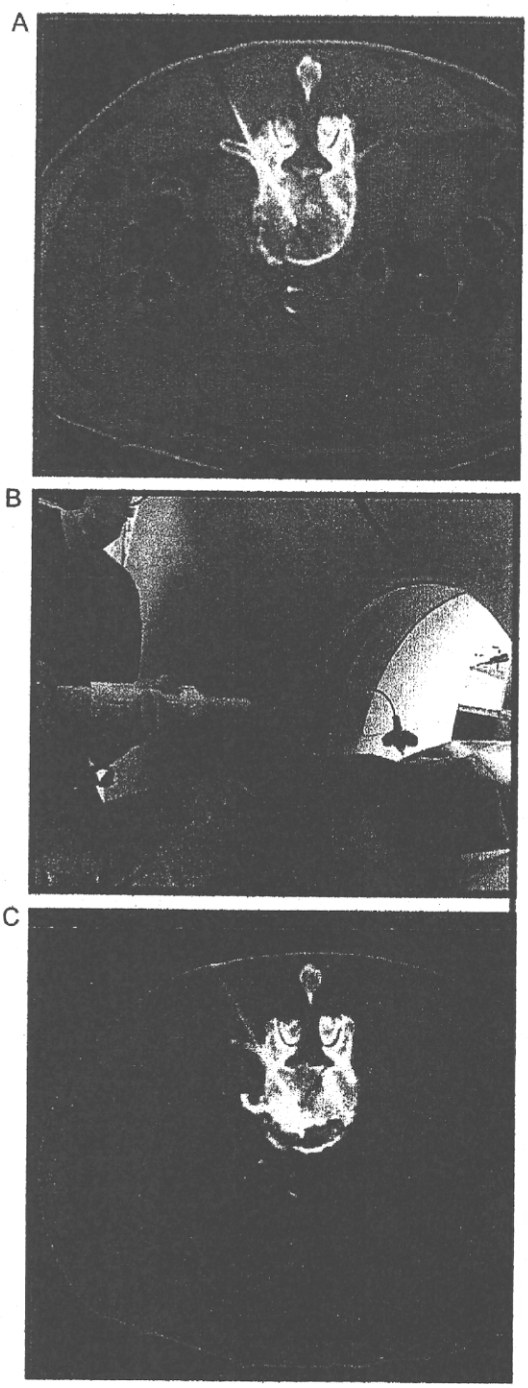

Figure 1. Interventional procedure of percutaneous vertebroplasty. (**A**) Insertion of 11–14 ga bone biopsy needle into the target vertebral bone through pedicle under fluoroscopic or computed tomography (CT)-fluoroscopic guidance. (**B**) Injection of acrylic bone cement under fluoroscopy or CT fluoroscopy monitoring. (**C**) Stop of the injection when adequate distribution is obtained.

combined and supportive therapies

To prevent possible infection, it is recommended that antibiotics be administered for 3 days following the procedure and that an anesthesiologist or other physician able to undertake emergency measures be present. Continued administration of any radiotherapy or analgesics, chemotherapy, and nerve block therapy used before therapy was permitted, including the wearing of corsets. With the exception of management of adverse events, surgical intervention for post-therapy pain, admixture of anticancer agents and/or antibiotics with the acrylic bone cement, and PVP using general anesthesia were not permitted.

observation items

The imaging findings including those of radiography and CT of the primary site and target vertebrae and compression grade were evaluated before therapy and at around 7 days after therapy. VAS score was determined at days 1, 3, and 7 and weeks 2 and 4. Also, before and after therapy, the patient items were evaluated at the specified times.

evaluation methods

The adverse events were evaluated by NCI-CTC version 2. The grade of pain was evaluated by the VAS. VAS scoring was done by having the patient himself note his degree of pain on a 10-cm long horizontal straight line. The efficacy of therapy was evaluated by changes in the VAS score noted 1 week after therapy. When the VAS score was ≤2 or when compared with before therapy a decrease of ≥5 was obtained, the therapy was judged to be significantly effective (SE). When the VAS score did not reach ≤2 but when compared with before therapy showed a decrease to <5 to ≥2, the therapy was judged to be moderately effective (ME). When despite therapy the VAS score decreased by <2 or showed an increase, the therapy was judged to be ineffective (NE). The efficacy of the therapeutic results was assessed by the proportion of the total cases achieving SE or ME. Regardless of any changes in the VAS score, the therapy was also judged to be NE if the need for analgesics increased as compared with before therapy. However, to investigate the timing of the pain-mitigating effect, VAS score was determined within 1 week before the start of therapy, the day after, 3 days after, and at 1, 2, 3, and 4 weeks.

In cases with painful bone metastases at multiple sites, treatment was permitted for all sites with indications for PVP at multiple sessions. However, one treatment session was limited to a maximum of three vertebrae. When all treatment sessions were finished, the degree of back pain was comprehensively evaluated by VAS.

results

There were no reports of severe adverse event in any of the nine cases enrolled in phase I. Thus, without any interruption the transition was made to phase II. There were a total of 33 cases from 10 institutions, comprising 16 males and 17 females with a mean age of 62 years (37–87 years) (Table 2). PS was zero in one case, one in seven cases, two in 12 cases, and three in 13 cases. Thirty cases had metastatic vertebral tumors, originating from lung, breast, and colon cancer in seven cases each, liver cancer in four cases, pancreas cancer in two cases, and tongue, esophagus, and skin cancer in one case each. The only primary vertebral tumor was multiple myeloma, which was present in three cases. Analgesics administered before therapy were NSAIDs alone in nine cases, opioids alone in 10, and both in 11. Radiotherapy was administered to the treated site in 11 cases. The mean interval between the two therapies was 46 days, and no pain-mitigating effect was obtained.

Forty-two vertebrae were targeted: 18 thoracic vertebrae (I, one; VII, three; VIII, three; IX, four; X, two; XI, two; and XII, three) and 24 lumbar vertebrae (I, one; II, seven; III, seven; IV, seven; and V, two). Changes in imaging findings at the treated sites comprised osteolytic changes in 35 vertebrae, mixed

doi:10.1093/annonc/mdp242 | 1945

changes in five vertebrae, and osteoblastic changes in two vertebrae, with the mean compression rate amounting to 75.8% (41%–106%). Three vertebral bodies, two vertebral bodies, and one vertebral body were treated in two, five, and 26 cases, respectively. In only a single case was the treatment divided into two sessions, being completed in a single session in all the other cases.

CT fluoroscopy was used in 15 cases, fluoroscopy in 15, and a combination of the two in three. The mean time required per case and per vertebra was 49 min (20–120 min) and 39 min, respectively. The volume of bone cement administered was 1–8 ml [mean 3.5 ml, standard deviation (SD) 1.8 ml]. The bone cement preparations used were Osteobond (Zimmer, IN) in 22 cases, Simplex (Stryker, MI) in 10, and Bone Cement (Zimmer) in one. The recommended antibiotics were used in 19 of 33 cases (58%). The technical success rate was 100%, and in no cases were the interventional procedures provided by the protocol terminated prematurely.

In the evaluation of safety, adverse events during the therapy were limited to bleeding from the puncture site in a single case (3%), in which the bleeding was stopped with 5-min manual pressure. Adverse events of grade 3 or 4 of NCI-CTC version 2 or other correspondingly severe adverse events related to PVP were not observed, while two patient deaths caused by the progression of primary disease were observed within 30 days of PVP. An adverse event of PVP could not be excluded in only a single case (3%) with grade 2 serum hypoalbuminemia.

In the evaluation of clinical efficacy, the response rate was 70% (95% confidence interval 54% to 83%), being SE in 20 cases (61%) and ME in three (9%). The mean time to response was 2.4 days (median 1 day, SD 3.2 days). VAS score was 6.2 + 2.1 within 1 week before the start of therapy, 3.6 + 2.6 the day after, 2.5 + 2.6 after 3 days, and 2.4 + 2.3 at 1 week (5–8 days), 2.3 + 2.7 at 2 weeks (11–15 days), 2.0 + 2.2 at 3 weeks (15–26 days), and 1.8 + 2.3 at 4 weeks (26–29 days) (Figure 2).

Pain recurrence at the treated site was noted in 5 of 23 (22%) of the SE or ME cases. On the other hand, in 4 of the 10 cases (40%) in which the therapy was evaluated as ineffective in the first week, the result was subsequently judged to be ME. At 4 months after completion of enrollment, 14 patients were alive, 18 had died, and the survival status of one was unknown. The median survival period was 194 days (mean 270 days, SD 240

Table 2. Background of enrolled cases

Patient characteristics	n
No. of patients	33[a]
Male	16
Female	17
Mean age, years	62 (37–87)
Primary disease	
Lung cancer	7
Breast cancer	7
Colorectal cancer	7
Liver cancer	4
Myeloma	3
Pancreatic cancer	2
Tongue cancer	1
Esophageal cancer	1
Skin cancer	1
Preradiotherapy to the target lesion	11 (mean interval 46 days)
Combined chemotherapy	16
Administered analgesics before therapy	
NSAIDs alone	9
Opioids alone	10
NSAIDs and opioids	11
Performance status (ECOG)	
0	1
1	7
2	12
3	13
Target VB (N = 42)	
1 VB	26
2 VBs	5
3 VBs	2
Thoracic VB (N = 18)	
I	1
VII	3
VIII	3
IX	4
X	2
XI	2
XII	3
Lumbar VB (N = 24)	
I	1
II	7
III	7
IV	7
V	2
Appearance of lesion	
Osteolytic	28 (35 VBs)
Mixed	3 (5 VBs)
Osteoblastic	2 (2 VBs)
Compression rate (height of target VB/height of next VB)	
Mean	75.8% (41%–106%)

[a]Nine for phase I and 24 for phase II.

NSAIDs, nonsteroidal anti-inflammatory drugs; ECOG, Eastern Cooperative Oncology Group; VB, vertebral bone.

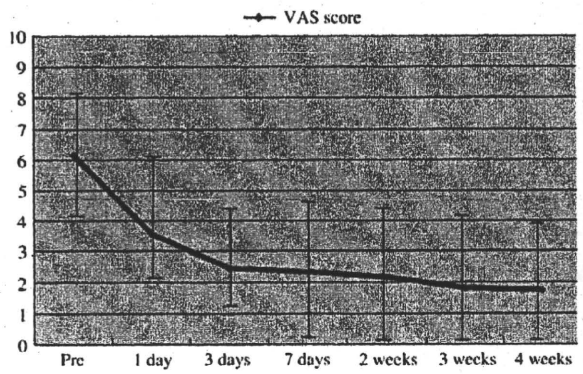

Figure 2. Changes in Visual Analogue Scale (VAS) score. The changes in the VAS values at the various observation time points are listed here. The curve shows the changes in mean values and the vertical line the standard deviation. Pain relief from the therapy is obtained by the third day, with a slow decrease in the VAS values also subsequently observed.

days). The median pain-mitigated survival period was 73 days (mean 230 days, SD 258 days).

discussion

The treatment of painful vertebral metastases and other conditions affecting vertebral bone remains a major challenge in patients under palliative care. Numerous studies have already validated the efficacy and safety of PVP in this context [4–7, 11]. However, all these were retrospective in nature, and no such prospective studies have yet been described. This prompted JIVROSG to undertake the present study to objectively evaluate this procedure by prospectively assessing its safety and clinical efficacy in a multi-institutional setting.

Regarding safety, we attributed the absence of severe complications in the present study to the strict patient selection criteria adopted by us, namely, the exclusion of cases with cardiac failure, a history of drug allergy, and tumors exposed within the vertebral canal, as well as the use of a highly precise fluoroscopy or CT fluoroscopy apparatus at the time of therapy, and the use during fluoroscopy of bone cement mixed with up to 30% bactericidal barium so as to facilitate the immediate recognition of extravertebral leakage. These results indicate that PVP is an extremely safe therapeutic intervention, provided that appropriate patient selection and apparatus use are adhered to, when carried out by an interventional radiology specialist.

In this study, pain was evaluated at 1 week after therapy, with an efficacy rate of 70% obtained, comparable to previously reported results of 70%–90% in the literature [4, 7, 10, 11]. However, most importantly, the therapeutic effect was apparent at a median 1 day (mean 2.4 days, SD 3.2 days), demonstrating a rapid pain-relieving effect. In contrast, the therapeutic response to the hitherto standard pain relief therapeutic modality used, namely, 10 sessions of radiotherapy at 3 Gy, has been reported to require 2–4 weeks to take effect [1, 2]. In this respect, thus, the rapidity of onset of the desired effect of PVP is clearly superior to that of radiotherapy. The median survival period of the enrolled cases was 194 days because ≥90 of them had bone metastases from malignant tumors and had a poor prognosis. In view of this fact, the selection of a therapeutic modality providing a prompt onset of pain relief becomes especially important. In contrast, in cases with vertebral body metastases highly sensitive to radiotherapy and/or with an anticipated long survival period, radiotherapy is the preferred option.

Recurrence of pain at the treated site was noted in 21% of cases. Since this therapy is not designed to exert an antitumor effect but rather to provide pain relief by strengthening weakened vertebrae, pain recurrence is unavoidable if the metastatic foci expand. The lack of a response in six patients was attributed to their poor general state. The present results based on a prospective study demonstrate that PVP can be carried out safely and shows marked efficacy, in particular fast-acting pain relief, provided that patient and equipment selection is appropriate and that an experienced physician is available. Since PVP is a therapeutic technique, its safety cannot be evaluated like that of a phase I trial for drugs in which drug doses are increased incrementally to determine the optimal doses to be administered. Therefore, in the present study, we adopted a modified design of phase I study for drugs. However, the number of cases in our study is not enough to confirm the safety of PVP. Additionally, the results of this study are insufficient to establish PVP as a standard therapy for patients with painful malignant vertebral body tumors. Thus, we are planning to conduct a phase III study comparing PVP and conventional treatments in this context.

conclusion

PVP was proved safe, clinically efficacious, and fast acting in this prospective study. Future studies enrolling larger groups of patients will be needed to further establish its role in the management of painful bone lesions as palliative care.

acknowledgements

This study is the first prospective one to evaluate the safety and efficacy of PVP as palliative care for end-stage cancer patients. The authors have received no funds related to this study and are aware of no conflict of interest. A part of this study was shown as a poster presentation at the meeting of the American Society of Clinical Oncology, Chicago 2007.

references

1. Bates T. A review of local radiotherapy in the treatment of bone metastases and cord compression. Int J Radiat Oncol Biol Phys 1992; 23: 217–221.
2. Ben-Josef E, Shamsa F, Williams O et al. Radiotherapeutic management of osseous metastases: a survey of current patterns of care. Int J Radiat Oncol Biol Phys 1998; 40: 915–921.
3. Deramond H, Depriester C, Galibert P et al. Percutaneous vertebroplasty with polymethylmethacrylate. technique, indication, and results. Radiol Clin North Am 1998; 36: 533–546.
4. Cotton A, Boutry N, Cortet B et al. Percutaneous vertebroplasty: state of the art. Radiographics 1998; 18: 311–320.
5. Barr JD, Barr MS, Lemley TJ et al. Percutaneous vertebroplasty for pain relief and spinal stabilization. Spine 2000; 25: 923–928.
6. Weill A, Chiras J, Simon JM et al. Spinal metastases; indications for and results of percutaneous injection of acrylic surgical cement. Radiology 1996; 199: 241–247.
7. Murphy KJ, Deramond H. Percutaneous vertebroplasty in benign and malignant disease. Neuroimaging Clin N Am 2000; 10: 535–545.
8. Baba K, Ookubo K, Hamada K et al. Percutaneous vertebroplasty for osteolytic metastasis: a case report. Radiat Med 1997; 57: 880–882.
9. Kobayashi T, Takanaka T, Matsui O et al. Efficacy of percutaneous vertebroplasty under CT fluoroscopic guidance. Jpn J Intervent Radiol 1999; 14: 343–348.
10. Kobayashi T, Takanaka T, Matsui O et al. Practice of percutaneous vertebroplasty. Jpn J Intervent Radiol 2002; 17: 17–22.
11. Jensen ME, Kallmes DE. Percutaneous vertebroplasty in the treatment of malignant spine disease. Cancer J 2002; 8: 194–206.
12. Scroop R, Eskridge J, Britz GW. Paradoxical cerebral arterial embolization of cement during intraoperative vertebroplasty: case report. AJNR Am J Neuroradiol 2002; 23: 868–870.
13. Kaaufmann TJ, Jensen ME, Ford G et al. Cardiovascular effects of polymethyl methacrylate use in percutaneous vertebroplasty. AJNR Am J Neuroradiol 2002; 23: 601–604.
14. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990; 13: 227–236.
15. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf (15 April 2009, date last accessed).

Cardiovasc Intervent Radiol (2009) 32:1059–1066
DOI 10.1007/s00270-009-9510-1

TECHNICAL NOTE

Development of a New Subclavian Arterial Infusion Chemotherapy Method for Locally or Recurrent Advanced Breast Cancer Using an Implanted Catheter–Port System After Redistribution of Arterial Tumor Supply

Kenji Takizawa · Hiroshi Shimamoto · Yukihisa Ogawa · Misako Yoshimatsu · Kunihiro Yagihashi · Yasuo Nakajima · Takashi Kitanosono

Received: 4 August 2008 / Accepted: 8 January 2009 / Published online: 24 February 2009

Abstract Locally or recurrent advanced breast cancers can receive arterial blood supply from various arteries, such as the internal thoracic artery (ITA), the lateral thoracic artery, and the other small arterial branches originating from the subclavian artery. Failure to catheterize and subsequent formation of collateral arterial blood supply from various arteries are some of the reasons why the response to conventional selective transarterial infusion chemotherapy is limited and variable. To overcome this problem, we developed a new subclavian arterial infusion chemotherapy method using an implanted catheter–port system after redistribution of arterial tumor blood supply by embolizing the ITA. We named this technique ("redistributed subclavian arterial infusion chemotherapy" (RESAIC)). Using RESAIC, patients can be treated on an outpatient basis for extended periods of time. Eleven patients underwent RESAIC, and the complete remission and partial response rate in 10 evaluable patients was 90%: complete remission [CR] $n = 4$, partial remission $n = 4$, stable disease $n = 1$, and not evaluable $n = 1$. Three of four patients with CR had no distant metastasis, and modified radical mastectomy was performed 1 month after conclusion of RESAIC. The resected specimens showed no residual cancer cells, and pathologically confirmed complete remission was diagnosed in each of these cases. Although temporary grade-3 myelosuppression was seen in three patients who were previously treated by systemic chemotherapy, there was no other drug-induced toxicity or procedure-related complications. RESAIC produced a better response and showed no major complications compared with other studies despite the advanced stage of the cancers.

Keywords Interventional Radiology · Breast cancer · Arterial infusion chemotherapy · Implanted port

K. Takizawa (✉) · H. Shimamoto · Y. Ogawa · M. Yoshimatsu · K. Yagihashi · Y. Nakajima
Department of Radiology, St. Marianna University School of Medicine, Sugao, Miyamae, Kawasaki, Kanagawa, Japan
e-mail: taki-lrl@vy.catv.ne.jp

H. Shimamoto
e-mail: hshima@k8.dion.ne.jp

Y. Ogawa
e-mail: yukky-p406c@nifty.com

M. Yoshimatsu
e-mail: misako_yosh@yahoo.co.jp

K. Yagihashi
e-mail: yagiku@hotmail.com

Y. Nakajima
e-mail: y3naka@marianna-u.ac.jp

T. Kitanosono
Department of Vascular/Interventional Radiology, University of Rochester Medical Center, 601 Elmwood Avenue, Box 648, Rochester, NY, USA
e-mail: tkita1@mac.com

Introduction

Locally or recurrent advanced breast cancers (ABC) are defined as large tumors with extensive regional lymph node involvement or direct invasion of the skin or underlying chest wall [1]. These cancers are considered stages IIIa and IIIb according to the tumor-node-metastasis classification system adopted by the Japanese Breast Cancer Society, which is based on the classification system of the International Union Against Cancer [2]. Inflammatory breast cancer showing extensive histologic infiltration of dermal lymphatics is a distinct subset.

Some previous reports showed that arterial infusion chemotherapy (AIC) was effective for ABC [3–5]. The local response rate was reported to be 70–90%, and rapid tumor regression was seen after the treatment [6–10]. However, problems associated with AIC should be resolved as will be described later. Conventionally in AIC procedures, the chemotherapeutic agents are selectively infused into subclavian and axillary branches supplying the tumor. This procedure is technically complicated and is usually repeated multiple times in each patient. In addition, such repeated infusions cause drug-induced damage to the infused arterial branches, and this promotes the development of collateral arterial blood supply [11, 12]. Therefore, the number of possible repetitions of AIC is limited, and long-term local control is not expected. To overcome this problem, we developed a new subclavian arterial infusion chemotherapy method using an implanted catheter–port system (CPS) after redistribution of the arterial blood supply to the tumor. The arterial redistribution was achieved by embolizing the internal thoracic artery (ITA) using a mixture of N-butyl cyanoacrylate (NBCA; B. Braun, Melsungen, Germany) and iodized oil (LPD) (Lipiodol Ultra-Fluide; Terumo, Tokyo, Japan) [13, 14]. Using this drug-delivery system, patients can be treated on an outpatient basis for extended periods of time. We believe that this new technique, named "redistributed subclavian arterial infusion chemotherapy" (RESAIC), is an epoch-making treatment method that, to the best of our knowledge, has not been reported previously. This study was an initial pilot study evaluating the effectiveness and safety of RESAIC.

Patients and Methods

Patients with ABC whose tumors were resistant to standard systemic chemotherapy or who were physically unable to tolerate systemic chemotherapy were the subjects of this study. In addition, patients >70 years of age with no previous treatment were also included. Eligibility criteria included histologically confirmed carcinoma of the breast, a life expectancy >2 months, World Health Organization performance status <3, adequate bone marrow reserve (white blood cell count >2500/ml, platelet count >50,000/ml), satisfactory renal and liver function (total bilirubin and creatinine <1.25 times the upper normal limits), and normal cardiac function by electrocardiogram (ECG). Any previous systemic chemotherapy except trastuzumab (Herceptin; Chugai, Japan) was discontinued for at least 4 weeks before protocol entry. Trastuzumab was continued to inhibit the development of distant metastases. Eleven patients were entered into this study between April 2006 and December 2007. All patients were female and had diagnosed stage IIIb or IV disease. A 52-year-old woman who had severe anemia (hemoglobin 5.6 g/dl) caused by bleeding from the primary tumor was entered because she was considered unable to tolerate standard systemic chemotherapy. All patients gave informed consent to participate in the trial. Table 1 shows demographics of the participating patients. The patients' ages ranged from 39 to 82 years (median of 61).

All patients were histologically diagnosed as having invasive ductal carcinoma, and one of the patients showed

Table 1 Patient's characteristics

Patient no.	Age	Tumor	Neoadjuvant or resistant	Stage	Distal metastasis	Symptom	Pathology	ER	PgR	Her2
1	58	Primary	Resistant	IV	Lung, liver	Pain	IDC/scirrhous carcinoma	+	+	1+
2	39	Primary	Resistant	IV	Lung, bone	Pain, ulcer, bleeding	IDC/papillo-tubular carcinoma	−	−	−
3	51	Recurrence	Resistant	IV	Lung, bone	Pain, ulcer, bleeding	IDC/scirrhous carcinoma	+	+	2+
4	52	Primary	Neoadjuvant	IIIb	–	Pain, bleeding, effusion	IDC	−	−	2+
5	72	Primary	Resistant	IIIb	–	Pain, ulcer, effusion	IDC	+	+	−
6	61	Recurrence	Resistant	IV	Liver	Pain, ulcer, effusion, arm edema	IDC/solid-tubular carcinoma	+	−	−
7	81	Primary	Neoadjuvant	IIIb	–	Pain, ulcer, effusion, arm edema	IDC	−	−	2+
8	78	Recurrence	Resistant	IIIb	–	Pain, erosion, induration	IDC (inflammatory breast cancer)	−	−	2+
9	70	Primary	Neoadjuvant	IV	Lung, bone	Pain, ulcer, bleeding, arm edema	IDC/scirrhous carcinoma	+	+	2+
10	82	Recurrence	Resistant	IV	Lung, liver	Pain, bleeding	IDC/solid-tubular carcinoma	+	−	−
11	52	Primary	Resistant	IV	Lung, liver, brain	Pain, bleeding, abscess formation	IDC/solid-tubular carcinoma	−	−	3+

IDC invasive ductal carcinoma

inflammatory breast cancer. Four patients had no distant metastasis. Three patients were previously untreated (neoadjuvant group) and eight were resistant to the previous systemic chemotherapy (resistant group). One patient had undergone mastectomy, and another patient had undergone radiotherapy. Overall tumor size ranged from 5.9 to 21.3 cm in diameter (median 10.5), from 10.5 to 13.9 cm (median 12.2) in the neoadjuvant group, and from 5.9 to 21.3 cm (median 6.7) in the resistant group. Tumor stages in the neoadjuvant group were IIIB in two patients and IV in one patient, and the stages in the resistant group were IIIB in two patients and IV in six patients.

Implantation of the CPS for RESAIC was performed by way of angiography with the patient under local anesthesia. First, embolization of the ITA was performed. In the first case, the ITA was embolized initially by way of a transfemoral approach. This was followed by implantation of the CPS by way of a brachial artery approach, and the port was placed in a subcutaneous pouch at the forearm (two-route method). In the other 10 patients, both embolization and implantation of the CPS were achieved with the ipsilateral brachial approach (one-route method). In the one-route method, the brachial artery was punctured at the level of the elbow joint, and a 4F 11-cm sheath was inserted. Subsequently, selective arteriograms of the subclavian artery and the internal thoracic artery were obtained with a 4F cobra-shaped catheter, a 4F pigtail catheter, or a hook-shaped catheter inserted through the sheath (Fig. 1A, B). Thereafter, embolization of the ITA was performed by a coaxial technique. To embolize the peripheral levels, a mixture of NBCA, which was diluted eight times with LPD (NBCA–LPD), was infused by way of a microcatheter advanced to approximately 3 cm distal to the tip of the parent catheter. To describing the procedure in more detail, the tip of the parent catheter was advanced up to the first corner of the ITA, and the tip of the microcatheter was further advanced to approximately 3 cm distal to the corner. The tip was placed in the straight-line part of the ITA. In eight cases, the proximal portion of the ITA was additionally embolized using one or two Tornado microcoils (Cook), 3–5 or 3–6 mm in diameter. After the embolization was confirmed with repeat arteriogram, implantation of the CPS was commenced (Fig. 1C, D). A long tapered Anthron-PU catheter (AP) with a distal shaft measuring 3.3F and 60 cm long and a proximal shaft measuring 5F and 40 cm long) was placed as an indwelling catheter with its tip positioned just distal to the ITA over a 0.025-inch guidewire. Before insertion, the length of the tapered 3.3F part of the AP was shortened to match the length from the puncture site to the placement site measured on the fluoroscopic monitor. The length ranged from 30 to 37 cm (median 32.4). After insertion of the AP, the distal end of the catheter was connected to a port (brachial type of Celsite port; Toray, Japan) and was implanted at the subcutaneous pouch approximately 5 cm distal to the puncture site in the forearm through the subcutaneous tunnel (Fig. 1E).

Treatment

To prevent perfusion to the arm, a sphygmomanometer cuff was used during injection of anticancer drugs. To evaluate drug distribution over the entire tumor, computed axial tomography arteriography (CTA) was performed while contrast material was infused by way of the implanted CPS. Drug distribution was evaluated in the most recent eight patients, except for one who had inflammatory breast cancer within the first treatment cycle of the protocol. CTA was started 30 seconds after injection of 30 ml contrast material, 50% diluted with saline, at a speed of 0.5 ml/s.

Bolus injections of anticancer agents were repeated weekly. Epirubicin (EP), 30 mg/body diluted with 20 ml distilled water, was injected during the implantation of the CPS as an initial treatment. From the second treatment onward, a treatment cycle consisted of cisplatin (10 mg/body) and 5-fluorouracil (5-FU) (750 mg/body) on days 1 and 8 and 15, and EP (20 mg/body) on days 22 of treatment. Both cisplatin and 5-FU were diluted with 20 ml normal saline, and EP was diluted with 20 ml distilled water. For two patients (patients no. 8 and 11), who had been treated with trastuzumab before undergoing our treatment, EP was excluded from the treatment protocol because of potential cardiac toxicity. In these patients, cisplatin (50 mg/body) and 5-FU (1000 mg/ body) were used at the initial injection instead of EP. Both drugs were diluted with normal saline, 100 and 20 ml, respectively. From the second treatment onward, the same doses of cisplatin and 5-FU were again injected. The drugs were injected at a speed of 1 ml/5 s for 60 seconds, and then the tourniquet was removed to reperfuse the arm for 30 seconds. This treatment cycle was repeated until all of the drugs were delivered for a particular session.

A decrease in leukocyte count <2,500 or platelet count <50,000 prompted us to interrupt the treatment until the counts increased. At leukocyte counts ranging from 2,500 to 3,000 or at platelet counts ranging from 50,000 to 100,000, the dosage of 5-FU was decreased to 500 mg/body. Cycles were repeated until sufficient regression was achieved. Blood counts and biochemistry tests were monitored weekly.

Treatment-related responses in the primary site tumors and regional lymph node metastases were evaluated by the change in the largest diameter of the lesion using the *Response Evaluation Criteria in Solid Tumors* (RECIST) manual [15]. Herein, measurable lesions are defined as tumors that can be measured accurately in at least one

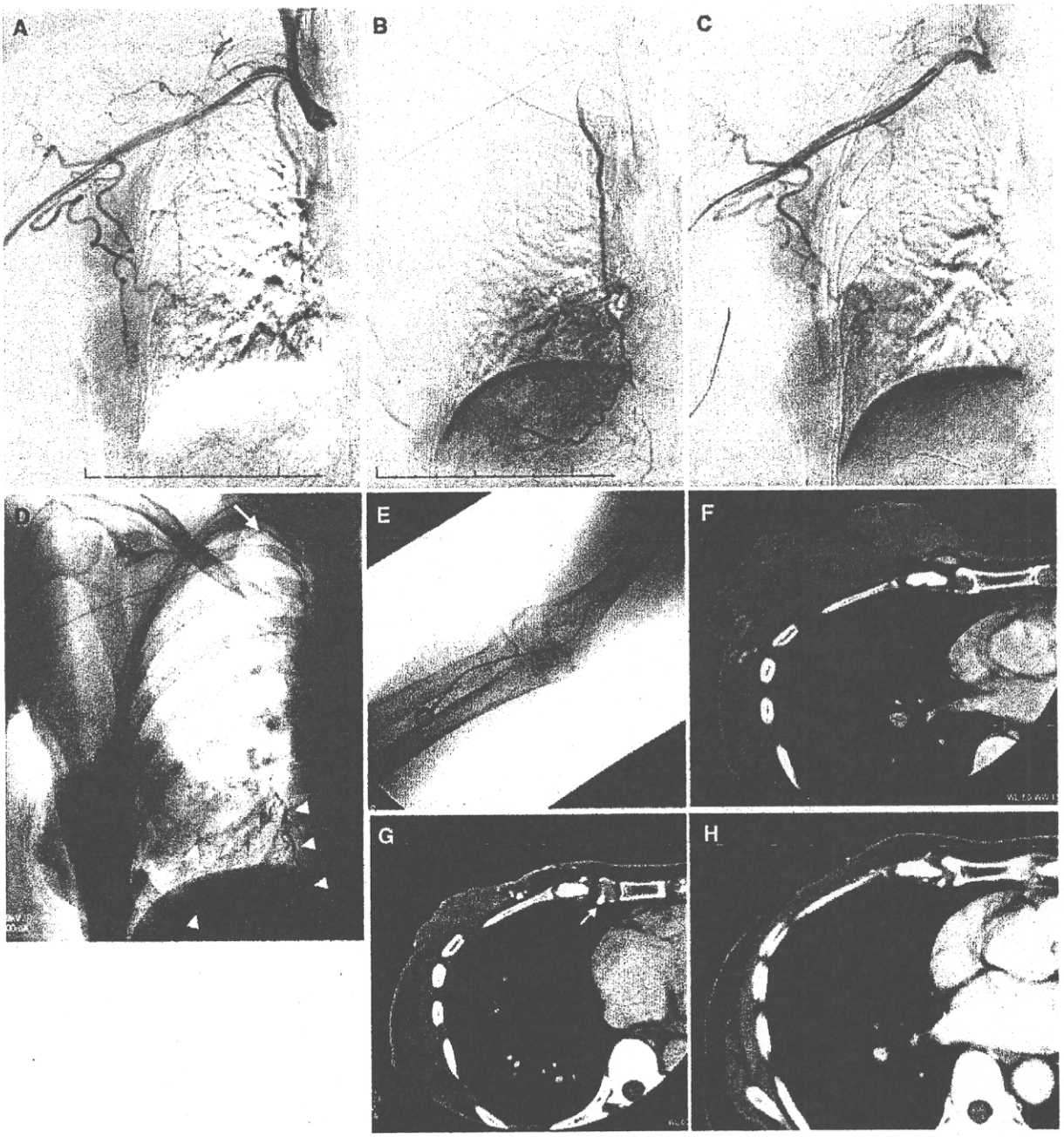

Fig. 1 (**A**) Digital subtraction angiography of subclavian artery by way of brachial approach in patient number 5 shows dilated internal and lateral thoracic arteries supplying advanced breast cancer. (**B**) A selective internal thoracic arteriogram was obtained using a 4F hook-shaped catheter. The medial part of the tumor is markedly opacified. (**C**) After embolization of the ITA using NBCA-LPD, a subclavian arteriogram was obtained by injection of contrast material by way of the indwelling catheter. The absence of opacification of the ITA was confirmed. (**D**) The scout film demonstrates the tip of the indwelling catheter (*white arrow*) placed just distal to the ITA as well as the accumulation of the infused NBCA-LPD (*white arrow heads*). (**E**) The distal end of the catheter was connected to the port and implanted at the subcutaneous pouch approximately 5 cm distal to the puncture site in the forearm through the subcutaneous tunnel. (**F**) Pretreatment CAT shows a huge tumor occupying the right-sided anterior chest wall. (**G**) CAT examination 1 month after starting RESAIC demonstrates a marked decrease in tumor size. Multiple high-density dots represent accumulation of NBCA-LPD in the ITA (*white arrow*) and its branches. (**H**) CAT examination 3 months later shows disappearance of the tumor. CR was diagnosed

dimension as being ≥10 mm and with a diameter that is more than twice the slice thickness (5 mm) by computed axial tomography (CAT) or magnetic resonance imaging (MRI). All measurable lesions, up to a maximum of 5, should be identified as target lesions, and these lesions should be selected in order of tumor size, starting with the largest.

Ten patients, except the one who had inflammatory breast cancer, were evaluated. Complete response (CR) was defined as disappearance of all target lesions. Partial response (PR) was defined as at least a 30% decrease in the sum of the largest diameters of the target lesions, using the baseline sum of the largest diameters as reference. Progressive disease (PD) was defined as at least a 20% increase in the sum of the largest diameters of the target lesions, using the baseline sum of the largest diameters as reference. Stable disease (SD) was defined as neither shrinkage sufficient to qualify for PR nor increase sufficient to qualify for PD. Not evaluable (NE) was defined when an evaluation by CT or MRI could not be done. CT and MRI scans were examined monthly. After the conclusion of RESAIC, clinical follow-up was carried out every 3 months. Procedure-related complications and treatment were scaled using version 3 of the National Cancer Institute's Common Terminology Criteria for Adverse Events [16].

Results

There were no serious procedure-related complications during CPS implantation nor were there any complications related to CPS during treatment. Two patients had grade 2 chest pain for a few days after embolization of ITA, but they had no visible dermal injury on the anterior chest wall, and the symptoms subsided without intervention. All patients were discharged within a few days after the procedure and continued infusions on an outpatient basis. The observation periods ranged from 90 to 553 days (average 310). Eight patients belonging to the resistant group required a dose-reduction of 5-FU because of decreased blood cell counts. Temporary grade-3 myelosuppression was seen in three patients belonging to the resistant group, requiring interruption of RESAIC for 2 weeks and administration of granulocyte colony-stimulating factor (G-CSF). The number of treatment cycles ranged from 3 to 10 (average 4.7), and the number of days when CPS was used ranged from 85 to 258 days (average 147.5).

The results of RESAIC are listed in Table 2. Nine of 10 (90%) patients showed PR or CR. The size of the tumor in one patient with inflammatory breast cancer could not be accurately measured on CT or MRI. In responder patients, at least some tumor reduction was observed within 1 treatment cycle. In three of four CR patients, resected specimens showed no residual cancer cells, and pathologic complete remission (PCR) was diagnosed in each of them. They have been alive and tumor free for 14, 9, and 2 months, respectively (Fig. 1F–H). The treatment of another CR patient in the resistant group with distant metastases was discontinued after 6 treatment cycles, and the patient was transferred to best supportive care after radiotherapy because of progression of her metastatic disease. The treatment of one patient with SD was discontinued after the patient had received 3 treatment cycles because of progression of lung metastasis. One patient (no. 3) with PR refused >3 treatment cycles because her preprocedural depression became worse. One patient who had inflammatory breast cancer underwent 5

Table 2 Treatment results

Patient no.	Treatment cycle	Beginning tumor size (cm)	Ending tumor size (cm)	Local response	Observation period (d)	Outcome
1	10	6.2	3.0	PR	553	Dead from metastasis
2	3	6.6	5.0	SD	351	Dead from metastasis
3	3	5.9	2.9	PR	141	Dead from metastasis
4	3	13.9	Scar	CR	539	Surgery → tumor free (14 mo)
5	5	6.8	Scar	CR	546	Surgery → tumor free (9 mo)
6	4	12.7	Scar	CR	373	Radiation, hepatic arterial chemotherapy
7	5	10.5	Scar	CR	252	Surgery → tumor free (2 mo)
8	5	–	–	NE	226	Observation
9	5	12.2	5.0	PR	192	Systemic chemotherapy
10	5	21.3	7.5	PR	144	Continuing SAIC
11	3	6.8	2.2	PR	90	Continuing SAIC

treatment cycles and had no exacerbation for 3 months after discontinuation of RESAIC. The treatment of one patient with PR (initial group) was interrupted after 5 treatment cycles because of bone metastasis progression. She was followed-up by systemic chemotherapy with aromatase inhibitors and capecitabine (Zeroda; Chugai, Japan). Currently, two patients have undergone RESAIC without complication. Entire tumors in the breast and axillary regions were remarkably enhanced on CTA in each of the eight patients examined. Even the recurrent tumor present in the medial portion of the chest wall after mastectomy was enhanced and responded to RESAIC (Fig. 2A–C). Symptoms-such as pain caused by skin ulceration, bleeding, foul odor, arm edema, or paresthesia-improved in all patients. The improvement of bleeding and pain was apparent a few days after the initial infusion, and arm edema improved as tumor size decreased.

All patients initially developed grade 1 skin hyperpigmentation in the infused areas ranging from the anterior chest wall to the back. Grade-1 alopecia occurred in two patients. The local symptoms improved, and RESAIC was continued on an outpatient basis without any significant complications in any patient.

Discussion

Currently, neoadjuvant systemic chemotherapy followed by local therapy is considered the standard treatment for controlling both local and inherent disseminated disease in patients with ABC [17]. However, an optimal chemotherapeutic regimen, local therapy, and optimal sequencing of those modalities have not been determined. Patients with ABC often suffer from symptoms, such as pain, bleeding, foul odor associated with infection, arm edema, or paresthesia. Therefore, preserving quality of life with local sterilization is given priority in such patients. AIC has often been applied as neoadjuvant chemotherapy for stage III tumors for the purpose of tumor downstaging [7, 8], as locoregional control of recurrent cancer [9], or as palliation [10]. In addition, it has been reported that AIC was feasible and effective in elderly patients [10]. However, selective and repeated infusion using the conventional procedure cause drug-induced damage of the infused arterial branches, and this promotes the development of a collateral arterial supply. Anatomically, the posterior intercostal and inferior epigastric arteries communicate to the anterior intercostal and superior epigastric arterial branches of the

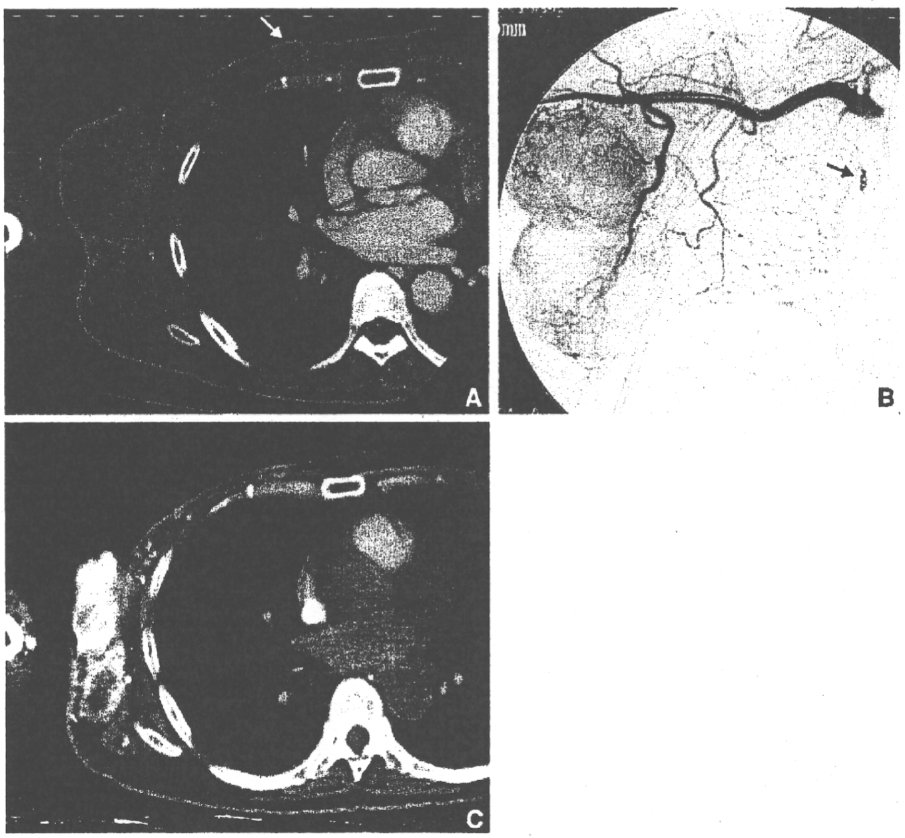

Fig. 2 (**A**) Pretreatment CTA of the patient number 6 shows a huge tumor metastasis in the right axillary region. Another metastatic tumor with ring enhancement (*white arrow*) is seen on the medial side of the anterior chest wall. (**B**) Pretreatment subclavian arteriogram by way of the implanted CPS demonstrates a huge tumor, which is mainly supplied by the lateral thoracic artery in the right axillary region. The *black arrow* represents embolized coils in the ITA. (**C**) CTA obtained by infusion of contrast material by way of the implanted CPS at the time of the third infusion chemotherapy demonstrates decreased sizes of both tumors and contrast enhancement of the tumors, which represents distribution of the infused drug

15. Padhani AR, Ollivier L (2001) The RECIST (response evaluation criteria in solid tumors) criteria: implications for diagnostic radiologists. Br J Radiol 74:983–986
16. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V et al (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176–181
17. Wang HC, Lo SS (1996) Future prospects of neoadjuvant chemotherapy in treatment of primary breast cancer. Semin Surg Oncol 12:59–66
18. Stoesslein F, Ditscherlein G, Romaniuk PA (1982) Experimental studies on new liquid embolization mixtures (histoacryllipiodol, histoacryl-panthopaque). Cardiovasc Intervent Radiol 5:264–267
19. Cakmakli S, Ersöz S, Tug T, Karaayvaz M, Akgül H (1997) Intra-arterial infusion chemotherapy in the treatment of locally advanced breast cancer. Acta Oncol 36:489–492
20. Grosso M, Zanon C, Mancini A, Garruso M, Gazzera C, Anselmetti GC et al (2000) Percutaneous implantation of a catheter with subcutaneous reservoir for intraarterial regional chemotherapy: technique and preliminary results. Cardiovasc Intervent Radiol 23: 202–210

Cardiovasc Intervent Radiol (2008) 31:86–90
DOI 10.1007/s00270-007-9189-0

CLINICAL INVESTIGATION

Hepatic Arterial Infusion Chemotherapy through a Port-Catheter System as Preoperative Initial Therapy in Patients with Advanced Liver Dysfunction due to Synchronous and Unresectable Liver Metastases from Colorectal Cancer

Toshihiro Iguchi · Yasuaki Arai · Yoshitaka Inaba · Hidekazu Yamaura · Yozo Sato · Masaya Miyazaki · Hiroshi Shimamoto

Received: 5 June 2007 / Accepted: 11 September 2007 / Published online: 10 October 2007

Abstract
Purpose We retrospectively evaluated the safety and efficacy of preoperative initial hepatic arterial infusion chemotherapy (HAIC) through a port-catheter system in patients with liver dysfunction due to synchronous and unresectable liver metastases. The aim of HAIC was to improve patients' clinical condition for later surgical removal of primary colorectal cancer.
Methods Port-catheter systems were placed radiologically in 21 patients (mean age 58.6 ± 8.1 years) with liver dysfunction due to synchronous liver metastases from colorectal cancer. Initial HAIC of 1,000 mg/m^2 5-fluorouracil was administered weekly as a 5 hr continuous infusion through this system. Surgical removal of the primary lesion was planned after HAIC improved the liver function.
Results Port-catheter system placement was successful in all patients without severe complications. Patients were followed up for a median of 309 days (range 51–998 days). After starting HAIC, no severe adverse events that caused drug loss and treatment postponement or suspension were observed in any of the patients. HAIC was performed a mean of 4.5 ± 3.0 times and the liver function improved in all patients. Curative (n = 18) or palliative (n = 1) surgical removal of the primary lesion was performed. The remaining 2 patients died because extrahepatic metastases developed and their performance status worsened; thus, surgery could not be performed. The median survival times of all patients and the operated patients were 309 and 386 days, respectively.
Conclusion Initial HAIC administration is a safe and efficacious method for improving liver function prior to operative resection of primary colorectal cancer in patients with liver dysfunction due to synchronous and unresectable liver metastases.

Keywords Colorectal cancer · Hepatic arterial infusion chemotherapy · Liver metastasis · Port-catheter system

T. Iguchi · Y. Inaba (✉) · H. Yamaura · Y. Sato · M. Miyazaki · H. Shimamoto
Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Nagoya, Chikusa-ku 464-8681, Japan
e-mail: 105824@aichi-cc.jp

Y. Arai
Department of Diagnostic Radiology, National Cancer Center Hospital, 5–1–1, Tsukiji, Tokyo, Chuo-ku 104–0045, Japan

Introduction

Colorectal cancer is the fourth most commonly diagnosed malignant disease worldwide [1], and synchronous liver metastases are identified in 10–20% of cases [2]. However, the treatment protocol for patients with stage IV colorectal cancer with synchronous liver metastases has not been firmly established [2, 3]. In such patients, the choice of treatment strategy differs based on various factors such as liver function, the patient's condition, the urgency of operating on the primary lesion, and the institution's protocols for dealing with liver metastases and primary lesions. For the primary lesion, it is desirable that surgical removal is selected to improve the quality of life of the patients, because colorectal cancer may cause obstruction, perforation, bleeding, or pain [3]. Additionally it has been reported that stage IV patients who underwent resection of their asymptomatic primary lesions had prolonged median and 2-year survival periods compared with stage IV

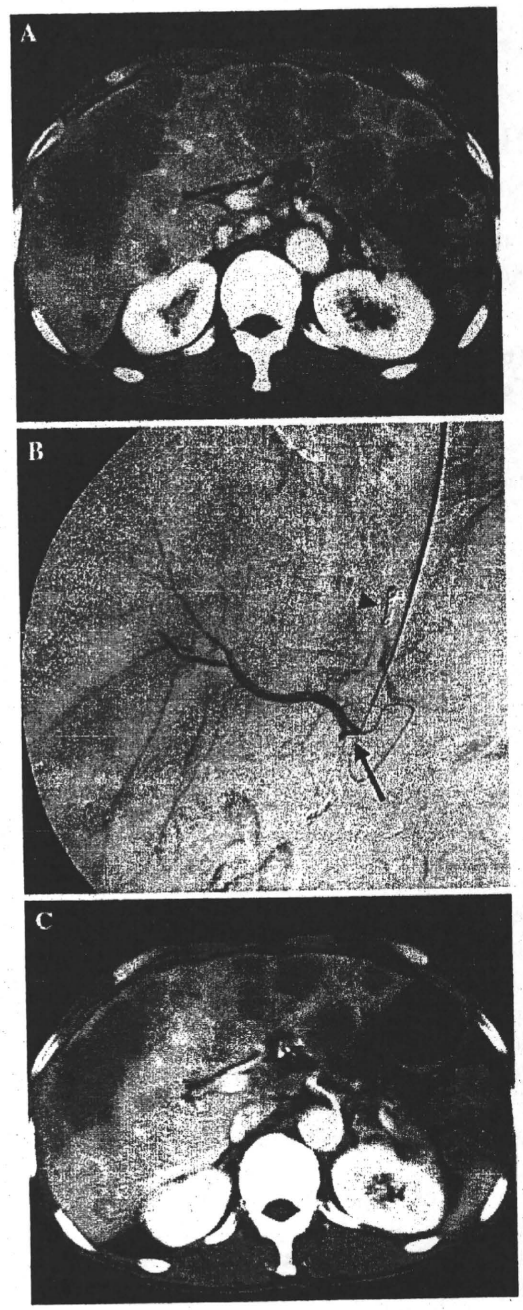

Fig. 2 A–C. A 55-year-old man with multiple liver metastases from rectal cancer. **A** Contrast-enhanced CT scan obtained before starting HAIC shows unresectable multiple liver metastases in both the right and left lobes. **B** An arteriogram via the port obtained before starting HAIC shows that all hepatic arteries are well visualized. The catheter tip was inserted into the deep segment of the gastroduodenal artery and embolized using microcoils and a mixture of *n*-butyl cyanoacrylate and iodized oil. The side hole was placed into the common hepatic artery (arrow). The accessory left hepatic artery, which branched from the left gastric artery, was embolized with microcoils (arrowhead) in order to establish hepatic arterial supply from a single vessel. **C** Contrast-enhanced CT scan obtained after five HAIC administrations shows slightly smaller multiple liver metastases. With the exception of T-BIL, the patient's liver function improved (AST improved from 83 to 26 IU/l, ALT improved from 49 to 18 IU/l, LDH improved from 1,155 to 458 IU/l, and ALP improved from 950 to 502 IU/l)

port-catheter system and surgery was 29 days (range 14–68 days). Of 13 patients who had no extrahepatic metastases prior to the surgery, 10 developed extrahepatic metastases. Among 16 of 19 patients, systemic chemotherapy with or instead of HAIC was administered after the surgery.

The overall median survival time of all the patients was 309 days and that of the patients who underwent surgery was 386 days (Fig. 1). At present, 20 patients have died.

A representative case is shown in Fig. 2.

Discussion

Many studies have reported the effectiveness of HAIC administration through a port-catheter system for liver metastases from colorectal cancer [6–8]. In Western countries, it has been reported that HAIC is effective in treating liver metastases; however, it does not improve the prognosis [6]. On the other hand, in Japan, good results have been reported after intermittent hepatic arterial infusion of a high dose of 5-FU: the response rate is reportedly 78% and the median survival time is 25.8 months [7].

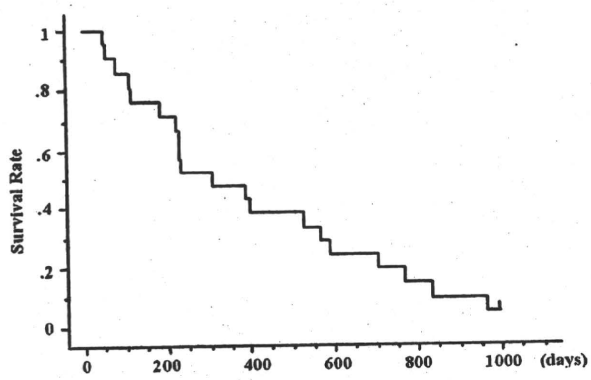

Fig. 1 Overall survival time

In general, systemic chemotherapy is usually selected for colorectal cancer with distant metastases [2]. Recently, the standard regimens such as FOLFILI (5-FU plus leucovorin with oxaliplatin) and FORFOX (5-FU plus leucovorin and irinotecan) are used, and the median survival after FOLFILI and FORFOX has been reported to be 12.6–21.5 months [12]. In many cases, systemic chemotherapy might be the first choice of treatment for patients with primary colorectal cancer and synchronous distant metastases, and we usually select systemic chemotherapy