Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma After Attempted Portal Vein Embolization in 25 Patients

OBJECTIVE. Portal vein embolization (PVE) has been widely used to facilitate major liver resection; however, curative surgery even after PVE may not be possible mainly because of inadequate hypertrophy of remnant liver or disease progression. For these patients, transcatheter arterial chemoembolization (TACE) is the next therapeutic option. We evaluated the safety and efficacy of TACE after PVE in 25 patients with hepatocellular carcinoma (HCC).

CONCLUSION. TACE using a single chemotherapeutic agent can be performed safely and effectively in HCC patients who previously underwent PVE. TACE after PVE allowed two of the patients to be downstaged so they could undergo surgical resection.

Keywords: hepatocellular carcinoma, portal vein embolization, transcatheter arterial chemoembolization

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reoperative portal vein embolization (PVE) is now considered a valid technique for increasing the safety of major resection in patients with hepatocellular carcinoma (HCC) and for extending the option of resection in patients with limited remnant liver. This technique allows greater remnant liver volume and function, thereby reducing complications and shortening hospital stays after resection [1]. However, curative surgery may not always be possible for various reasons, such as disease progression or insufficient remnant liver hypertrophy after PVE in some patients with HCC [2–4]. The postembolization unresectability rate is as high as 20% [2–4]. For these patients, transcatheter arterial chemoembolization (TACE) is the next therapeutic option.

Generally, TACE has been contraindicated in patients with advanced HCC resulting in major portal vein (PV) invasion or thrombosis because of the possibility of liver failure after embolization [5–8]. Theoretically, the degree of portal occlusion may be more extensive and peripheral in patients after PVE than in patients with tumor PV thrombosis, thereby theoretically increasing the risk of hepatic infarction if TACE is performed after PVE [9].

However, recent studies have shown that TACE using less aggressive embolization can be performed safely in HCC patients with major PV thrombosis, with no subsequent increase in morbidity or mortality [10–12]. Furthermore, Wallace et al. [9] reported three cases of TACE after PVE in HCC patients. Two of their three patients also underwent TACE before PVE. In all three cases, TACE was well tolerated, and there was no morbidity or mortality. However, a large study will be required to obtain satisfactory information regarding the efficacy and safety of the sequential approach using PVE followed by TACE. In the current study, we evaluated the safety and efficacy of TACE after PVE in 25 patients with HCC.

Materials and Methods

Patient Population

The institutional review board at our institution approved the retrospective review of patients’ medical and imaging records, and informed consent was obtained from each patient. From November 1996 through September 2008, 243 patients underwent PVE for scheduled lobectomy of the liver for HCC. The detailed technique for PVE was similar to that in previous reports [13–15]. Among our study patients, 29 (12%, 29/243) underwent PVE for HCC. The detailed technique for PVE was similar to that in previous reports [13–15]. Among our study patients, 29 (12%, 29/243) underwent TACE after PVE because curative surgery could not be performed for the following reasons: inadequate remnant liver hypertrophy on follow-up CT even after successful PVE (n = 16), aggravation of the HCC on follow-up CT (n = 8), intraoperative conformation of severe liver cirrhosis (n = 3), and deterioration of the liver function after PVE (n = 2). Four patients were excluded from the initial cohort of 29 patients because of recanalization of the portal veins at the time of TACE.

The demographics of our study patients and their tumors are summarized in Table 1. Our study
patients consisted of 23 men and two women ranging in age from 42 to 74 years (mean [SD], 58.8 ± 8.7 years). PVE was performed using only a gelatin sponge in 12 patients, using liquid embolic material [14] in seven patients, a gelatin sponge with an Amplatzer Vascular Plug (AVP) (AGA Medical) in four patients, gelatin sponge with coils in one patient, and a gelatin sponge with an AVP and coils in one patient. Fifteen patients underwent 1–5 sessions of TACE (median, 1 session) before PVE.

**Transcatheter Arterial Chemoembolization**

Superior mesenteric and celiac arteriography was initially performed to assess patient anatomy, tumor burden, vascularity, and portal vein patency. Cisplatin was then infused into the hepatic artery for 15 minutes without embolic particle administration. The infused dose of cisplatin was 2 mg/kg of the patient’s weight. After selective catheterization of the feeding artery with a microcatheter, an emulsion of iodized oil (Lipiodol, Laboratoire Guerbet) and cisplatin was infused into the feeding arteries. Embolization of the feeding arteries was then performed using 1-mm-diameter absorbable gelatin sponge particles (Gelfoam; Upjohn) until arterial flow stasis was achieved.

**Follow-Up**

Liver function, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, was evaluated after TACE. Thereafter, follow-up physical examination and laboratory tests, i.e., blood count, $\alpha$-fetoprotein, and liver function tests, were performed on a routine basis at 1-month intervals.

Follow-up CT was performed 18–43 days (median, 30 days) after TACE to evaluate tumor response or possible complications such as hepatic infarction or abscess. Repeated TACE was indicated if new or residual tumor was detected on follow-up CT in addition to elevation of serum $\alpha$-fetoprotein. Treatment was terminated if a patient could not tolerate the procedure due to a decline in clinical status [16]. When patients did not show up for treatment, they or their families were contacted by telephone for information regarding their current health status.

**Data Definition and Analysis**

Morbidity or mortality rates were evaluated after the procedure. Morbidity was defined as clinical signs of subacute liver failure (i.e., encephalopathy or new or worsening ascites) within 6 weeks after chemoembolization, formation of a liver abscess or biloma, acute renal failure, and significant hepatic infarction [10]. Mortality was defined as death within 30 days from the time of TACE [12]. Postembolization syndrome including transient fever, nausea, vomiting, or abdominal pain was not regarded as morbidity.

We divided the study patients into two groups: patients who had undergone PVE using temporary embolic material (gelatin sponge only) (group A) and patients who had undergone PVE using permanent embolic materials (gelatin sponge with AVP, gelatin sponge with coils, or gelatin sponge with AVP and coils) (group B). Univariate analysis was performed to compare the variables in the two groups. The Mann-Whitney U test was used to compare continuous variables, and the Fisher’s exact test was used to compare categoric variables.

The overall patient survival period was calculated using the Kaplan-Meier method and was measured in months from the date of the first TACE. Patients who were alive or were lost to follow-up were censored to calculate their survival rate. The survival period was compared between the two groups using the log-rank test.

All statistical analysis was performed using SPSS version 14 (SPSS). A two-sided p value less than 0.05 was considered to indicate statistical significance.

**Results**

**Morbidity and Mortality**

TACE was technically successful in all patients (Fig. 1). The median number of sessions

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<th>TABLE 1: Demographics of the Patient Population</th>
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Note—PVE = portal vein embolization, AVP = Amplatzer Vascular Plug (AGA Medical), TACE = transcatheter arterial chemoembolization.
per patient was two (range, 1–14 sessions). Eleven patients underwent only one session of TACE, and 14 patients underwent additional sessions of TACE with a median 3-month interval (range, 1–15 months) between TACE sessions. The majority of patients experienced nausea, vomiting, pain, or fever after the procedure; however, these symptoms disappeared within 10 days.

A small area of hepatic infarction at the lateral portion of the mass was found on CT in three patients (Fig. 2). However, these three patients experienced only mild postembolization syndrome and their postprocedural laboratory values, including AST, ALT, and total bilirubin, returned to baseline levels within 12 days. The median hospital stay after TACE was 5 days (range, 2–12 days). None of the patients who received TACE after PVE died within 30 days.

Change of Liver Enzymes

The laboratory values (AST, ALT, and total bilirubin) peaked within 3 days after the procedure in most of the study patients (Fig. 3). The mean normalization time of AST, ALT, and total bilirubin to baseline levels was 8.2 days (range, 3–12 days), 11.3 days (range, 2–14 days) and 12.1 days (range, 2–23 days), respectively.

Survival Period

During the median follow-up period of 11 months (range, 4–108 months), 14 patients died (disease progression [n = 13], variceal bleeding [n = 1]), one was lost to follow-up, and 10 were still alive. The HCCs in two patients (8%) were downstaged by TACE. These two patients underwent curative surgery and were still alive at the end of this study (11 months and 108 months after TACE, respectively). The median survival period was 25 months (95% CI, 0.81–49.19 months) (Fig. 4A). The survival rates were 67% at 1 year, 55% at 2 years, 48% at 3 years, and 32% at 4 years.

Comparison of Groups A and B

The comparative results of the two patient groups are summarized in Table 2. There was no significant difference between the two groups in terms of the baseline tumor or patient characteristics. Furthermore, the length of the hospital stay after TACE, change of liver enzymes (peak minus baseline values), and the frequency of TACE after PVE did not differ significantly. The median survival period was longer in group B (39 months) than in group A (11 months) (Fig. 4B); however, the difference was not statistically significant (p = 0.168).

Discussion

PVE has been increasingly used recently to facilitate major liver resection, thereby making more patients suitable for liver resection. However, curative surgery even after PVE may not be possible for various reasons. Abulkhir et al. [17] reported a meta-analysis of preoperative PVE for major liver resection. They analyzed 37 provided studies including 1,088 patients. In their study, resection was not possible in 158 patients (14.5%). Ribero et al. [4] reported that 15% of patients could not undergo curative surgery after PVE. In these two studies, the major reasons for nonresection after PVE included inadequate hypertrophy of remnant liver and disease progression.

Fig. 1—60-year-old woman with single hepatocellular carcinoma in right lobe of liver. A, Radiograph shows patient underwent right portal vein embolization using gelatin sponge with Amplatz Vascular Plug (AGA Medical) (arrowhead) and multiple coils (arrows). However, curative surgery could not be performed because of inadequate remnant liver hypertrophy. B, Contrast-enhanced axial CT image (arterial phase) obtained 2 days before transarterial chemoembolization (TACE) shows heterogeneously enhancing mass (5.8 × 5 cm) (arrowheads) in segment VII (larger than in prior studies). C, Contrast-enhanced axial CT image (arterial phase) obtained 8 months after TACE shows compact iodized oil (Lipiodol, Laboratoire Guerbet) uptake in tumor (arrowheads) and decrease in tumor size (4 × 4 cm).
In our study, the nonresection rate after PVE in HCC patients was 12% (29/243), with the reasons for nonresection similar to those of previous studies [4, 17].

Theoretically, chemoembolization after PVE increases the risk of hepatic infarction with occlusion of both the arterial and portal branches. Consistent with the previous study [9] reporting three cases of TACE after PVE in HCC patients, our data indicate that TACE is not contraindicated in HCC patients after PVE. TACE after PVE was well tolerated in all of our 25 study patients. The majority of these patients experienced only mild postembo-

Fig. 2—76-year-old man with single hepatocellular carcinoma in right lobe of liver.
A and B, Contrast-enhanced axial CT images (portal phase) obtained 35 days after transarterial chemoembolization show compact iodized oil (Lipiodol, Laboratoire Guerbet) uptake in tumor (arrowheads, A) occupying segments VII and VIII. Small area of hepatic infarction (arrow, B) developed at inferolateral portion of Lipiodol uptake in tumor.

Fig. 3—Chronological changes in laboratory values.
A–C, Graphs show changes over time in aspartate aminotransferase (AST) (A), alanine aminotransferase (ALT) (B), and total bilirubin (C) values. pre = before transarterial chemoembolization.

Fig. 4—Survival data.
A and B, Graphs show overall cumulative survival period (A) and survival rates in group A (solid line) and group B (broken line) (B).
In a previous study reporting TACE after PVE [9], the technical end point was the reduction of arterial inflow without stasis. The authors infused a 1:1 emulsion of iodized oil and chemotherapeutic agent into the right hepatic artery without subsequent particle embolization. By applying this technical end point, there was no morbidity or mortality. In our study, selective infusion of an emulsion of iodized oil and cisplatin and subsequent particle embolization of the feeding arteries were performed until arterial flow stasis was achieved. We believe that even particle embolization in the setting of TACE after PVE is safe when we can selectively embolize the feeding arteries.

It is well known that the survival rate of patients with HCC who have undergone TACE not only relates to tumor burden but also depends on underlying liver function. In patients presenting with a combination of well-compensated cirrhosis and limited tumor burden than in patients presenting with advanced liver dysfunction or more advanced tumors. In our study, the median survival period after TACE was 25 months, which is similar to that (approximately 23 months) for patients with well-compensated cirrhosis and early-stage tumors [20] and longer than that (6–9.5 months) for patients with a high risk for TACE [10, 12, 22].

With TACE, downstaging of advanced HCC is possible. For instance, Chapman et al. [23] reported that 18 of 76 (23.6%) patients with stage III/IV disease were successfully downstaged by TACE, and 17 of these 18 patients subsequently underwent liver transplantation. After liver transplantation, both disease-specific and overall survival were excellent with only one tumor recurrence. In our study, curative surgery could not be performed after TACE because of aggravation of the HCC seen on follow-up CT in eight patients. Two of these eight patients were successfully downstaged by TACE. These two patients subsequently underwent curative surgery, and they were still alive during the follow-up period (11 months and 108 months after TACE). In addition, it is possible that after PVE there is a compensatory increase in hepatic arterial flow to the embolized segments, resulting in insufficient nonembolized liver hypertrophy or rapid tumor growth.

In general, permanent, nonabsorbable material is used for PVE because it provides effective, permanent vascular occlusion. However, absorbable material theoretically allows safer subsequent TACE in cases in which the embolized liver is not resected. We compared the two groups according to the embolic materials used for PVE. Unexpectedly, there was no significant difference in the two groups in terms of hospital days after TACE, change of liver enzymes, or the frequency of TACE after PVE.

Moreover, the median survival period was longer in group B (39 months) than in group A (11 months), although it failed to reach statistical significance, probably because of the small sample size. Given that cancerous tissue of the tumor–nontumor boundary is nourished not only by tumor-feeding arteries but also by sinusoidal blood from the portal vein, it has been suggested that complete embolization of both the tumor-feeding arteries and the portal branches may be effective to decrease the recurrence rate and to prolong the survival rate after therapy [27, 28]. In addition, TACE combined with PVE may have a strong antitumor effect by suppression of arteriopetal shunts in HCC patients [29]. For these reasons, the survival rate can be prolonged with PVE with nonabsorbable material followed by TACE because of effective and permanent PV occlusion.

Recently, chemoembolization using drug-eluting beads has shown promising results for the palliative treatment of patients with hepatic malignancies including HCC, intrahepatic cholangiocarcinoma, or hepatic metastasis from neuroendocrine neoplasm or colorectal cancer. Delivery of drug-eluting beads loaded with a chemotherapeutic agent in the feeding arteries of the target tumor leads to lumen occlusion and ischemia, and the chemotherapeutic agent is gradually released locally over time. Chemoembolization using drug-eluting beads may achieve major tumor necrosis, and the side effects of chemotherapy may be reduced because of its reduced passage into the systemic circulation. However, this new therapeutic option has not been tried in HCC patients with PV occlusion [30, 31]. Given its great effect on tumor necrosis while maintaining minimal systemic side effects, chemoembolization using drug-eluting beads may be well tolerated in HCC patients with PV occlusion.
TACE for HCC After Portal Vein Embolization

The principal limitation of this study is its nonrandomized and retrospective nature, which may decrease the statistical strength. In addition, the number of patients in this study is too small to draw definite conclusions.

In conclusion, TACE using a single chemotherapeutic agent can be performed safely and effectively in HCC patients who previously underwent PVE. TACE after PVE allowed two of the patients to be downstaged so they could undergo surgical resection.

References