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Polyvinyl alcohol terminal chemoembolization for hepatocellular carcinoma with hepatic arteriovenous shunts: Safety, efficacy, and prognostic factors

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ABSTRACT

Purpose: To evaluate the safety and efficacy of polyvinyl alcohol (PVA) terminal chemoembolization and to identify the prognostic factors associated with survival in hepatocellular carcinoma (HCC) patients with hepatic arteriovenous shunts (HAVS).

Materials and methods: Of 133 patients' managements were retrospectively analyzed. HAVS was classified into three types: slow-flow, intermediate-flow and high-flow. The size of the PVA used was determined following the scheme: slow-flow HAVS: 300–500 μm PVA; intermediate-flow HAVS: 500–710 μm PVA; high-flow HAVS: 710–1000 μm PVA. The HCCs with slow-flow and intermediate-flow HAVS were embolized by PVA plus chemotherapeutic agents lipiodol emulsion, while the high-flow HAVS were treated by PVA with chemotherapeutic agents. Survival curves were calculated by Kaplan-Meier method and compared by log-rank test. The influence of possible prognostic factors on survival were analyzed by multivariate Cox proportional-hazards method.

Results: The median overall survival (OS) of 133 patients was 9.1 months. The median OS of the slow-flow type, intermediate-flow type and high-flow type patients were 10.8, 9.1 and 7.3 months, respectively. There was no statistically significant difference among different HAVS types ($P = 0.239$). The 30-day mortality was 3.8%. Cox multivariate survival analysis revealed that initial preoperative AFP value ≥ 400 ng/ml (HR = 2.105, $P = 0.006$) was an independent risk factor. While multiple embolization (HR = 0.482, $P = 0.011$), tumor remission (HR = 0.431, $P = 0.041$) and multimodality therapy (HR = 0.416, $P = 0.004$) were independent protection factors.

Conclusion: It is safe and effective for HCCs with HAVS treated by terminal chemoembolization therapy with PVA plus chemotherapeutic agents lipiodol emulsion (or PVA plus chemotherapeutic agents). The HCCs with HAVS achieves good prognosis with multiple embolization, tumor remission and multimodality therapy, while achieves poor prognosis with inital preoperative high AFP value (≥400 ng/ml).

1. Introduction

Hepatocellular carcinoma (HCC) frequently accompanies hepatic arteriovenous shunts (HAVS), with a reported incidence of 31.2% [1]. Including hepatic artery-portal vein shunts (A-PVS), hepatic artery-hepatic vein shunts (A-HVS) and mixed type. The presence of an A-PVS has been reported in 27.0–63.2% of HCC cases [2,3]. HAVS is considered a poor prognostic factor for several reasons. When HAVS appears, either subsequent chemoembolization had to be abandoned or the dose of embolic agents had to be reduced. More than that, chemotherapeutic agents lipiodol emulsion will be diverted instead to the portal vein or hepatic vein and thence to normal areas in the liver or lungs instead of being deposited intratumorally. Severe A-PVS can result in hyperkinetic portal hypertension, bleeding varices and hepatic encephalopathy. To be most effective, we believed that particle embolization should result in terminal vessel occlusion to maximize arteriovenous shunts embolism. PVA is not absorbable and it is more likely to produce a permanent occlusion because of the low frequency of recanalization [4,5]. Moreover, as a particulate embolizing agent, it is easy to handle, and is available in a wide range of sizes [6]. The purpose of the present study was to evaluate whether PVA terminal chemoembolization could be performed safely and effectively in patients with HAVS of HCC and to identify the prognostic factors associated with survival.

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2. Materials and methods

2.1. Patients

From January 2013 to December 2014, 133 patients (121 males and 12 females; median age, 51 years; range, 25–77 years) underwent transarterial chemoembolization (TACE) with PVA for HCC with HAVS at our institution. The diagnosis was made using the American Association for Study of Liver Diseases (AASLD) consensus guidelines for imaging diagnosis of HCC [7]. Before the embolism, a selective angiogram was performed to identify A-PVS or A-HVS, and the type of HAVS. The exclusion criteria were (i) Eastern Cooperative Oncology Group performance status (ECOG PS) >2, (ii) Child-Pugh class C, (iii) portal venous trunk completely blocked by tumor emboli and periportal collateral circulation undeveloped. All patients gave informed consent.

2.2. PVA chemoembolization

Celiac and superior mesenteric arteriograms were routinely performed via a 5-F RH catheter to show the hepatic arterial, portal venous anatomy and HAVS. The total volume of contrast medium used was 16 ml with a flow rate of 4 ml/s. Selective hepatic or extrahepatic arteriograms were performed to demonstrate the parenchymal tumor, portal venous tumor, arterial supplies, and HAVS. The tip of the catheter was placed as close to the feeding artery as possible before embolization. When it was difficult to advance the catheter selectively, a microcatheter (Renegade Hi-Flo [Boston Scinentific Corporation, Natick, MA] or Progreat [Terumo Corporation, Tokyo, Japan]) was used.

HAVS was classified into three types according to the timing of visualization of the arterial to venous(A-V)on arteriogram images: slow-flow HAVS: A-V>3 s; intermediate-flow HAVS: A-V = 1.6–3 s; high-flow HAVS: A-V = 0.5–1.5 s [8]. According to the timing of visualization of A-V, the size of the PVA (COOK Corporation, USA) used was determined following the scheme: slow-flow HAVS: PVA-300 (300–500 μm); intermediate-flow HAVS: PVA-500 (500–710 μm); high-flow HAVS: PVA-700 (710–1000 μm). The cases with slow-flow and intermediate-flow HAVS were treated by 0.5–1 vial of PVA particulate following chemotherapeutic agents lipiodol emulsion. The drug emulsion was performed by the administration of 10–20 mg of pirarubicin, 50–100 mg of oxaliplatin and 10 mg of mitomycin C, dissolved in 5–15 ml contrast medium mixed with lipiodol (Lipiodol Ultra-Fluide; Laboratoires Guerbet, Aulnay-sous-Bois, France) at a 1:1 vol ratio. At the beginning of the embolization, 1–2 ml of drug emulsion was injected to confirm deposition within the tumor. If not, drug emulsion could be mixed with PVA particulate. The high-flow type embolized by PVA-700 plus only with chemotherapeutic agents. The embolization was stopped when the target vessel flow decreased significantly or stagnantly compared with the initial flow by using real-time digital subtraction fluoroscopic guidance. Care was taken not to reach total stasis of arterial flow to prevent acute hepatic dysfunction, especially in patients with main portal vein thrombosis or large tumor burden involved both lobes of the liver. If multiple feeding arteries involved, embolization was performed by single or staged.

2.3. Follow-up and effect evaluation

In this study, follow-up was done by clinical visits and telephone. Patients were followed up until death or to the end of the study period (June 30, 2015). Overall survival (OS) was defined as the time interval between the initial PVA chembolization of the shunts and death or last follow-up. Progression-free survival (PFS) was defined as the duration of time from the date of the initial PVA chemoembolization to the date of the first sign of tumor progression for patients who showed radiological evidence of disease progression or the date on which the patients died from any cause. Angiography was performed immediately after completion of the procedure to check for occlusion of the shunts. The degree of shunts occlusion was divided into three categories: complete occlusion, nearly complete occlusion and incomplete occlusion. Angiographic complete occlusion was defined as “complete occlusion” of the shunts; nearly complete occlusion was a small residual stagnant shunts, which was defined as a “minor residual shunts”; and incomplete occlusion was defined as flow decrease only with one class. Modified Response Evaluation Criteria In Solid Tumors (mRECIST) [9] were employed to assess the tumor response on enhanced CT/MRI scans. Efficacy was assessed based on the following parameters: (1) OS, PFS; (2) tumor response; (3) immediate angiogram occlusion rate; (4) the characteristics of patients of pre and post-embolisation: Child-pugh class, ECOG PS score, ascites, AFP value and tumor size et al.; (5) postoperative complications.

2.4. Statistical analysis

Continuous data are expressed as means standard deviation ($x \pm s$). One-way ANOVA analysis was utilized to compare the measurement data. The Wilcoxon signed-rank test was employed for comparison of noncategoric variables. Survival curves were calculated by Kaplan–Meier method and compared by log-rank test. Univariate analysis was performed to select potentially explanatory variables. Multivariate analysis was carried out to determine the significant prognostic factors by using the Cox proportional-hazards model. A two-tailed P value <0.05 was considered statistically significant. Data were analyzed with IBM SPSS statistics version 22.

3. Results

3.1. Patient characteristics

The present study enrolled 133 patients, including 36 cases with slow-flow HAVS, 58 cases with intermediate-flow HAVS and 39 cases with high-flow HAVS. There were 121 males (91.0%) and 12 females (9.0%) with median age 51 years (range, 25–77 years). Of 103 patients (77.4%) had underlying liver cirrhosis diagnosed on imaging. Hepatitis B surface antigen was positive in 132 patients (99.2%). The dominant tumor size ranged from 1 to 22.3 cm in maximal dimension before the initial embolization. The baseline characteristics of the patients are summarized in Table 1. There were no significant difference in baseline characteristics of patients except for gastroesophageal variceal or hemorrhage and the number of tumor lesions.

3.2. Tumor response

A total of 268 sessions of embolization were performed, with each patient receiving a median of two sessions (range, 1–8). Of 93 patients with complete evaluation of imaging data after the embolization procedure. One case showed complete response (CR), 15 cases showed partial response (PR), 30 cases showed stable disease (SD) and 45 cases showed progressive disease (PD), for an objective response rate (ORR) of 17.2% (16/93). The ORR were no different significantly between three types of HAVS ($\chi^2 = 0.348$, $P = 0.840$).

3.3. HAVS immediate angiogram occlusion rate

Of the 268 sessions performed, 214 sessions of shunts embolization were performed. Of 140 sessions showed complete occlusion, 40 sessions showed nearly complete occlusion and 34 cases showed