Efficacy of percutaneous ethanol injection in the adjuvant treatment of hepatocellular carcinoma after TACE

Mingzhi Hao¹, Hailan Lin¹, Youhong Shen², Linan Tang², Ruoyuan Yan², Jianxiong Zheng¹, Qizhong Chen¹, Jing Chen², Zhougui Wu²

¹ Department of Interventional Radiology, Fujian Provincial Tumor Hospital, Fuzhou 350014, China
² Department of Ultrasound, Fujian Provincial Tumor Hospital, Fuzhou 350014, China

Received: 20 June 2008 / Revised: 25 July 2008 / Accepted: 24 September 2008

Abstract  Objective: To evaluate the efficacy of percutaneous ethanol injection (PEI) in the adjuvant treatment of hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (TACE) by primary end points of time to progress (TTP).

Methods: The study population consisted of 73 consecutive patients with inoperable HCC (China Classification System IIA/IIB). Among them, 22 patients were treated with TACE and PEI (experimental group), and the rest 51 were treated only with TACE (control group), and then the time to progress (TTP) and overall survival (OS) of these two groups were analyzed. Results: The median TTP was 10 months [95% confidence interval (CI), 7.9–12.1 months] in experimental group and 6 months (95% CI, 4.7–7.3 months) in control group. The 3-month, 6-month, and 1-year Progression Free Survival (PFS) rates were respectively 77.3%, 63.6%, and 48.1% in experimental group, and 76.5%, 42.15%, and 24.8% in control group. The TTP of experimental group was significantly longer than that of control group (P < 0.05). The median survival period was 17 months [95% confidence interval (CI), 11–23 months] of experimental group and 12 months (95% CI, 10–14 months) of control group (P > 0.05). Conclusion: Compared with single TACE, the combination of TACE and PEI can obviously postpone disease progress and prolong survival of HCC patients.

Keywords: carcinoma; hepatocellular; chemoembolization; therapeutic; ethanol; time to progress; progression free survival; postembolization syndrome

Hepatocellular carcinoma (HCC) is a highly malignant tumour with a very high morbidity and mortality, carrying a poor prognosis and presenting considerable management [1]. In addition, because of the lack of early symptoms, most patients present with advanced disease for which the outcome has generally been poor. Transcatheter arterial chemoembolization (TACE) has been shown to reduce systemic toxicity and increase local effects and thus improve the therapeutic results, it has become one of the most common forms of interventional therapy. Because the recurrence rate post-TACE is still high and the long-term survival is unsatisfactory, it is a challenge to postpone disease progression and prolong survival of inoperable HCC. It is well known that improving the overall therapeutic effects of HCC depends on the combined therapies. Compared with TACE, the combination of TACE and PEI can get more complete necrosis rates of tumor and prolong overall survival [2]. As a result of interventional therapy, most patients with inoperable HCC only get a relatively longer remission stage, and thus time to progress (TTP) is a better indicator of efficacy of interventional therapy. In order to accurately evaluate the efficacy of TACE combined PEI, TTP, Progression Free Survival (PFS), and overall survival (OS) were compared in two groups.

Materials and methods

Patients

Chemonaïve (no intra-arterial or systemic chemotherapy) patients with inoperable HCC diagnosed from August 2004 to February 2007 (China Classification System IIA/IIB) at our hospital were included in this study. Diagnosis of HCC was based on high serum alpha-fetoprotein (AFP ≥ 400 ng/mL), ultrasonography, computed tomography (CT), or needle liver biopsy while AFP < 400 ng/mL [3]. Patients were to have received TACE two times or more, and have a Karnofsky score ≥ 60. Patients were also required to be between 18 and 75 years of age and
have child-pugh score A to B and an anticipated life expectancy of at least 12 weeks. Patients with viral hepatitis were on anti-viral treatment, other therapies such as cytokine induced-killer cell (CIK), tumor angiogenesis inhibitor (thalidomide) were not prohibited in this study \(^4, \, 5\). Patient characteristics were summarized in Table 1.

### Methods

TACE was carried out according to Seldinger’s technique of arterial embolization. Hepatic arteriography were performed to define the size and location of tumor nodules. During the sequential scanning of the liver, Iodipamide 100–150 mL was injected using a power injector to evaluate the vascularity of the tumor. The arteries supplying the tumor were catheterized superselectively followed by an infusion of a mixture of Gemcitabine 0.8–1.6 g, Oxaliplatin 50–200 mg, and lipiodol 5–30 mL or Epirubicin 10–50 mg, Floxuridine 0.5–1.0 g, and lipiodol 5–30 mL. The aim was to deliver a sufficient amount of emulsion to the tumor areas without retrograde flow. Under fluoroscopic control, the feeding arteries were subsequently embolized with 2–3 mm strips of Gelfoam until complete flow stagnation was achieved.

In TACE and PEI group (experimental group), TACE was performed first, then ultrasound scan was performed 7–10 days after the completion of TACE, and PEI was then administered to the remaining viable part of the tumor nodule as reflected by ultrasound scan showing hypoechoic patterns. Ethanol 3–20 mL was injected with a 22-gauge needle one times or more after TACE. Ethanol was slowly injected until the echogenic area appearing immediately after injection covered the entire tumor and the ethanol injection was stopped if the patient complained of pain. After the injection was complete, the needle was left in place for 1–3 min to prevent reflux of ethanol into the peritoneal cavity. For patients with multiple tumors, PEI was performed first on the main tumor (one with the largest diameter), followed by treating the smaller ones until all tumors were successfully treated.

Six patients in experimental group and 6 patients in TACE (control) group received additional CIK. 15 patients in experimental group and 25 patients in control group received additional thalidomide. Post-treatment follow-up included CT scan and measurement of serum AFP levels every month. Treatment response was evaluated 1 month after the second treatment cycle of PEI in both groups. Additional treatment cycles were administered once tumor recurrence or viable tumor was found. When patients developed a diffuse, infiltrative HCC, they were considered non-responsive and not treated.

### Statistical analysis

Primary and secondary end points for this study were TTP and OS, respectively. TTP was defined as the interval from the onset of treatment to disease progression or death. All patients were followed until death or August 1, 2007. OS was defined as the time from the date of the first TAE to date of death or the last date of follow-up. The median follow-up time was 13 months (range: 4–38 months). Survival curves were estimated by the Kaplan–Meier method, and the differences were evaluated using log-rank test. Then, 95% confidence intervals (95% CI) for the survival proportion were calculated using standard errors. The frequency of each variable was analyzed by the \(\chi^2\) test and comparisons between group means were performed using student’s \(t\) test. Univariate and multivariate analyses using Cox proportional hazard