Chemoembolization for Hepatocellular Carcinoma: Multivariate Analysis of Predicting Factors for Tumor Response and Survival in a 362-Patient Cohort

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ABSTRACT

Purpose: To evaluate the factors associated with tumor response and survival after chemoembolization in 362 patients with hepatocellular carcinoma (HCC).

Materials and Methods: Between January 2006 and August 2006, 362 patients who underwent chemoembolization for unresectable HCC were evaluated. The endpoints were tumor response and patient survival. Factors associated with tumor response were evaluated using multivariate logistic regression analysis. Factors associated with patient survival were evaluated using multivariate Cox regression analysis.

Results: After chemoembolization, 69% of the study patients showed a tumor response. On multivariate analysis, tumor size (centimeter) (odds ratio [OR] 2.85, $P = .002$), tumor number (OR 4.58, $P < .001$), tumor vascularity (OR 11.97, $P < .001$), and portal vein invasion (OR 4.24, $P < .001$) were significant factors for tumor response. The median survival was 23 months. On multivariate analysis, Child-Pugh class (hazard ratio [HR] 2.43, $P < .001$), maximal tumor size (HR 1.66, $P = .002$), tumor vascularity (HR 2.13, $P = .001$), portal vein invasion (HR 2.39, $P < .001$), tumor number (HR, 1.92, $P < .001$), and alpha fetoprotein (AFP) value (HR 1.54, $P = .003$) were significant factors associated with patient survival after chemoembolization.

Conclusions: Tumor size, tumor vascularity, tumor number, and portal vein invasion are significant independent predictors of tumor response after chemoembolization in patients with unresectable HCC. Child-Pugh class B or C, large tumor size (≥ 4 cm), multiple tumors (five or more), portal vein invasion, and a high AFP value (> 83 ng/mL) indicated poor prognosis for overall patient survival after chemoembolization.

ABBREVIATIONS

AFP = alpha fetoprotein, HCC = hepatocellular carcinoma, HR = hazard ratio, OR = odds ratio, RECIST = Response Evaluation Criteria in Solid Tumors

Hepatocellular carcinoma (HCC) is a common cause of cancer-related death worldwide and usually is at an advanced stage at the time of diagnosis because of the absence of symptoms until late in the disease (1–4). Although hepatic resection and transplantation offer curative therapy, most patients with HCC (70%–80%) are not candidates for curative resection or transplantation because of either advanced cancer at the time of initial presentation or underlying cirrhosis (1,2). The median survival time of patients with untreated, unresectable HCC is generally < 6 months (5). Systemic chemotherapy and radiation therapy are generally regarded as ineffective in patients with unresectable HCC (6–8).

Chemoembolization is indicated for certain patients with unresectable HCC for palliative purposes. Chemoembolization increases survival rates in certain selected patients with unresectable HCC, and it is currently considered the mainstay of therapy for this subset of patients (3,9,10). Although sorafenib recently showed a significant survival

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benefit in randomized controlled trials of advanced HCC, it is difficult to accept this targeted therapy as a standard therapy for all patients with advanced HCC because patients with vascular invasion or extrahepatic spread could have a heterogeneous prognosis according to the degree of portal vein invasion or tumor burden in addition to the degree of liver function impairment (11–14).

Determining the factors predictive of tumor response and survival after chemoembolization is important. At the present time, the assessment of therapeutic efficacy of chemoembolization relies on evaluating multiple imaging characteristics of the tumor as seen on cross-sectional imaging. Although many studies have evaluated the prognostic factors for survival (15–19), only a few studies (5,20) have evaluated the predictive factors associated with tumor response after chemoembolization in patients with unresectable HCC. These study results are limited because of the relatively small number (< 80) of patients who were included over a relatively long period (approximately 4 y) and the use of univariate analysis to find the factors associated with tumor response (5,20). In the present study, we performed multivariate analysis to determine the predictive factors associated with tumor response after chemoembolization in 362 patients. We also evaluated the survival rates and the factors associated with survival after chemoembolization in these patients.

MATERIALS AND METHODS

Patient Population

The study protocol was approved by our institutional review board, and informed consent was obtained for chemoembolization. Indications of chemoembolization for HCC in our institution are (*i*) imaging or pathologic diagnosis of HCC; (*ii*) unresectable HCC because of either advanced stage or insufficient hepatic reserve; and (*iii*) tumors that are unsuitable for other local treatments (radiofrequency ablation or percutaneous ethanol injection) because of tumor size > 5 cm, multiple lesions (more than three), vascular invasion, or subcapsular lesions. The exclusion criteria for treatment with chemoembolization were any contraindication to an arterial procedure, such as impaired clotting tests (platelet count $< 50{,}000/mm^3$ or prothrombin activity $< 50\%$), bacterial infection, or renal failure. Advanced liver disease (Child-Pugh class C), portal vein thrombosis, and extrahepatic metastasis were not contraindications to chemoembolization.

Between January 2006 and August 2006, we retrospectively reviewed the collected data of 501 consecutive patients who underwent chemoembolization for unresectable HCC. We excluded 139 patients from this study because of a previous history of percutaneous radiofrequency ablation ($n = 35$), previous chemoembolization procedures that had been performed at other institutions ($n = 82$), or lack of computed tomography (CT) scans before or after chemoembolization ($n = 22$). Contrast-enhanced four-phase CT (nonenhanced phase, hepatic arterial phase [by using bolus-tracking methods or 36-s delay], portal venous phase [by using a 72-s delay], and equilibrium phase [3 min delay]) was performed 1–2 weeks before the initial chemoembolization session to evaluate the tumor characteristics and the presence of extrahepatic metastasis.

Chemoembolization

We adopted SIR reporting standards for the terminology (21). Patients received intravenous fluid and premedications (antiemetics or steroids) before treatment. Superior mesenteric and celiac arteriography was initially performed to assess the anatomy, tumor burden, and portal vein patency. Then 0.5 mg/mL of cisplatin (Cisplan; Dong-A Pharm Co, Seosan, Korea), dissolved in distilled water, was infused into the right lobar, left lobar, or proper hepatic artery according to the location of tumor for 15 minutes without embolic particle administration (22). The infused dose of cisplatin was 2 mg/kg (4 mL/kg) of the patient's weight. After cisplatin infusion for 15 minutes, an emulsion of iodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-Sous-Bois, France) and cisplatin in a 1:1 ratio was infused selectively into the feeding arteries. The dose of iodized oil depended on the tumor size and ranged from 2–20 mL. Embolization of the feeding arteries was performed using 1-mm diameter, absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Michigan) until arterial flow stasis up to the segmental artery level was achieved. When extrahepatic feeding arteries were present, embolization of these extrahepatic feeders was performed using the emulsion of iodized oil and cisplatin and Gelfoam. Patients were observed overnight after chemoembolization for control of possible postembolization syndrome (pain, nausea, or fever) and other adverse effects. Patients were discharged when there was no discomfort or after improvement of complications.

Follow-Up

Follow-up physical examination and laboratory tests (blood count and liver function tests) were performed routinely at 1-month intervals. Tumor response was evaluated by two interventional radiologists (H.T.H. and J.H.K, with consensus) based on initial contrast-enhanced four-phase CT scans obtained 4–6 weeks after chemoembolization. Tumor response was classified into four grades according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) (23) as follows: complete response, the disappearance of any intratumoral enhancement in all target lesions; partial response, decrease $\geq 30\%$ in the sum of the greatest dimension of viable (enhancing) target lesions; progressive disease, increase $\geq 20\%$ in the sum of the greatest dimension of viable (enhancing) target lesions; and stable disease, not enough shrinkage or sufficient increase to qualify as a partial response or as progressive disease. After the initial CT scan, subsequent follow-up contrast-enhanced CT scans were repeated every 2–3 months. Re-