# Phase I/II Multicenter Study of Transarterial Chemoembolization with a Cisplatin Fine Powder and Porous Gelatin Particles for Unresectable Hepatocellular Carcinoma: Japan Interventional Radiology in Oncology Study Group Study 0401

Keigo Osuga, MD, Yasuaki Arai, MD, Hiroshi Anai, MD, Yoshito Takeuchi, MD, Takeshi Aramaki, MD, Eiji Sugihara, MD, Takanobu Yamamoto, MD, Yoshitaka Inaba, MD, Fumikiyo Ganaha, MD, Hiroshi Seki, MD, Shunichi Sadaoka, MD, Mikio Sato, MD, Takeshi Kobayashi, MD, Yoshihisa Kodama, MD, Shinichi Inoh, MD, and Koichiro Yamakado, MD

## ABSTRACT

**Purpose:** A multicenter phase I/II study of transarterial chemoembolization with a fine cisplatin powder and gelatin particles (GPs) for multifocal hepatocellular carcinoma (HCC) was conducted. Primary endpoints were dose-limiting toxicity (DLT) and recommended dose (RD). Secondary endpoints were the incidence and severity of adverse events and tumor response.

**Materials and Methods:** Nonselective transarterial chemoembolization was performed until all tumor enhancement disappeared. Lipiodol was not used. In the phase I study, the cisplatin dose was escalated from 35 mg/m$^2$ to 65 mg/m$^2$ in 15-mg/m$^2$ increments to determine DLT and RD. In the phase II study, 40 patients were treated with the RD. Toxicity was assessed by Common Toxicity Criteria for Adverse Effects (version 3.0), and tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) and European Association for the Study of the Liver (EASL) criteria.

**Results:** A total of 46 patients were enrolled. As no DLT occurred at any dose level in the phase I study, RD was determined as 65 mg/m$^2$. In the phase II study, the treatment was discontinued in one patient as a result of vasovagal response. Toxicities of grade 3 or higher included nausea (2.2%), pancreatitis (2.2%), cholecystitis (2.2%), thrombocytopenia (8.7%), hyperbilirubinemia (2.2%), and increased aspartate aminotransferase (28.3%) and alanine aminotransferase (21.7%) levels. Tumor response rates under RD were 25.6% and 64.1% by RECIST and EASL criteria, respectively.

**Conclusions:** Nonselective transarterial chemoembolization with fine cisplatin powder and GPs was well tolerated and effective in patients with multifocal HCC at the RD of 65 mg/m$^2$.

## ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CR = complete response, DEB = drug-eluting bead, DLT = dose limiting toxicity, EASL = European Association for the Study of the Liver, GP = gelatin particle, HAIC = hepatic arterial infusion chemotherapy, HCC = hepatocellular carcinoma, MTD = maximum tolerated dose, RD = recommended dose, RECIST = Response Evaluation Criteria in Solid Tumors, NE = not evaluable, PR = partial response

From the Department of Diagnostic and Interventional Radiology (K.O.), Osaka University Graduate School of Medicine, Suita; Department of Diagnostic Radiology (Y.A., Y.T.), National Cancer Center; Department of Radiology (S.S.), Jikei University School of Medicine; Department of Radiology (S.I.), Graduate School of Medicine, University of Tokyo, Tokyo; Department of Radiology (H.A.), Nara Medical University, Kashihara; Division of Diagnostic Radiology (T.A.), Shizuoka Cancer Center, Shizuoka; Department of Diagnostic Radiology (E.S.), Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; Department of Radiology (T.Y.), Tochigi Cancer Center Hospital, Utsunomiya; Department of Diagnostic and Interventional Radiology (Y.I.), Aichi Cancer Center Hospital, Nagoya; Department of Radiology (F.G.), Okinawa Prefectural Nanbu Medical Center and Children's Medical Center,

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality worldwide (1). In patients with HCC who are not eligible for curative therapies such as surgical resection or radiofrequency ablation, transarterial chemoembolization has been the prevailing treatment and has proven survival benefits (2). Conventionally, a mixture of chemotherapeutic agents and lipiodol has been used for transarterial chemoembolization. However, the choice of chemotherapy regimen has not been standardized, and use of lipiodol chemoembolization in both liver lobes can increase liver damage (3,4). For localized tumors of small number or size, selective lipiodol chemoembolization has been safely performed by using a segmental or subsegmental approach (5), whereas, for bilobar multifocal tumors, multistaged lipiodol chemoembolization may be considered. Newer technologies such as chemoembolization with drug-eluting beads and radioembolization with yttrium-90 ($^{90}$Y) microspheres have been increasingly applied to treat unresectable HCC. Although these techniques have been investigated in clinical trials (6–8), neither are approved in Japan. Recently, two commercial products, a fine cisplatin powder and porous gelatin particles (GPs), have been specifically approved for transarterial treatment of HCC in Japan. The cisplatin powder was originally designed for use in hepatic arterial infusion chemotherapy (HAIC). However, the indication for HAIC with the fine cisplatin powder remains unclear, because the role of HAIC for HCC has not been well established (9). Therefore, this fine powder is being used for transarterial chemoembolization in situations in which lipiodol chemoembolization may be inappropriate, such as nonselective embolization of multifocal HCC. However, the dose of cisplatin fine powder for transarterial chemoembolization has not been optimized. The purpose of the present study was to evaluate the safety and efficacy of nonselective transarterial chemoembolization for multifocal HCC with the use of a combination of fine cisplatin powder and porous GPs. This study was conducted as a multicenter phase I/II study by the Japan Interventional Radiology in Oncology Study Group (study code 0401).

Haebaru; Department of Diagnostic Radiology (H.S.), Niigata Cancer Center Hospital, Niigata; Department of Gastroenterology and Hepatology (M.S.), Ryugasaki Saiseikai Hospital, Ryugasaki; Department of Diagnostic and Interventional Radiology (T.K.), Ishikawa Prefectural Central Hospital, Kanazawa; Department of Radiology (Y.K.), Teine Keijinkai Hospital, Sapporo; and Department of Diagnostic Radiology, Mie University Graduate School of Medicine, Tsu (K.Y.). Received January 29, 2012; final revision received June 21, 2012; accepted June 26, 2012. **Address correspondence to** K.O., Department of Diagnostic and Interventional Radiology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; E-mail: osuga@radiol.med.osaka-u.ac.jp

Present address of E.S.: Department of Radiology, Kaizuka City Hospital, Kaizuka, Japan.

This study was supported by Grant-in-Aid from the Ministry of Health and Welfare of Japan. None of the authors have identified a conflict of interest.



*J Vasc Interv Radiol 2012; 23:1278–1285*

http://dx.doi.org/10.1016/j.jvir.2012.06.028

## MATERIALS AND METHODS

### Study Endpoints

The primary endpoints were dose-limiting toxicity (DLT) and recommended dose (RD) of fine cisplatin powder used for nonselective transarterial chemoembolization in multifocal HCC. Secondary endpoints were incidence and severity of adverse events and tumor response to therapy.

### Patient Eligibility

Patients were considered for enrollment if they had (i) unresectable bilobar multifocal HCC (or multifocal recurrent HCC in the remnant liver after surgery) confirmed by histologic examination or diagnostic imaging; (ii) measurable hypervascular lesions confined to the liver that showed early enhancement on contrast-enhanced dynamic computed tomography (CT); (iii) no tumor thrombus in the first branch or main trunk of the portal vein; (iv) no extrahepatic metastases; (v) Eastern Cooperative Oncology Group performance status of 0, 1, or 2; (vi) Child–Pugh classification of A or B; (vii) no lingering effect of any previous treatment (at least a 4-wk interval from most recent treatment); (viii) adequate bone marrow, renal, and cardiac function demonstrated by laboratory test results obtained within 2 weeks of signing the study consent (ie, leukocyte count $\geq$ 3,000 mm$^2$, platelet count $\geq$ 50,000/mm$^3$, hemoglobin level $\geq$ 9.5 g/dL, serum creatinine level no greater than the upper limit of normal range, blood urea nitrogen level $\leq$ 25 mg/dL, and no abnormality on electrocardiogram); (ix) age at least 20 years and younger than 75 years; and (x) life expectancy of at least 8 weeks. Patients were excluded from the study if they had (i) previous transarterial chemoembolization with a platinum-containing drug; (ii) an extrahepatic collateral tumor supply suspected or confirmed by contrast-enhanced CT or previous angiography; (iii) previous surgical bile duct reconstruction or endoscopic sphincterotomy; (iv) lymph node or other distant metastases; (v) severe comorbidity including cardiac failure, myocardial infarction, pulmonary fibrosis, interstitial pneumonia, intractable diabetes mellitus, or renal failure; (vi) an active infection except for viral hepatitis; (vii) another concurrent malignancy; (viii) a known allergy to iodinated contrast media, platinum-containing drugs, or gelatin-containing drugs or foods; (ix) pregnancy or lactation; or (x) any condition judged by the investigators to potentially jeopardize patient safety or compliance with the study protocol.

The study protocol was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of each participating hospital. All patients signed an informed consent document for the research protocol and the procedure.

### Chemotherapeutic and Embolic Agents

Cisplatin fine powder (IA Call; Nippon Kayaku, Tokyo, Japan) was the first platinum-containing drug specifically approved for HAIC for HCC. The mean size of the fine-powder granules is 28.5 $\mu$m, and the dissolution rate of the