# Transcatheter Arterial Chemoembolization Using Cisplatin Powder Mixed with Degradable Starch Microspheres for Colorectal Liver Metastases after FOLFOX Failure: Results of a Phase I/II Study

Hideyuki Nishiofuku, MD, PhD, Toshihiro Tanaka, MD, PhD, Masaki Matsuoka, MD, Toshio Otsuji, MD, Hiroshi Anai, MD, PhD, Satoru Sueyoshi, MD, Yoshitaka Inaba, MD, PhD, Fumikazu Koyama, MD, PhD, Masayuki Sho, MD, PhD, Yoshiyuki Nakajima, MD, PhD, and Kimihiko Kichikawa, MD, PhD

## ABSTRACT

**Purpose:** To report the results of a phase I/II study of a transcatheter arterial chemoembolization protocol using cisplatin powder and degradable starch microspheres (DSM) for unresectable colorectal liver metastases after failure of FOLFOX (5-flourouracil, leucovorin plus oxaliplatin) chemotherapy conducted to determine the recommended dose of cisplatin powder and to assess the efficacy and safety of the protocol.

**Materials and Methods:** A fine-powder formulation of cisplatin was mixed with DSM and administered via the hepatic artery every 4 weeks. In phase I, three cohorts of patients received escalating doses of cisplatin powder: 50 mg/m$^2$, 65 mg/m$^2$, and 80 mg/m$^2$. In phase II, tumor response, toxicity, and survival times were assessed.

**Results:** The study enrolled 24 patients. Previously, FOLFOX had been administered to all patients, an irinotecan-containing regimen had been administered to 12 patients, and bevacizumab or cetuximab or both had been administered to 14 patients. In phase I, dose-limiting toxicity did not appear at any level, and the recommended dose of cisplatin powder was determined to be 80 mg/m$^2$. In phase II, a tumor response rate of 61.1% was achieved. The median hepatic progression-free survival and overall survival were 8.8 months (95% confidence interval [CI], 4.06–13.5 mo) and 21.1 months (95% CI, 8.37–33.8 mo). The following grade 3 toxicities were observed: thrombocytopenia (12.5%), aspartate transaminase elevation (33.3%), alanine transaminase elevation (12.5%), hyponatremia (8.3%), and cholecystitis (4.2%).

**Conclusions:** This study shows that transcatheter arterial chemoembolization with cisplatin powder at a dose of 80 mg/m$^2$ mixed with DSM is well tolerated and can produce a high response rate with a long survival time for patients with unresectable colorectal liver metastases after failure of FOLFOX.

## ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CEA = carcinoembryonic antigen, CI = confidence interval, DLT = dose-limiting toxicity, DSM = degradable starch microspheres, 5-FU = 5-fluorouracil, FOLFIRI = 5-FU, leucovorin plus irinotecan, FOLFOX = 5-FU, leucovorin plus oxaliplatin, H-PFS = hepatic progression-free survival, OS = overall survival, PFS = progression-free survival, RECIST = Response Evaluation Criteria In Solid Tumors

In metastatic colorectal cancer, FOLFOX (5-fluorouracil [5-FU], leucovorin plus oxaliplatin) or FOLFIRI (5-FU, leucovorin plus irinotecan) chemotherapy is widely used in combination with biologic agents. These chemotherapeutic regimens have improved outcome, resulting in high response rates of 34.8%–45% and long survival times of 18.6–24.9

From the Departments of Radiology (H.N., T.T., H.A., S.S., K.K.) and Surgery (F.K., M.S., Y.N.), Nara Medical University, 840 Shijo-cho, Kashihara, 634-8522, Nara, Japan; Department of Internal Medicine (M.M., T.O.), Dongo Hospital, Yamatotakada; and Department of Diagnostic and Interventional Radiology (Y.I.), Aichi Cancer Center Hospital, Nagoya, Japan. Received January 31, 2012; final revision received August 27, 2012; accepted September 4, 2012. **Address correspondence to** H.N.; E-mail: hmn@naramed-u.ac.jp

A phase I portion of this study was presented at the SIR 2009 Annual Meeting.

None of the authors have identified a conflict of interest.



*J Vasc Interv Radiol 2013; 24:56–65*

http://dx.doi.org/10.1016/j.jvir.2012.09.010

months (1–6). However, after failure of first-line treatment, second-line treatment using FOLFOX or FOLFIRI as crossover treatment is less effective, with response rates ranging from 4%–15% and survival time of around 9 months (1,7).

Approximately 60% of patients with colorectal cancer develop liver metastases during the course of their disease, and most of these patients die of liver failure (8). For patients with unresectable, liver-dominant disease, it is vital to identify potential therapies that can provide high response rates and improve survival times. Several investigators have performed hepatic arterial infusion chemotherapy or chemoembolization using 5-FU, oxaliplatin, or irinotecan as a second-line or third-line treatment for patients with colorectal liver metastases (9–13). However, response rates were lower compared with the use of these chemotherapeutic agents as first-line treatment because of acquired drug resistance.

Although several randomized trials have demonstrated failure of systemic chemotherapy using cisplatin in colorectal cancer (14,15), we postulated that intraarterial cisplatin after failure of standard systemic chemotherapy might be effective for the following reasons. First, previous studies of first-line arterial infusion of cisplatin showed high tumor response rates of $> 50\%$ (16,17). Second, cisplatin has a different spectrum of activity from and low cross-resistance to oxaliplatin, which is generally administered in FOLFOX as first-line or second-line systemic chemotherapy (18). Third, in an experimental study using human colorectal tumor cell lines, the cytotoxicity of cisplatin was similar to the cytotoxicity of oxaliplatin (19).

Combination with drug carriers or embolic materials enhances the pharmacologic advantages of intraarterial cisplatin. This technique prolongs exposure of the tumor to the drug, increasing uptake and decreasing systemic availability. Several previous reports (20,21) showed that cisplatin solution combined with degradable starch microspheres (DSM; mean diameter of 40 μm/L ± 5, half-life of 15–30 min at 37°C), an embolic material used to occlude the tumor feeding arteries temporarily, increased tumor platinum concentration to approximately 4.5 times that achieved with arterial infusion alone. A fine-powder formulation of cisplatin (IA-Call; Nippon Kayaku, Tokyo, Japan) was developed more recently in Japan. Several clinical trials of cisplatin powder delivered intraarterially for hepatocellular carcinoma showed promising results in terms of safety and effectiveness (22,23). The advantage of this formulation of cisplatin is the high solubility in saline solution or water-soluble iodinated contrast material. This property allows cisplatin to mix with embolic materials or to load into drug carriers effectively (24,25).

We have developed a transcatheter arterial chemoembolization technique using a fine-powder formulation of cisplatin mixed with DSM. The aim of the present phase I/II study of this therapy for unresectable hepatic metastases from colorectal cancer after failure of FOLFOX chemotherapy was to determine the recommended dose of cisplatin powder and to assess the efficacy and safety of this technique.

## MATERIALS AND METHODS

### Study Design

This study was a single-center, single-arm, open-label trial (University Hospital Medical Information Network Clinical Trials Registry registration number 000001168). The study protocol was approved by the institutional review board of Nara Medical University. The objective of the phase I part (hereinafter referred to as phase I) was to assess the frequency of dose-limiting toxicity (DLT) and to estimate the recommended dose for cisplatin powder by dose escalation. In the phase II part (hereinafter referred to as phase II), new patients were enrolled at the estimated recommended dose, and tumor response in the liver metastases was evaluated (primary endpoint). In addition, toxicity, overall progression-free survival (PFS), hepatic progression-free survival (H-PFS), and overall survival (OS) were evaluated (secondary endpoints).

### Eligibility Criteria

The eligibility criteria for inclusion in this study were as follows: unresectable liver metastases from colorectal adenocarcinoma confirmed histologically; measurable hepatic lesions that were considered to be the prognosis-determining factor (extrahepatic metastases were allowed if they were considered to have relatively low influence on the prognosis); failure of FOLFOX therapy (progression or toxicity or both); no lingering adverse effects from previous therapies (at least a 2-week interval after cessation of the previous therapy); Eastern Cooperative Oncology Group performance status of 0–2; maintenance of adequate bone marrow, renal, and cardiac function; clinical laboratory test criteria including white blood cell count $\geq 3{,}000/mm^3$ and $\leq 12{,}000/mm^3$, platelet count $\geq 7.5 \times 10^4/mm^3$, serum total bilirubin $\leq 2.5$ mg/dL, serum creatinine $\leq 1.5$ mg/dL, blood urea nitrate $\leq 2$ 5 mg/dL, and prothrombin time $\geq 50\%$; age 20–80 years; life expectancy $> 8$ weeks; and written informed consent. All patients underwent contrast-enhanced computed tomography (CT) within the 2 weeks preceding enrollment.

Exclusion criteria were as follows: previous pancreatobiliary surgery or endoscopic sphincteropapillotomy; serious complications other than chronic hepatitis or cirrhosis; active clinically serious infections (other than hepatitis C virus); concomitant malignancy; a history of allergy to iodine-containing agents or contrast media, platinum drugs, or starch; pregnancy; and hepatic arterial occlusion diagnosed on contrast-enhanced CT or arteriography. This study protocol did not require examination of *KRAS* gene status in the enrolled patients.